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Retrograde Amnesia in LGI1 and CASPR2 Limbic Encephalitis: Two Case Reports and a Systematic Literature Review

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ABSTRACT

Background: Both anterograde and retrograde amnesia can typically co-occur in limbic autoimmune encephalitis (LAE), including the forms associated with antibodies to CASPR2/LGI1, two protein complexed with the voltage-gated potassium channel (VGKC). However, isolated retrograde amnesia is very rare, and it has never been described in LAE.

Methods: We report two patients with CASPR2 LAE who showed isolated retrograde amnesia, without other significant cognitive impairments. A systematic literature review was performed in accordance with the PRISMA guidelines on patients with LAE, antibodies to the VGKC complex (including LGI1, CASPR2, or the VGKC), and memory impairment.

Results: We identified 467 patients from 29 studies. Fourteen/467 had retrograde amnesia (2.9%), which co-occurred with anterograde amnesia in 12 with VGKC antibodies (7 with LGI1 LAE-like clinical phenotypes). Our two cases with CASPR2 LAE (2/469, 0.4%) were the only ones with isolated retrograde amnesia, which was actively investigated in only 56/467 patients. Thirteen/14 patients, including the two with isolated retrograde amnesia, had partial or poor cognitive improvement.

Conclusions: Retrograde amnesia is rare but likely under-recognized in VGKC-complex antibodies LAE and associates with poor recovery. When isolated, it adds to the spectrum of CASPR2 LAE. These findings promote insights into retrograde amnesia pathophysiology, deserving investigation across the whole spectrum of AE.

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1 | Introduction

Limbic autoimmune encephalitis (LAE) is characterized by memory loss, disorientation, mood changes, and epileptic seizures [1]. Brain magnetic resonance imaging (MRI) often shows fluid-attenuated inversion recovery (FLAIR)/T2 hyperintensity and subsequent atrophy within the medial temporal lobes and the hippocampus, namely the brain regions important for learning and memory [2, 3].

Patients with LAE can harbor several autoantibodies targeting intracellular or cell surface neuronal antigens. In the latter group, autoantibodies directed against the contactin-associated protein-like 2 (CASPR2) and the leucine-rich glioma-inactivated 1 (LGI1) are among the most common and have shown a direct pathogenic role [4–6]. These antibodies were originally identified as targeting the voltage-gated potassium channel (VGKC) complex, but, later on, LGI1 and CASPR2 (two proteins associated with the VGKC) were discovered to be the actual targets, and the term "VGKC antibodies" is now considered obsolete [7].

Amnesia is one of the key features in all forms of LAE, including those associated with LGI1/CASPR2 antibodies [8]. Memory loss in LAE patients is typically both anterograde (affecting the ability to store new memories) and retrograde (affecting existing recent or remote memories). Retrograde amnesia is in most cases temporally graded, with more recent memories being first affected according to Ribot's law [9, 10], but cases showing temporally ungraded retrograde amnesia, with the inability to recall scattered episodes of the past, have also been reported [10]. Conversely, isolated retrograde amnesia is exceptionally rare and has been mainly reported after electroshock therapy or as psychological mechanisms linked to the "blocking" of traumatic memories ("dissociative amnesia"; [11]). In addition, isolated retrograde amnesia can be experimentally induced through the administration/consumption of psychoactive drugs and alcohol, but the mechanisms of memory loss are largely unknown [12]. Notably, isolated retrograde amnesia has never been reported in LAE [13–19].

Here we report two patients with CASPR2 antibody-positive LAE with isolated episodic-autobiographical temporally graded, in one case, and ungraded, in the other, retrograde amnesia, along with a systematic literature review on memory impairment in LAE associated with antibodies to LGI, CASPR2, or the VGKC.

2 | Materials and Methods

Information regarding the two case reports was collected from the hospital charts. To assess the retrograde amnesia, the Autobiographical Memory Interview (AMI; [20]) was performed. This is a structured interview that evaluates autobiographical and personal semantic memories over three distinct time periods: recent events (within the previous year), early adulthood (between the ages of 19 and 29), and childhood (up to 18 years old). LAE diagnosis was assessed according to Graus' consensus-based criteria [1]. CASPR2 antibodies were assessed using a combination of in-house tissue-based assay (TBA), and live CBA, as previously described [21] together with a commercial fixed cell-based assay (CBA; Euroimmun, Germany), in accordance with manufacturer's instructions.

2.1 | Study Selection, Inclusion, and Exclusion Criteria for the Systematic Review

On June 15th, 2024, we searched the PubMed, Scopus, and Embase databases for articles about patients diagnosed with LAE in accordance with PRISMA guidelines [22]. In the final analysis, we included patients with the following characteristics: (a) diagnosis of definite LAE [1]; (b) serum and/or CSF positive for antibodies targeting the VGKC-complex (either targeting LGI, CASPR2, or VGKC without further specification); (c) memory impairment; (d) sufficient information to classify the memory impairment (neuropsychological tests to assess the memory impairment had to be specified).

Table S1 shows search strategies with MeSH terms, and Figure 1 PRISMA flow chart with inclusion and exclusion criteria. We obtained systematic review protocol registration on PROSPERO (CRD42025649987), whereas the PRISMA 2020 checklist is reported in Appendix S2.

2.2 | Data Extraction and Quality Assessment

We extracted the following data: the first author's last name, year of publication, patients' demographic and clinical data, amnesic syndrome characteristics, associated neurologic deficits, neuroimaging data, etiology, and outcome.

Quality of studies included in the systematic review was independently assessed by two authors (A.M. and D.C.) using the NIH Quality Assessment Tool for Case Report/Series and Retrospective studies (Table S2). A risk of bias assessment, graphs, and a map were then generated and visually represented (Figures S1 and S2).

2.3 | Data Synthesis and Descriptive Analysis

Data were summarized using descriptive statistics, with means and standard deviations for continuous variables and frequencies and percentages for dichotomous variables. All descriptive statistical analyses were performed using GraphPad Version 9 (GraphPad Software, San Diego, CA, USA).

3 | Clinical Case Description

3.1 | Case 1

In May 2021, a 72-year-old male presented, in a 2-week period, with recurrent episodes of altered consciousness lasting a few seconds, and behavioral changes, and was admitted to the Mondino neurology ward. His medical history revealed hypertension, atrial fibrillation, and previous bullous pemphigus. After neurological evaluation, he underwent a brain MRI that showed only mild signs of cerebrovascular pathology, and a normal EEG that was unremarkable. In suspicion of temporal

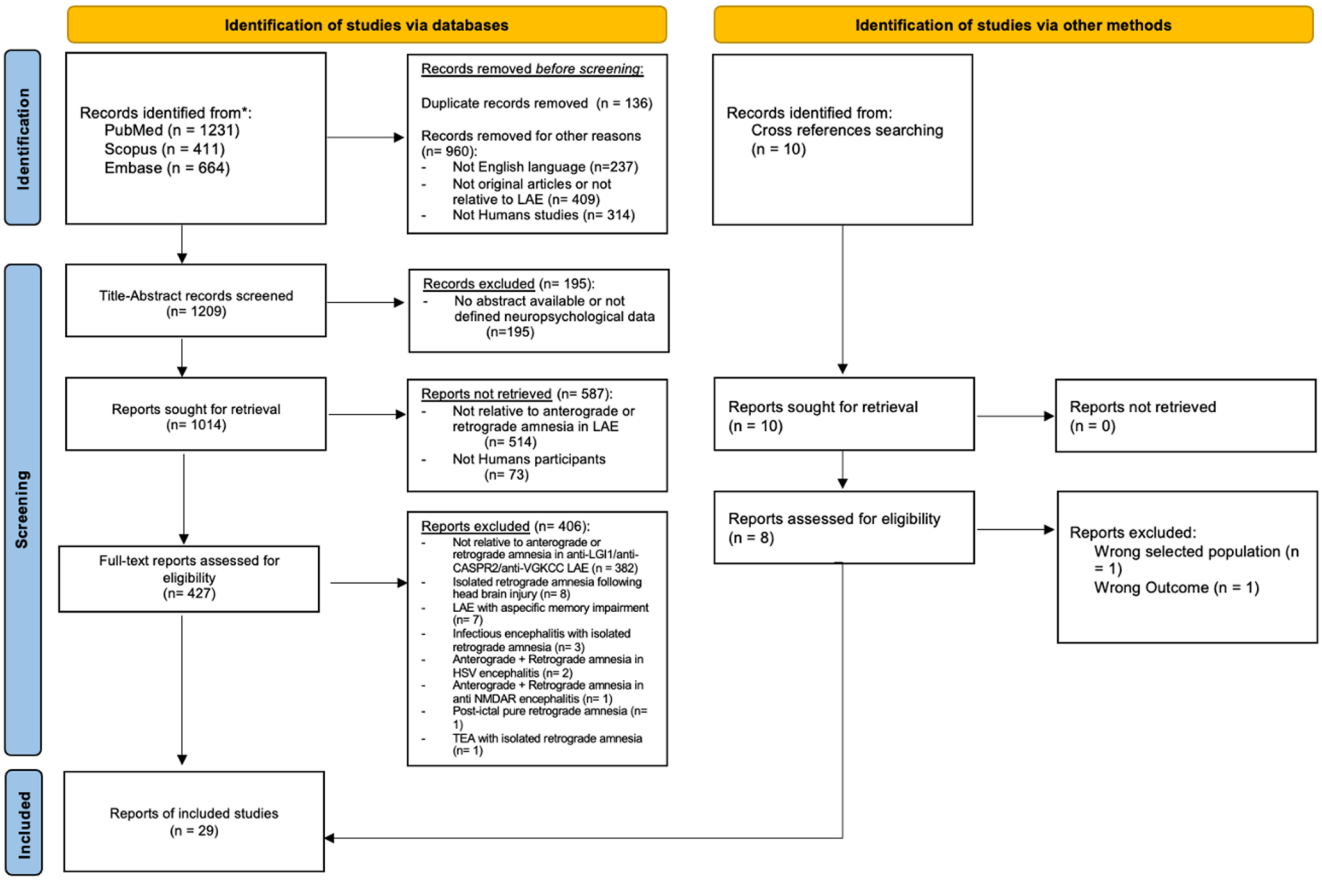

FIGURE 1 | Flowchart of the search process based on the PRISMA systematic review of the literature. LAE, limbic autoimmune encephalitis. * PubMed, Scopus, and Embase databases analyzed with and without MeSH terms in the search strings.

seizures, antiepileptic therapy with Levetiracetam was started with symptoms' resolution. After 4 months, the patient presented a cluster of generalized tonic–clonic seizures and was hospitalized for further investigation. Immediately after recovering from the seizures, he complained of almost complete loss of episodic autobiographical memory dating back roughly 12 months before, attributable to temporally graded retrograde amnesia. At the time of the hospitalization the patient was unable to recall any episode from that period, including major life events, such as his son's graduation. Notably, according to his wife, his behavior and memory during that 12-month-long period were completely unaffected. Brain MRI demonstrated bilateral FLAIR/T2 mild hyperintensity and thinning of the limbic structures (Figure 2) and EEG revealed only a slight asymmetry of the posterior background rhythm amplitude. Cerebrospinal fluid (CSF) analysis showed mild blood-CSF barrier (B-CSF-B) damage, pleocytosis (20 cells/mm^3, lymphomonocytoids), oligoclonal IgG bands (OCBs) that were identical in serum and CSF (mirror pattern), and negative PCRs for neurotropic viruses. Indirect immunofluorescence on transfected EU 90 cells ("Euroimmun") found high titer anti-CASPR2 antibodies in both CSF and serum (1:200, superficial neuronal antigens; 1:10 synaptic neuronal antigens) (Figure 2). Brain and total body FDG-PET scans showed no pathological findings. A full battery of neuropsychological testing including Mini Mental State Examination (MMSE), Trail Making Test (TMT), Symbol Digit Test (SDT), Buschke's Memory test, Clock drawing test, semantic and phonemic fluencies, executive functions, and tests for visuo-spatial functions were unremarkable. The Autobiographical Memory Interview (AMI; [20, 23]) confirmed the presence of retrograde amnesia. A final diagnosis of autoimmune CASPR2 encephalitis was made, and intravenous 6-methylprednisolone (1 g/day for 5 days) was given, followed by slow tapering over 3 months. At the 2-year follow-up, the patient remained stable and seizure-free, without any recovery of the amnesic gap. At this stage, the AMI interview scores pertaining to recent events were completely normalized.

3.2 | Case 2

In September 2009, a 52-year-old male presented weekly episodes of staring and unresponsiveness lasting a few seconds, followed by confusion, behavioral changes, and depersonalization while he was working in Venezuela. In addition, the patient complained of being unable to recall specific and even major life events of the recent and remote past. For example, he could not remember his wedding day or the birth of his children (occurred, respectively, 30 and 32 years before). Once he returned to Italy, he underwent a neurological evaluation and performed a brain MRI that showed slight hyperintensity of the mesial temporal lobes, at the thalamic-capsular level, and of the corona radiata (Figure 2). CSF analysis showed mild B-CSF-B damage, without pleocytosis, identical in serum and CSF OCBs (mirror pattern), and negative PCRs for neurotropic viruses. Tau protein was within normal levels. To rule out a paraneoplastic LAE, a total body FDG-PET and onconeural antibody testing

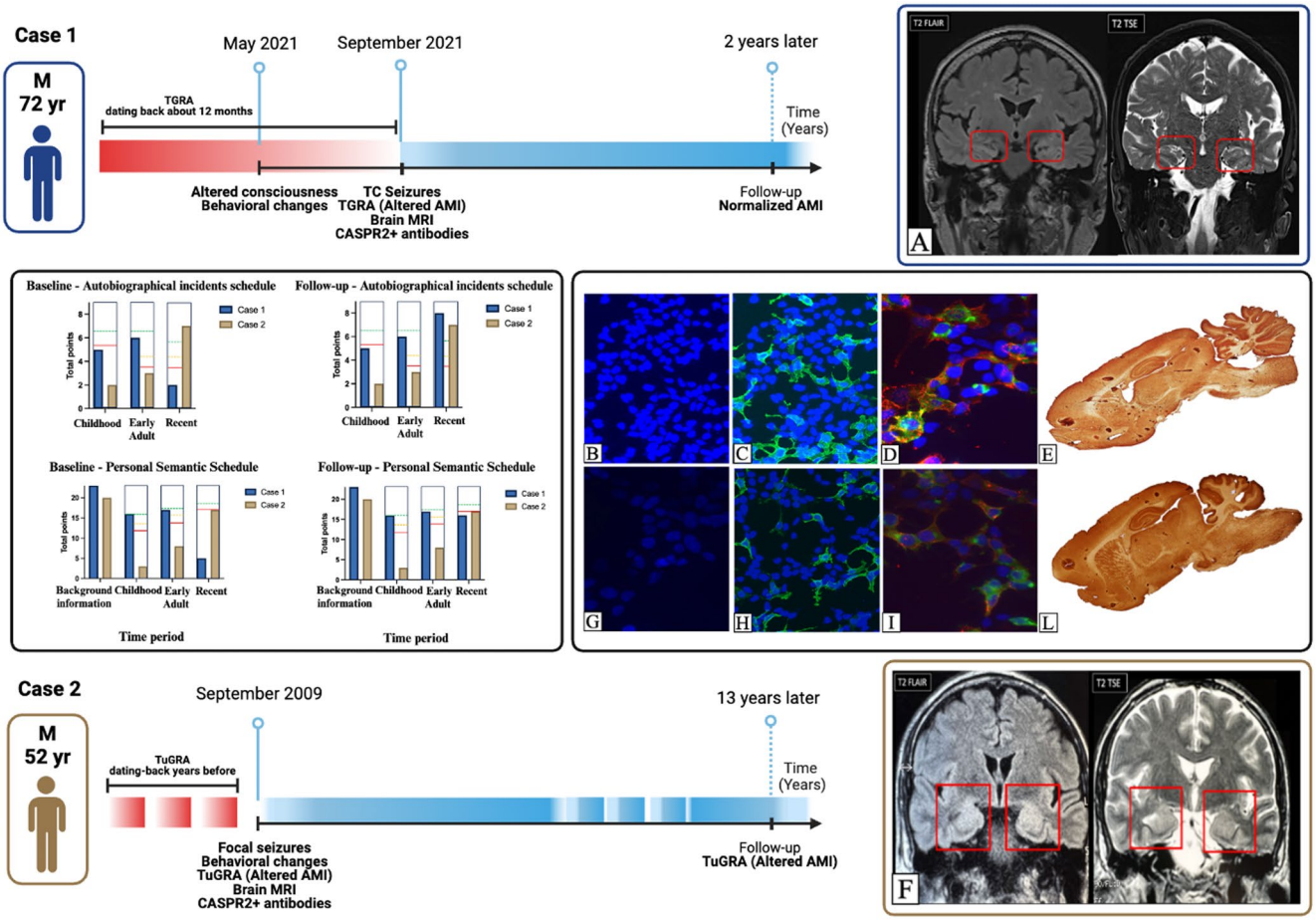

FIGURE 2 | Timeline of neurological symptoms of our two CASPR2 LAE patients. The results of AMI (autobiographical incidents and personal semantic schedules, at baseline and 2-year follow-up); AMI scores were defined as follows; "Acceptable": ±1 SD of the mean derived from literature data on healthy controls (dotted green line); "borderline": All the values falling between 1 SD and 2 SD below the mean; "probably abnormal": > 2 SD below the mean (dotted orange line; not always assessed); "definitely impaired": Scores at or below the lowest score among the healthy controls (red line) (Kopelman et al. 1989 [20]). Brain MRI, case 1 (A) and case 2 (F): coronal sections showing bilateral hippocampal hyperintensity (on the left) and swelling on Fluid-attenuated-inversion-recovery (FLAIR) and T2 sequences (on the right). CASPR2 antibody detection assays (case 1, B–E; case 2, G–L). Serum of patient 1 (B–E) and of patient 2 (F–L) did not bind to untrasfected HEK293 cells (B, G), but provided membrane surface staining on fixed cell-based assay (CBA, green, anti-human IgG), and on live CBA (D, I; red, anti-human IgG; green, EGFP tag) on CASPR2-transfected HEK293 cells. Blue: DAPI. The presence of CASPR2 antibodies was confirmed on IHC on lightly fixed rat brain slices showing neuropilar staining patterns compatible with CASPR2 antibody reactivity (E, case 1; L, case 2; brown: anti-human IgG). Staining intensity on both CBAs and IHC in case 1 was more intense than in case 2. AE, autoimmune encephalitis; AMI, autobiographical memory interview; IHC, immunohistochemistry; LAE, limbic AE; MRI, magnetic resonance imaging; NS, non-significant; TC, tonic-clonic; TGRA, temporally graded retrograde amnesia; TuGRA, temporally ungraded retrograde amnesia; yr, years.

were performed and resulted negative. Neuropsychological tests, including MMSE, TMT, SDT, Buschke's Memory test, Clock drawing test, semantic and phonemic fluencies, and tests for visuospatial functions, showed a normal profile except for a slight impairment in spatial organization and abstraction. The AMI test [20] revealed temporally ungraded retrograde amnesia (Figure 2). The patient started levetiracetam and add-on therapy with carbamazepine (400 mg bis in die), with complete resolution of the episodes. After 6 months, he performed a follow-up brain MRI, which confirmed the temporomesial alterations, with a slight increase in the left amygdala.

In 2022, 13 years after the first admission, the patient suffered from mild obsessive behavior, apathy, difficulty in managing emotions, and dysarthria, and was admitted to the neurology ward. Brain MRI showed resolution of the previous lesions, and FDG-PET, EEG, and neuropsychological tests were unremarkable. For the first time, neuronal antibody serostatus was assessed through indirect immunofluorescence on transfected EU 90 cells ("Euroimmun") finding a low titer of anti-CASPR2 antibodies (1:10) in serum (Figure 2), supporting the diagnosis of CASPR2 LAE. Unfortunately, the lumbar puncture was refused by the patient. The AMI was re-administered, confirming the same temporally ungraded retrograde amnesia detected at the previous test. In the presence of normal paraclinical studies and the stability of the clinical picture, the patient was not treated. The amnesic gap remains unchanged at the last follow-up after 13 years.

4 | Systematic Review Findings

The literature search in PubMed, Scopus, and Embase databases resulted in the identification of 2306 articles. After removing 136 duplicates and 960 records removed for other reasons (e.g., no full-text available, articles not written in the English language, review, opinion article, book chapters or articles not related to memory impairment and LAE), 1209 studies were selected for title-abstract screening. After this phase, 195 articles were excluded due to the absence of reported neuropsychological data or because no abstract was available. After a second phase of screening, 587 articles were eliminated because they did not address anterograde or retrograde amnesia in LAE patients or did not involve human participants. In this phase, case reports and case series were included in the assessment. A total of 427 out of 1014 studies were suitable for full-text assessment. After cross-reference checking, only 29 studies were finally included in this review.

4.1 | Patients With VGKC-Complex LAE and Memory Impairment

Among the 29 studies included, we found a total number of 467 patients with memory impairment and VGKC-complex antibodies which, together with our two patients, were included in the final analysis. Mean age was 57.5 years (range, 36.0–77.7). Three hundred and nineteen out of 469 patients (68.3%) were male, and mean follow-up was 18 months. Patients harbored LGI1 (346/469, 73.8%), CASPR2 (13/469, 2.8%), co-occurring LGI1 and CASPR2 (5/469, 1%; data not represented in the graphs), or VGKC antibodies (48/469, 10.2%; specific assays for LGI1/CASPR2 antibodies unavailable at the time of testing) (Table 1). All patients had a clinical syndrome classified as LAE.

Overall, 189 patients underwent extensive neuropsychological tests, while 146 were studied only using MOCA and/or MMSE tests. In 132 patients, no specific neuropsychological battery assessment was mentioned, but nonetheless, sufficient information was provided to classify the type of memory impairment. Only 58/469 patients (12.4%) underwent tests that actively investigate retrograde amnesia, such as AMI, Adult Memory and Information Processing Battery (AMIPB), or Doors and People test (D&P).

The most common cognitive alteration was isolated anterograde amnesia, found in 406/469 patients (86.6%). Retrograde amnesia was detected in only 14/469 patients (2.9%). Detailed information about these patients is reported in Table 2. Sixty-two/469 patients (13%) complained of attention deficits, and 94/469 (20%) presented executive function impairment, 38/469 (8%) with spatial disorientation, 59/469 (13%) with language impairment, and 17/469 (4%) with processing speed deficits. Overall, 68/469 (15%) showed other unspecified cognitive impairment (Table 1).

4.2 | Patients With LGI1/CASPR2 LAE and Retrograde Amnesia

Among the 14 patients with retrograde amnesia (described in 4 studies plus our case reports), the mean age was 61.5 (range 43–75 years old). Twelve of 14 patients (85.7%) were male, and the mean follow-up was 12 months. Autoantibody profiles included VGKC in 12 of 14 (85.7%) and CASPR2 in 2 of 14 (14.3%), and none with LGI1 (Figure 3, Table 2). However, seven cases with VGKC antibodies had a clinical phenotype highly suggestive of LGI1 LAE (Lad et al. 2019 [39]).

Three/14 (21.4%) showed temporally graded retrograde amnesia, while 5/14 (35.7%) temporally ungraded retrograde amnesia. In 9/14 cases (64.3%) amnesia was among the initial symptoms reported, while developing later over the disease course in the remaining cases. Notably, in all patients, except the two reported in this paper (2/469, 0.4%), retrograde amnesia occurred concomitantly with anterograde amnesia (12/469; 2.6%) (Figure 3).

Thirteen/14 (92.8%) had partial or poor cognitive improvement on follow-up (namely, selective memory deficits involving both the anterograde and retrograde memory) after the administration of various immunotherapies. Only one out of 14 patients (7.1%) showed total clinical/cognitive recovery after IVIg therapy (Table 2).

We then compared patients with retrograde amnesia with those with isolated anterograde amnesia and found no substantial differences in terms of clinical phenotype and disease course. Patients with mixed anterograde–retrograde amnesia showed unilateral or bilateral hippocampal atrophy more frequently (11/12; 91.6%) than those with isolated anterograde amnesia (78/107; 72.9%).

5 | Discussion

In this study, we highlight for the first time that isolated retrograde amnesia can be part of the spectrum of CASPR2 LAE. In addition, through a systematic literature review, we underline how retrograde amnesia, when in association with anterograde amnesia, occurs very rarely and in patients with VGKC-complex LAE.

Amnesia is a hallmark of LAE and inherently depends on the pathological involvement of the hippocampus in these disorders [39]. This brain region represents a key structure implicated in new memory formation, and whose damage is typically associated with episodic memory impairment [26]. Conversely, the role of the hippocampus in the storage and retrieval of remote memories, whose impairment is a core feature of retrograde amnesia, remains debated [12, 51, 52]. According to the Standard Consolidation Theory, hippocampal involvement in memory formation is necessary to create a coherent memory and to maintain it for a relatively short period, while consolidated memories are stored within the neocortex and can be accessed without hippocampal intervention [53, 54]. In contrast, both the multiple traces and the disconnection theories suggest that the hippocampus is actively involved in the recall of episodic memories regardless of their age [55, 56]. The latter theories would be more coherent with the observation derived from our cases and the results of the literature review, as LAE patients can show both long-term temporally graded and ungraded amnesia.

TABLE 1 | Characterization of patients with LAE and memory impairment.

Authors	Study ($n=29$; 467 of pts)	Mean age ± SD or range	Sex	Memory impair-ment	Antibody	Clinical phenotype ($n=459$/467 of pts)	EEG ($n=311$/467 of pts)	CSF and/or serum analysis (antibody testing, inflammatory abnormalities) ($n=56$/388 of pts)	Brain MRI, T0 ($n=462$/467 of pts)	Brain MRI, T1; 2–48 mts ($n=127$/467 of pts)	Clinical follow-up, mts	Therapy ($n=448$/467 of pts)
Thieben et al. (2004) [24]	Case series	61.6 ± 10.8	M ($n=5$) F ($n=2$)	AA	VGKC	• Simple motor + CPS • CPS + status epilepticus • GTC • Secondary GTC • Behavioral changes • HypoNa • Autonomic alterations	Slow activity Epileptiform activity	Serum ($n=7$) CSF ($n=3$) OCBs	• Bilateral MTL hyperintensity • Unilateral MTL hyperintensity	Mild MTA	24	1st line: Steroids
Vincent et al. (2004) [4]	Case series	62 ± 10.8	M ($n=9$) F ($n=1$)	AA ($n=9$) AA + RA ($n=1$)	VGKC	• GTC or CPS • Gait abnormalities • Hallucinations • Agitation and behavioral changes • Impaired verbal and visual memory • Global cognitive impairment at onset • Neuromyotonia • Autonomic alterations	Normal Slow activity Epileptiform activity	Serum ($n=10$) CSF ($n=5$) Pleocytosis OCBs	• Bilateral MTL hyperintensity • Unilateral MTL hyperintensity	Mild bilateral or unilateral MTA	6	1st line: Steroids, steroids + IVIg + PLEX, steroids + IVIg, steroids + PLEX, IVIg + PLEX 2nd line: AZA
Chan et al. (2007) [10]	Case series	51 ± 7	M ($n=3$)	AA + RA	VGKC	• GTC • Hallucinations • Behavioral changes • Psychiatric symptoms	NA	Serum ($n=3$)	• Hippocampi hyperintensity	Mild bilateral or unilateral MTA	6	1st line: Steroids + PLEX
Kartsounis et al. (2011) [25]	Case report	65	M	AA + RA	VGKC	NA	Normal	Serum ($n=1$)	• Hippocampi hyperintensity	Normal	36	1st line: Steroids + IVIg 2nd line: MMF

(Continues)

TABLE 1 | (Continued)

Authors	Study ($n=29$; 467 of pts)	Mean age ± SD or range	Sex	Memory impairment	Antibody	Clinical phenotype ($n=459/467$ of pts)	EEG ($n=311/467$ of pts)	CSF and/or serum analysis (antibody testing, inflammatory abnormalities) ($n=56/388$ of pts)	Brain MRI, T0 ($n=462/467$ of pts)	Brain MRI, T1; 2–48 mts ($n=127/467$ of pts)	Clinical follow-up, mts	Therapy ($n=448/467$ of pts)
Butler et al. (2014) [26]	Case series	59.5 ± 14.8	M ($n=12$) F ($n=6$)	AA	LGI1 ($n=9$) CASPR2 ($n=1$) VGKC ($n=8$)	• Seizures • Delusions • Neuromyotonia • Hallucinations • Executive functions abnormalities • Autonomic alterations	NA	Serum ($n=18$)	• Hippocampi hyperintensity • MTL hyperintensity	NA	21	1st line: Steroids, steroids + IVIg, steroids + PLEX, PLEX, steroids + IVIg + PLEX
Malter et al. (2014) [27]	Case series	54 ± 28.3	M ($n=11$) F ($n=5$)	AA	LGI1 ($n=9$) CASPR2 ($n=2$) VGKC ($n=5$)	• FBDS • Seizures	NA	Serum ($n=16$) Pleocytosis	• Hippocampi hyperintensity ($n=12$)	Mild bilateral or unilateral hippocampal atrophy	26	1st line: Steroids 2nd line: MMF
Szots et al. (2014) [28]	Case series	49 ± 1.4	M ($n=2$)	AA	LGI1	• FBDS • GTC • Cognitive impairment • Psychiatric symptoms • SIADH	Epileptiform activity	Serum ($n=2$)	• Hippocampi hyperintensity	Bilateral hippocampal atrophy	44,5	NA
Dodich et al. (2016) [29]	Case series	66 ± 12.7	M ($n=2$) F ($n=1$)	AA	LGI1 ($n=2$) CASPR2 ($n=1$)	• FBDS • GTC • Partial seizure • Behavioral changes	NA	Serum ($n=3$)	• Hippocampi hyperintensity	NA	NA	NA
Yu et al. (2016) [30]	Case series	54 ± 13	M ($n=2$) F ($n=2$)	AA	LGI1	• FBDS • Seizures • Behavioral changes	Normal	Serum ($n=4$) CSF ($n=4$) Pleocytosis	• Bilateral MTA • Hippocampi hyperintensity • Thalamus hyperintensity	Reduced hyperintensity in bilateral MTL	12 (improvement, hypomnesia persisted)	1st line: Steroids + IVIg

(Continues)

TABLE 1 | (Continued)

Authors	Study ($n=29$; 467 of pts)	Mean age ± SD or range	Sex	Memory impairment	Antibody	Clinical phenotype ($n=459$/467 of pts)	EEG ($n=311$/467 of pts)	CSF and/or serum analysis (antibody testing, inflammatory abnormalities) ($n=56$/388 of pts)	Brain MRI, T0 ($n=462$/467 of pts)	Brain MRI, T1; 2–48 mts ($n=127$/467 of pts)	Clinical follow-up, mts	Therapy ($n=448$/467 of pts)
Zhao et al. (2016) [31]	Case series	54 ± 18	M ($n=1$) F ($n=2$)	AA	LGI1	• Myoclonus • Seizures	Slow activity	Serum ($n=3$) CSF ($n=2$) Pleocytosis	• Bilateral MTL hyperintensity • Periventricular regions, putamen and corpus caudate nuclei hyperintensity	NA	14	1st line: Steroids + IVIg
Ariño et al. (2016) [32]	Retrospective	60 Range: 32–80	M ($n=42$) F ($n=21$)	AA	LGI1	• Seizures • Behavioral changes • Gait abnormalities • Psychiatric symptoms • Sleep disturbances • HypoNa	NA	Serum ($n=47$) CSF ($n=51$) Pleocytosis	• Bilateral MTL hyperintensity • Unilateral MTL hyperintensity	NA	~18	1st line: Steroids, steroids + IVIg, IVIg 2nd line: RTX, RTX + CTX, AZA, CTX, MMF
Miller et al. (2017) [33]	Case–control	64 ± 2.6	M ($n=15$) F ($n=3$)	AA	LGI1 ($n=17$)	• Cognitive dysfunctions (attention and executive domains)	NA	NA	• MTL hyperintensity	Unilateral hippocampal atrophy	12	NA
Finke et al. (2017) [34]	Case–control	65.7 ± 12	M ($n=11$) F ($n=19$)	AA ($n=29$)	LGI1	• FBDS • Behavioral changes • CPS or GTC • Seizures • Psychiatric symptoms • Sleep disturbances	Epileptiform activity Slow activity	Serum ($n=30$) CSF ($n=30$)	• MTL hyperintensity	Unilateral hippocampal: atrophy/ sclerosis	~18	1st line: Steroids, PLEX, IVIg 2nd line: AZA, RTX, MTX, CTX
Bing-Lei et al. (2019) [35]	Case series	53 ± 9.8	M ($n=1$) F ($n=2$)	AA	LGI1	• FBDS • GTC	Abnormalities	Serum ($n=3$) CSF ($n=1$)	• Bilateral MTL hyperintensity • Unilateral MTL hyperintensity	NA	3	1st line: Steroids, steroids + IVIg

(Continues)

TABLE 1 | (Continued)

Authors	Study ($n=29$; 467 of pts)	Mean age ± SD or range	Sex	Memory impairment	Antibody	Clinical phenotype ($n=459/467$ of pts)	EEG ($n=311/467$ of pts)	CSF and/or serum analysis (antibody testing, inflammatory abnormalities) ($n=56/388$ of pts)	Brain MRI, T0 ($n=462/467$ of pts)	Brain MRI, T1; 2–48 mts ($n=127/467$ of pts)	Clinical follow-up, mts	Therapy ($n=448/467$ of pts)
Kim et al. (2018) [36]	Case report	37	M ($n=1$)	AA	LGI1	• Behavioral changes • GTC • SIADH	Epileptiform activity	Serum ($n=1$) CSF ($n=1$)	• Bilateral MTL hyperintensity	Bilateral MTAl	7.5	NA
Heine et al. (2018) [37]	Case–control	NA	NA	AA	LGI1	• Seizures	Abnormalities	NA	• Hippocampi hyperintensity	Unilateral/ bilateral hippocampal atrophy	26	NA
Li et al. (2018) [38]	Retrospective	63.4 ± 10	M ($n=5$) F ($n=3$)	AA	LGI1	• FBDS • GTC • CPS • Hallucinations • Seizures • Sleep disturbances • Psychiatric symptoms • Autonomic alterations	Normal Slow activity Epileptiform activity	Serum ($n=8$) CSF ($n=4$)	• Hippocampi hyperintensity • Unilateral hippocampus hyperintensity—Bilateral or unilateral Insula, caudate nucleus hyperintensity	NA	6	1st line: Steroids, steroids + IVIg
Lad et al. (2019) [39]	Case series	66 Range: 51–70	M ($n=5$) F ($n=2$)	AA + RA	VGKC[a]	NA	NA	Serum ($n=7$)	• Hippocampi hyperintensity • Unilateral hippocampus hyperintensity	Unilateral/ bilateral hippocampal atrophy	48	NA
Loane et al. (2019) [40]	Case–control	63.9 ± 11.3	M ($n=20$) F ($n=4$)	AA	LGI1 ($n=14$) VGKC ($n=6$) LGI1 + CASPR2 ($n=4$)	• FBDS • CPS • GTC—Myoclonic seizures	NA	Serum ($n=6$)	• Hippocampi hyperintensity • Unilateral hippocampus hyperintensity • Amigdala hyperintensity	-Bilateral hippocampal atrophy -Thalamus atrophy	NA	1st line: Steroids, steroids +IVIg, steroids + IVIg + PLEX, steroids + PLEX, IVIg, IVIg +PLEX
Yang et al. (2019) [41]	Case series	56.9 ± 10.9	M ($n=15$) F ($n=3$)	AA	LGI1	• FBDS • Seizures	Abnormalities paroxysmal sharp/spike waves	Serum ($n=18$) CSF ($n=13$) Pleocytosis	• Bilateral MTL hyperintensity	NA	NA	1st line: Steroids + IVIg

(Continues)

TABLE 1 | (Continued)

Authors	Study ($n=29$; 467 of pts)	Mean age ± SD or range	Sex	Memory impairment	Antibody	Clinical phenotype ($n=459$/467 of pts)	EEG ($n=311$/467 of pts)	CSF and/or serum analysis (antibody testing, inflammatory abnormalities) ($n=56$/388 of pts)	Brain MRI, T0 ($n=462$/467 of pts)	Brain MRI, T1; 2–48 mts ($n=127$/467 of pts)	Clinical follow-up, mts	Therapy ($n=448$/467 of pts)
Iorio et al. (2020) [42]	Retrospective	Range: 62–65.5	M ($n=21$) F ($n=22$)	AA	LGI1 ($n=5$) CASPR2 ($n=2$) LGI1 + CASPR2 ($n=1$)	• Behavioral changes • Seizures	Normal Slow activity Epileptiform activity	Serum ($n=6$) CSF ($n=1$) Pleocytosis OCBs	• Bilateral MTL hyperintensity • Unilateral MTL hyperintensity	NA	12	1st line: Steroids, IVIg, steroids + IVIg 2nd line: AZA, CYC
Uribe-San-Martín et al. (2020) [43]	Case series	55.8 ± 10.9	M ($n=2$) F ($n=4$)	AA ($n=1$)	LGI1 ($n=1$)	• Sensitive abnormalities—Piloerection • Seizures • FBDS • Sleep disturbances • Psychiatric symptoms	Normal Slow activity	Serum ($n=6$)	• Unilateral MTL hyperintensity	NA	15	1st line: Steroids
Hang et al. (2020) [44]	Observational	51 ± 14.7	M ($n=13$) F ($n=8$)	AA ($n=19$)	LGI1 ($n=19$)	• FBDS • Seizures • Psychiatric symptoms • HypoNa	Normal Abnormalities	Serum ($n=20$) CSF ($n=18$)	• Bilateral MTL hyperintensity • Unilateral MTL hyperintensity	NA	12	1st line: Steroids, steroids + IVIg 2nd line: MMF
Ma et al. (2020) [45]	Retrospective	54.3 ± 12.3	M ($n=9$) F ($n=6$)	AA	LGI1	• FBDS • Behavioral changes • Spatial disorientation	Normal Abnormalities	Serum ($n=15$) CSF ($n=8$)	• Bilateral MTL hyperintensity • Unilateral MTL hyperintensity	NA	NA	NA
Qiao et al. (2021) [46]	Restrospective	57 Range: 52–67	M ($n=46$) F ($n=20$)	AA ($n=51$)	LGI1 ($n=51$)	• Behavioral changes • FBDS • Focal seizure • GTC • Cognitive impairment • Sleep disturbances • Autonomic abnormalities • HypoNa	Normal Abnormalities	Serum ($n=66$) CSF ($n=66$)	• Hippocampi hyperintensity • Unilateral hippocampus hyperintensity • Basal ganglia, occipital lobe and corpus callosum hyperintensity	NA	33	1st line: Steroids, steroids + IVIg, IVIg 2nd line: MMF, AZA, CTX

(Continues)

TABLE 1 | (Continued)

Authors	Study ($n=29$; 467 of pts)	Mean age ± SD or range	Sex	Memory impairment	Antibody	Clinical phenotype ($n=459$/467 of pts)	EEG ($n=311$/467 of pts)	CSF and/or serum analysis (antibody testing, inflammatory abnormalities) ($n=56$/388 of pts)	Brain MRI, T0 ($n=462$/467 of pts)	Brain MRI, T1; 2–48 mts ($n=127$/467 of pts)	Clinical follow-up, mts	Therapy ($n=448$/467 of pts)
Karvigh et al. (2022) [47]	Case series	21 ± 4.2	F ($n=2$)	AA ($n=2$)	LGI1	• FBDS • GTC • Hallucinations • Behavioral changes	Abnormalities	Serum ($n=2$) CSF ($n=2$) OCBs	• Unilateral MTL hyperintensity • Bilateral basal ganglia hiperintensity	Bilateral hippocampal sclerosis	6–24	1st line: Steroids, IVIg 2nd line: RTX
Li et al. (2022) [48]	Retrospective	54.6 Range: 14–65	M ($n=52$) F ($n=10$)	AA ($n=62$)	LGI1 ($n=57$) CASPR2 ($n=5$)	• Morvan syndrome • Seizures • Behavioral changes • Hallucinations • Autonomic abnormalities • Movement disorders • HypoNa	Slow activity Epileptiform activity	Serum ($n=62$) CSF ($n=55$)	• Unilateral MTL hyperintensity • Occipital lobe hyperintensity	NA	25	1st line: Steroids, steroids + IVIg, IVIg 2nd line: AZA, MMF
Chen et al. (2023) [49]	Retrospective	10 ± 4.1	M ($n=2$) F ($n=2$)	AA ($n=4$)	LGI1	• FBDS • Behavioral changes • Seizure • Ataxia	Normal Epileptiform activity	Serum ($n=3$) CSF ($n=1$) Pleocytosis	• Unilateral MTL hyperintensity • Unilateral putamen and caudate hyperintensity	NA	NA	1st line: Steroids, PLEX, IVIg 2nd line: MMF, RTX, TCZ
Huang et al. (2023) [50]	Retrospective ($n=8$)	64 ± 11	M ($n=3$) F ($n=5$)	AA	LGI1 ($n=5$)	• FBDS • Focal seizures • Hallucinations • Behavioral changes • Cognitive dysfunctions (attention, executive and language domains)	Slow activity Epileptiform activity	Serum ($n=3$) CSF ($n=5$) Pleocytosis	• Bilateral MTL hyperintensity • Unremarkable	Bilateral MTA	60	1st line: Steroids, steroids + IVIg, IVIg 2nd line: RTX, CYC

Abbreviations: AA, Anterograde amnesia; AZA, Azathioprine; CPS, complex partial seizures; CSF, cerebrospinal fluid; CTX, Cyclophosphamide; EEG, Electroencephalography; F, female; FBDS, facio-brachial dystonic seizures; GTC, Generalized Tonic–clonic seizure; HypoNa, hyponatremia; IVIg, intravenous immunoglobulins; M, male; MMF, Mycophenolate; MTA, medial temporal atrophy; MTL, mesial temporal lobe; mts, months; NA, not available/not defined/not performed; OCBs, oligoclonal bands; PLEX, plasma exchange; pts., patients; RA, Retrograde amnesia; RTX, Rituximab; SIADH, Syndrome of inappropriate antidiuretic hormone secretion.
[a]LGI1 clinical phenotype defined. VGKC seropositive.

TABLE 2 | Characterization of patients with retrograde amnesia at onset and during disease progression.

Study	Sex, age	Amnesia	Additional clinical features	MRI findings (acute phase; T2 or FLAIR)	MRI atrophy	Antibody (CSF and/or serum)	CSF findings	NPS tests	Treatment	Cognitive outcome/ recovery
Lad et al. (2019) [39]	M 70 years	AA + RA	GTC	Normal	Bilateral hippocampal	VGKC (serum)	NA	AMI, D&P	Steroids + PLEX	Selective memory residual deficit
Lad et al. (2019) [39]	M 51 years	AA + RA	GTC	Left hippocampal enhancement	Left hippocampal	VGKC (serum)	NA	AMI, D&P	Steroids + PLEX	Selective memory residual deficit
Lad et al. (2019) [39]	F 73 years	AA + RA	FBDS	Left hippocampal enhancement	Bilateral hippocampal	VGKC (serum)	NA	AMI, D&P	Steroids + PLEX	Selective memory residual deficit
Lad et al. (2019) [39]	F 75 years	AA + RA (TG)	FBDS, behavioral changes	Left hippocampal enhancement	Bilateral hippocampal	VGKC (serum)	NA	AMI, D&P	Steroids + IVIg + MTX	Selective memory residual deficit
Lad et al. (2019) [39]	M 63 years	AA + RA	GTC	Normal	Bilateral hippocampal	VGKC (serum)	NA	AMI, D&P	Steroids + IVIg	Selective memory residual deficit
Lad et al. (2019) [39]	M 62 years	AA + RA	Focal seizure	Bilateral T2 hyperintensity in hippocampus (> left)	Bilateral hippocampal	VGKC (serum)	NA	AMI, D&P	Steroids	Selective memory residual deficit
Lad et al. (2019) [39]	M 69 years	AA + RA (TG)	Focal seizures	Bilateral T2 hyperintensity in hippocampus (> right)	Bilateral hippocampal	VGKC (serum)	NA	AMI, D&P	Steroids	Selective memory residual deficit
Kartsounis et al. (2011) [25]	M 65 years	AA + RA	Anxiety and behavioral changes	Bilateral T2 hyperintensity in hippocampus	None	VGKC (serum)	NA	AMI	Steroids, IVIg and MMF	Partial improvement
Chan et al. (2007) [10]	M 52 years	AA + RA (TU)	GTC, hallucinations, disorientation	Bilateral T2 hyperintensity in hippocampus	Bilateral hippocampal	VGKC (serum)	NA	AMIPB	Steroids and PLEX	Partial recovery of RA
Chan et al. (2007) [10]	M 43 years	AA + RA (TU)	Behavioral changes	Bilateral T2 hyperintensity in hippocampus	Mild bilateral hippocampal	VGKC (serum)	NA	AMIPB	Steroids and PLEX	Partial recovery of RA

(Continues)

TABLE 2 | (Continued)

Study	Sex, age	Amnesia	Additional clinical features	MRI findings (acute phase; T2 or FLAIR)	MRI atrophy	Antibody (CSF and/or serum)	CSF findings	NPS tests	Treatment	Cognitive outcome/ recovery
Chan et al. (2007) [10]	M 57 years	AA + RA (TU)	Behavioral changes, focal seizures	Bilateral T2 hyperintensity in hippocampus	Mild right hippocampal	VGKC (serum)	NA	AMIPB	Steroids and PLEX	Partial recovery of RA
Vincent et al. (2004) [4]	M 57 years	AA + RA (TU)	Hallucinations, neuromyotonia, GTC	Bilateral T2 hyperintensity in hippocampus	Bilateral hippocampal	VGKC (CSF and serum)	Pleocytosis	AMIPB	Steroids + PLEX, IVIg	Improvement after IVIg
Malvaso et al. (2024)	M 72 years	RA (TG)	GTC, behavioral changes	Bilateral T2 hyperintensity in hippocampus	None	CASPR2 (CSF and serum)	B-CSF-B damage, pleocytosis (20 cells/ mm3), IEF mirror pattern	AMI	Steroids	Improvement with persisting RA
Malvaso et al. (2024)	M 52 years	RA (TU)	Confusion, behavioral changes, speech impairment	Bilateral T2 hyperintensity in hippocampus and thalamic-capsular region	None	CASPR2 (serum)	B-CSF-B damage, IEF mirror pattern	AMI	Antiepileptic drugs	Improvement with persisting RA

Abbreviations: AA, anterograde amnesia; AMI, Autobiographical Memory Interview; AMIPB, Adult Memory and Information Processing Battery; D&P, verbal and visual recall and recognition (Baddeley & Nimmo-Smith, 1994); F, female; FBDS, facio-brachial dystonic seizures; GTC, generalized tonic–clonic seizures; IVIg, intravenous immunoglobulins; M, male; MMF, mycophenolate; MTX, methotrexate; NA, not available/not defined/not performed; PLEX, plasma exchange; RA, retrograde amnesia; TG, temporally graded; TU, temporally ungraded.

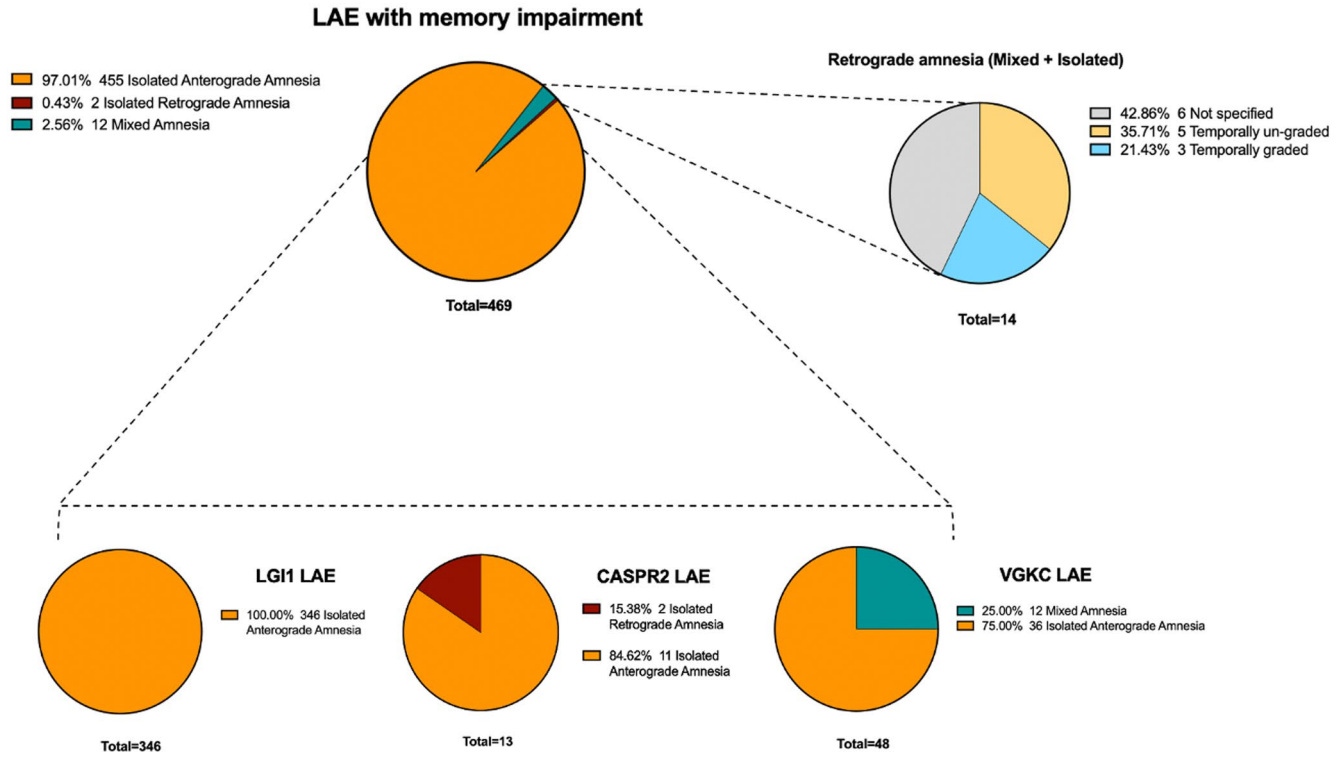

FIGURE 3 | Results of the systematic review: VGKC, LGI1 and CASPR2 Limbic Autoimmune Encephalitis with memory impairment.

As a novelty, in our two cases, retrograde amnesia occurred in the absence of anterograde amnesia. Overall, retrograde amnesia occurring concomitantly with anterograde amnesia in only 0.4% of LAE patients with VGKC-complex antibodies, and 11% of those with CASPR2 LAE, and was not associated with other forms of AE. However, since retrograde amnesia is rarely tested in routine clinical practice, and the currently available tests have inherent limited sensitivity [20], it is possible that this phenomenon may be underestimated (only 12.4% of the patients in our systematic review performed specific tests for retrograde amnesia). Notably, a recent study reported retrograde amnesia, labeled as "lacunar autobiographical amnesia" in 21% of patients with CASPR2 LAE [57]. Even though this study could not be included in the systematic review due to insufficient information regarding the neuropsychological tests used to assess the memory impairment, it shows how retrograde amnesia might represent a frequent feature in CASPR2 LAE patients. The variable neuropsychological testing in the literature is a limitation to the results of our review, and future case series will have to investigate, and report retrograde amnesia systematically.

Isolated retrograde amnesia has been associated with heterogeneous etiologies including multifocal brain damage due to traumatic brain injury [58], herpes simplex encephalitis, and hypoxia [59]. It has also been reported after electroshock treatment [60], alcohol consumption, and following a minor physical injury, often associated with psychogenic factors [61]. The underlying mechanisms remain currently unknown [12]. At the cellular level, it has been suggested that this amnesia might be related to altered intracellular calcium homeostasis, possibly linked with neuronal loss [51]. At present, the mechanisms through which CASPR2 antibodies could cause isolated retrograde amnesia are a matter of speculation. Indeed, the symptom does not invariably occur in all the affected patients, and we found no clinical and paraclinical differences between our two patients with the isolated symptom and the 12 cases from the literature with mixed anterograde–retrograde amnesia. In CASPR2 LAE, memory impairment has been associated with hippocampal neuronal damage at the CA3 level, which corresponds to the area with more severe atrophy [34]. CASPR2 antibodies are pathogenic by reducing density of CASPR2 at the neuronal surface, impairing its interaction with TAG1 [52], and concomitantly reducing the surface levels of the potassium channel Kv1.1 and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR; [62, 63]). In animal models, the infusion of CASPR2 antibodies induces both short-and long-term memory loss in a reversible fashion [52, 64]. These antibodies can therefore alter the synaptic transmission mediated by AMPAR, which are crucially involved in long-term potentiation and long-term depression, the major synaptic substrates of learning and memory [65–67]. However, whether these mechanisms are involved in the development of retrograde amnesia is still uncertain and should be investigated.

Our two patients showed persistent hippocampal involvement at brain MRI, and retrograde amnesia recovery was poor. This suggests that retrograde amnesia could be likely due to irreversible damage, rather than to the transient functional impairment, as shown in an experimental model [52].

6 | Conclusions and Future Directions

Retrograde amnesia is rare but likely under-recognized in LAE with VGKC-complex antibodies and associates with poor recovery. Our findings suggest that isolated retrograde amnesia is part

of the spectrum of CASPR2 LAE. Future studies should assess the frequency of retrograde amnesia in the whole AE spectrum and possibly explore its pathophysiology.

Author Contributions

Antonio Malvaso: conceptualization, writing – original draft, writing – review and editing, visualization, validation, software, methodology, investigation, formal analysis, data curation. **Denise Cerne:** writing – original draft, writing – review and editing, investigation, formal analysis, data curation. **Sara Bernini:** methodology, formal analysis, data curation. **Sara Bottiroli:** data curation, methodology, formal analysis. **Enrico Marchioni:** writing – review and editing. **Pietro Businaro:** methodology. **Stefano Masciocchi:** methodology. **Chiara Morandi:** methodology. **Silvia Scaranzin:** methodology. **Emanuela Maria Mobilia:** methodology. **Stefano F. Cappa:** writing – review and editing, supervision, data curation. **Luana Benedetti:** project administration, writing – review and editing, supervision, data curation. **Diego Franciotta:** writing – review and editing, data curation, supervision. **Matteo Gastaldi:** conceptualization, project administration, writing – review and editing, supervision, data curation, funding acquisition.

Consent

All patients included in the study provided their informed consent under the project code 0020308/23 (nstitutional Review Board of the IRCCS Policlinico San Matteo, Pavia, approved on 14/4/23).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data are available for consultation in the Zenodo repository at the following link: https://doi.org/10.5281/zenodo.13380271.

References

1. F. Graus, M. J. Titulaer, R. Balu, et al., "A Clinical Approach to Diagnosis of Autoimmune Encephalitis," *Lancet Neurology* 15, no. 4 (2016): 391–404, https://doi.org/10.1016/S1474-4422(15)00401-9.

2. A. Chatzikonstantinou, K. Szabo, C. Ottomeyer, R. Kern, and M. G. Hennerici, "Successive Affection of Bilateral Temporomesial Structures in a Case of Non-Paraneoplastic Limbic Encephalitis Demonstrated by Serial MRI and FDG-PET," *Journal of Neurology* 256, no. 10 (2009): 1753–1755, https://doi.org/10.1007/s00415-009-5165-8.

3. E. Lancaster, E. Martinez-Hernandez, and J. Dalmau, "Encephalitis and Antibodies to Synaptic and Neuronal Cell Surface Proteins," *Neurology* 77, no. 2 (2011): 179–189, https://doi.org/10.1212/WNL.0b013e318224afde.

4. A. Vincent, C. Buckley, J. M. Schott, et al., "Potassium Channel Antibody-Associated Encephalopathy: A Potentially Immunotherapy-Responsive Form of Limbic Encephalitis," *Brain* 127, no. Pt 3 (2004): 701–712, https://doi.org/10.1093/brain/awh077.

5. S. R. Irani, S. Alexander, P. Waters, et al., "Antibodies to Kv1 Potassium Channel-Complex Proteins Leucine-Rich, Glioma Inactivated 1 Protein and Contactin-Associated Protein-2 in Limbic Encephalitis, Morvan's Syndrome and Acquired Neuromyotonia," *Brain* 133, no. 9 (2010): 2734–2748, https://doi.org/10.1093/brain/awq213.

6. M. Lai, M. G. Huijbers, E. Lancaster, et al., "Investigation of LGI1 as the Antigen in Limbic Encephalitis Previously Attributed to Potassium Channels: A Case Series," *Lancet Neurology* 9, no. 8 (2010): 776–785, https://doi.org/10.1016/S1474-4422(10)70137-X.

7. B. Lang, M. Makuch, T. Moloney, et al., "Intracellular and Non-Neuronal Targets of Voltage-Gated Potassium Channel Complex Antibodies," *Journal of Neurology, Neurosurgery, and Psychiatry* 88, no. 4 (2017): 353–361, https://doi.org/10.1136/jnnp-2016-314758.

8. J. A. Witt and C. Helmstaedter, "Neuropsychological Evaluations in Limbic Encephalitis," *Brain Sciences* 11, no. 5 (2021): 576, https://doi.org/10.3390/brainsci11050576.

9. T. Ribot, *Diseases of the Memory: An Essay in the Positive Psychology* (Kegan Paul, Trench & Co, 1882), https://doi.org/10.1037/12818-000.

10. D. Chan, S. M. Henley, M. N. Rossor, and E. K. Warrington, "Extensive and Temporally Ungraded Retrograde Amnesia in Encephalitis Associated With Antibodies to Voltage-Gated Potassium Channels," *Archives of Neurology* 64, no. 3 (2007): 404–410, https://doi.org/10.1001/archneur.64.3.404.

11. A. Staniloiu and H. J. Markowitsch, "Dissociative Amnesia," *Lancet Psychiatry* 1, no. 3 (2014): 226–241, https://doi.org/10.1016/S2215-0366(14)70279-2.

12. J. Q. Lee, R. J. McDonald, and R. J. Sutherland, "Hippocampal Damage Causes Retrograde Amnesia and Slower Acquisition of a Cue-Place Discrimination in a Concurrent Cue-Place Water Task in Rats," *Neuroscience* 412 (2019): 131–143, https://doi.org/10.1016/j.neuroscience.2019.05.061.

13. A. R. Damasio, N. R. Graff-Radford, P. J. Eslinger, H. Damasio, and N. Kassell, "Amnesia Following Basal Forebrain Lesions," *Archives of Neurology* 42, no. 3 (1985): 263–271, https://doi.org/10.1001/archneur.1985.04060030081013.

14. N. R. Graff-Radford, D. Tranel, G. W. Van Hoesen, and J. P. Brandt, "Diencephalic Amnesia," *Brain* 113, no. Pt 1 (1990): 1–25, https://doi.org/10.1093/brain/113.1.1.

15. W. B. Barr, E. Goldberg, J. Wasserstein, and R. A. Novelly, "Retrograde Amnesia Following Unilateral Temporal Lobectomy," *Neuropsychologia* 28, no. 3 (1990): 243–255, https://doi.org/10.1016/0028-3932(90)90018-j.

16. N. Kapur, D. Ellison, M. P. Smith, D. L. McLellan, and E. H. Burrows, "Focal Retrograde Amnesia Following Bilateral Temporal Lobe Pathology. A Neuropsychological and Magnetic Resonance Study," *Brain* 115 (1992): 73–85, https://doi.org/10.1093/brain/115.1.73.

17. N. Kapur, "Focal Retrograde Amnesia in Neurological Disease: A Critical Review," *Cortex* 29, no. 2 (1993): 217–234, https://doi.org/10.1016/s0010-9452(13)80177-3.

18. R. J. Sutherland, M. P. Weisend, D. Mumby, et al., "Retrograde Amnesia After Hippocampal Damage: Recent vs. Remote Memories in Two Tasks," *Hippocampus* 11, no. 1 (2001): 27–42, https://doi.org/10.1002/1098-1063(2001)11:1<27::AID-HIPO1017>3.0.CO;2-4.

19. G. C. McKay and M. D. Kopelman, "Psychogenic Amnesia: When Memory Complaints Are Medically Unexplained," *Advances in Psychiatric Treatment* 15, no. 2 (2009): 152–158, https://doi.org/10.1192/apt.bp.105.001586.

20. M. D. Kopelman, B. A. Wilson, and A. D. Baddeley, "The Autobiographical Memory Interview: A New Assessment of Autobiographical and Personal Semantic Memory in Amnesic Patients," *Journal of Clinical and Experimental Neuropsychology* 11, no. 5 (1989): 724–744, https://doi.org/10.1080/01688638908400928.

21. M. Gastaldi, S. Mariotto, M. P. Giannoccaro, et al., "Subgroup Comparison According to Clinical Phenotype and Serostatus in Autoimmune Encephalitis: A Multicenter Retrospective Study," *European Journal of Neurology* 27, no. 4 (2020): 633–643, https://doi.org/10.1111/ene.14139.

22. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *BMJ* 372 (2020): n71, https://doi.org/10.1136/bmj.n71.

23. M. D. Kopelman, "The Autobiographical Memory Interview (AMI) in Organic and Psychogenic Amnesia," *Memory* 2, no. 2 (1994): 211–235, https://doi.org/10.1080/09658219408258945.

24. M. J. Thieben, V. A. Lennon, B. F. Boeve, A. J. Aksamit, M. Keegan, and S. Vernino, "Potentially Reversible Autoimmune Limbic Encephalitis With Neuronal Potassium Channel Antibody," *Neurology* 62, no. 7 (2004): 1177–1182, https://doi.org/10.1212/01.wnl.0000122648.19196.02.

25. L. D. Kartsounis and R. de Silva, "Unusual Amnesia in a Patient With VGKC-Ab Limbic Encephalitis: A Case Study," *Cortex* 47, no. 4 (2011): 451–459, https://doi.org/10.1016/j.cortex.2010.01.009.

26. C. R. Butler, T. D. Miller, M. S. Kaur, et al., "Persistent Anterograde Amnesia Following Limbic Encephalitis Associated With Antibodies to the Voltage-Gated Potassium Channel Complex," *Journal of Neurology, Neurosurgery, and Psychiatry* 85, no. 4 (2014): 387–391, https://doi.org/10.1136/jnnp-2013-306724.

27. M. P. Malter, C. Frisch, J. C. Schoene-Bake, et al., "Outcome of Limbic Encephalitis With VGKC-Complex Antibodies: Relation to Antigenic Specificity," *Journal of Neurology* 261, no. 9 (2014): 1695–1705, https://doi.org/10.1007/s00415-014-7408-6.

28. M. Szots, A. Marton, F. Kover, et al., "Natural Course of LGI1 Encephalitis: 3-5 Years of Follow-Up Without Immunotherapy," *Journal of the Neurological Sciences* 343, no. 1–2 (2014): 198–202, https://doi.org/10.1016/j.jns.2014.05.048.

29. A. Dodich, C. Cerami, S. Iannaccone, et al., "Neuropsychological and FDG-PET Profiles in VGKC Autoimmune Limbic Encephalitis," *Brain and Cognition* 108 (2016): 81–87, https://doi.org/10.1016/j.bandc.2016.07.010.

30. J. Yu, X. Yu, S. Fang, Y. Zhang, and W. Lin, "The Treatment and Follow-Up of Anti-LGI1 Limbic Encephalitis," *European Neurology* 75, no. 1–2 (2016): 5–11, https://doi.org/10.1159/000441944.

31. P. P. Zhao, Y. Zhang, L. Gao, and L. Sun, "Assessing the Clinical Features of LGI1 Antibody Encephalitis," *Acta Neurologica Belgica* 116, no. 1 (2016): 109–112, https://doi.org/10.1007/s13760-015-0517-x.

32. H. Ariño, T. Armangué, M. Petit-Pedrol, et al., "Anti-LGI1-Associated Cognitive Impairment: Presentation and Long-Term Outcome," *Neurology* 87, no. 8 (2016): 759–765, https://doi.org/10.1212/WNL.0000000000003009.

33. T. D. Miller, T. T. Chong, A. M. Aimola Davies, et al., "Focal CA3 Hippocampal Subfield Atrophy Following LGI1 VGKC-Complex Antibody Limbic Encephalitis," *Brain* 140, no. 5 (2017): 1212–1219, https://doi.org/10.1093/brain/awx070.

34. C. Finke, H. Prüss, J. Heine, et al., "Evaluation of Cognitive Deficits and Structural Hippocampal Damage in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 Antibodies," *JAMA Neurology* 74, no. 1 (2017): 50–59, https://doi.org/10.1001/jamaneurol.2016.4226.

35. W. Bing-Lei, Z. Jia-Hua, L. Yan, et al., "Three Cases of Antibody-LGI1 Limbic Encephalitis and Review of Literature," *International Journal of Neuroscience* 129, no. 7 (2019): 642–648, https://doi.org/10.1080/00207454.2018.1512985.

36. S. Y. Kim, Y. H. Um, S. C. Lim, and J. H. Jeong, "Limbic Encephalitis Manifesting as Selective Amnesia and Seizure-Like Activity: A Case Report," *Clinical Psychopharmacology and Neuroscience* 16, no. 1 (2018): 109–113, https://doi.org/10.9758/cpn.2018.16.1.109.

37. J. Heine, H. Prüss, U. A. Kopp, et al., "Beyond the Limbic System: Disruption and Functional Compensation of Large-Scale Brain Networks in Patients With Anti-LGI1 Encephalitis," *Journal of Neurology, Neurosurgery, and Psychiatry* 89, no. 11 (2018): 1191–1199, https://doi.org/10.1136/jnnp-2017-317780.

38. W. Li, S. Wu, Q. Meng, et al., "Clinical Characteristics and Short-Term Prognosis of LGI1 Antibody Encephalitis: A Retrospective Case Study," *BMC Neurology* 18, no. 1 (2018): 96, https://doi.org/10.1186/s12883-018-1099-z.

39. M. Lad, S. L. Mullally, A. L. Houston, T. Kelly, and T. D. Griffiths, "Characterizing Memory Loss in Patients With Autoimmune Limbic Encephalitis Hippocampal Lesions," *Hippocampus* 29, no. 11 (2019): 1114–1120, https://doi.org/10.1002/hipo.23150.

40. C. Loane, G. P. D. Argyropoulos, A. Roca-Fernández, et al., "Hippocampal Network Abnormalities Explain Amnesia After VGKCC-Ab Related Autoimmune Limbic Encephalitis," *Journal of Neurology, Neurosurgery, and Psychiatry* 90, no. 9 (2019): 965–974, https://doi.org/10.1136/jnnp-2018-320168.

41. X. Yang, A. N. Li, X. H. Zhao, X. W. Liu, and S. J. Wang, "Clinical Features of Patients With Anti-Leucine-Rich Glioma Inactivated-1 Protein Associated Encephalitis: A Chinese Case Series," *International Journal of Neuroscience* 129, no. 8 (2019): 754–761, https://doi.org/10.1080/00207454.2019.1567507.

42. R. Iorio, V. Damato, G. Spagni, et al., "Clinical Characteristics and Outcome of Patients With Autoimmune Encephalitis: Clues for Paraneoplastic Aetiology," *European Journal of Neurology* 27, no. 10 (2020): 2062–2071, https://doi.org/10.1111/ene.14325.

43. R. Uribe-San-Martín, E. Ciampi, R. Santibañez, et al., "LGI1-Antibody Associated Epilepsy Successfully Treated in the Outpatient Setting," *Journal of Neuroimmunology* 345 (2020): 577268, https://doi.org/10.1016/j.jneuroim.2020.577268.

44. H. L. Hang, J. H. Zhang, D. W. Chen, J. Lu, and J. P. Shi, "Clinical Characteristics of Cognitive Impairment and 1-Year Outcome in Patients With Anti-LGI1 Antibody Encephalitis," *Frontiers in Neurology* 11 (2020): 852, https://doi.org/10.3389/fneur.2020.00852.

45. X. Ma, L. Ma, Z. Wang, et al., "Clinical Features and Gut Microbial Alterations in Anti-Leucine-Rich Glioma-Inactivated 1 Encephalitis-A Pilot Study," *Frontiers in Neurology* 11 (2020): 585977, https://doi.org/10.3389/fneur.2020.585977.

46. S. Qiao, H. K. Wu, L. L. Liu, et al., "Clinical Features and Long-Term Outcomes of Anti-Leucine-Rich Glioma-Inactivated 1 Encephalitis: A Multi-Center Study," *Neuropsychiatric Disease and Treatment* 17 (2021): 203–212, https://doi.org/10.2147/NDT.S292343.

47. S. A. Karvigh, S. Salehizadeh, and F. Vahabizad, "Anti-Leucine-Rich Glioma-Inactivated 1 Encephalitis: Two Case Reports and a Review of the Literature," *Journal of Medical Case Reports* 16, no. 1 (2022): 409, https://doi.org/10.1186/s13256-022-03650-x.

48. H. Y. Li, S. Qiao, C. S. Cui, F. Feng, X. W. Liu, and X. D. Yang, "Clinical Features and Outcomes of Leucine-Rich Glioma-Inactivated Protein 1 and Contactin Protein-Like 2 Antibody-Associated Autoimmune Encephalitis in a Chinese Cohort," *Journal of Clinical Neuroscience* 101 (2022): 137–143, https://doi.org/10.1016/j.jocn.2022.05.007.

49. L. Chen, T. Su, and Y. Liu, "Clinical Characteristics of Leucine-Rich Glioma-Inactivated Protein 1 Antibody-Mediated Autoimmune Encephalitis in a 6-Year-Old Girl: Case Report and Literature Reviews," *BMC Neurology* 23, no. 1 (2023): 253, https://doi.org/10.1186/s12883-023-03299-z.

50. E. Y. Huang, H. Gao, and N. Zhong, "Heterogeneity of Clinical Features, EEG and Brain Imaging Findings in Anti-Leucine-Rich Glioma-Inactivated Protein 1 Autoimmune Encephalitis: A Retrospective Case Series Study and Review of the Literature," *Acta Epileptologica* 5, no. 1 (2023): 21, https://doi.org/10.1186/s42494-023-00132-5.

51. D. Montag, "Retrograde Amnesia—A Question of Disturbed Calcium Levels?," *Frontiers in Cellular Neuroscience* 15 (2021): 746198, https://doi.org/10.3389/fncel.2021.746198.

52. B. Joubert, M. Saint-Martin, N. Noraz, et al., "Characterization of a Subtype of Autoimmune Encephalitis With Anti-Contactin-Associated

Protein-Like 2 Antibodies in the Cerebrospinal Fluid, Prominent Limbic Symptoms, and Seizures," *JAMA Neurology* 73, no. 9 (2016): 1115–1124, https://doi.org/10.1001/jamaneurol.2016.1585.

53. L. R. Squire and P. Alvarez, "Retrograde Amnesia and Memory Consolidation: A Neurobiological Perspective," *Current Opinion in Neurobiology* 5, no. 2 (1995): 169–177, https://doi.org/10.1016/0959-4388(95)80023-9.

54. J. M. Reed and L. R. Squire, "Retrograde Amnesia for Facts and Events: Findings From Four New Cases," *Journal of Neuroscience* 18, no. 10 (1998): 3943–3954, https://doi.org/10.1523/JNEUROSCI.18-10-03943.1998.

55. L. Nadel and M. Moscovitch, "Memory Consolidation, Retrograde Amnesia and the Hippocampal Complex," *Current Opinion in Neurobiology* 7, no. 2 (1997): 217–227, https://doi.org/10.1016/s0959-4388(97)80010-4.

56. G. Winocur and M. Moscovitch, "Memory Transformation and Systems Consolidation," *Journal of the International Neuropsychological Society* 17, no. 5 (2011): 766–780, https://doi.org/10.1017/S1355617711000683.

57. J. Benoit, S. Muñiz-Castrillo, A. Vogrig, et al., "Early-Stage Contactin-Associated Protein-Like 2 Limbic Encephalitis: Clues for Diagnosis," *Neurology: Neuroimmunology & Neuroinflammation* 10, no. 1 (2022): e200041.

58. H. J. Markowitsch, P. Calabrese, J. Liess, M. Haupts, H. F. Durwen, and W. Gehlen, "Retrograde Amnesia After Traumatic Injury of the Fronto-Temporal Cortex," *Journal of Neurology, Neurosurgery, and Psychiatry* 56, no. 9 (1993): 988–992, https://doi.org/10.1136/jnnp.56.9.988.

59. M. O'Connor, N. Butters, P. Miliotis, P. Eslinger, and L. S. Cermak, "The Dissociation of Anterograde and Retrograde Amnesia in a Patient With Herpes Encephalitis," *Journal of Clinical and Experimental Neuropsychology* 14, no. 2 (1992): 159–178, https://doi.org/10.1080/01688639208402821.

60. E. De Renzi and F. Lucchelli, "Dense Retrograde Amnesia, Intact Learning Capability and Abnormal Forgetting Rate: A Consolidation Deficit?," *Cortex* 29, no. 3 (1993): 449–466, https://doi.org/10.1016/s0010-9452(13)80253-5.

61. S. Arzy, S. Collette, M. Wissmeyer, F. Lazeyras, P. W. Kaplan, and O. Blanke, "Psychogenic Amnesia and Self-Identity: A Multimodal Functional Investigation," *European Journal of Neurology* 18, no. 12 (2011): 1422–1425, https://doi.org/10.1111/j.1468-1331.2011.03423.x.

62. K. R. Patterson, J. Dalmau, and E. Lancaster, "Mechanisms of Caspr2 Antibodies in Autoimmune Encephalitis and Neuromyotonia," *Annals of Neurology* 83, no. 1 (2018): 40–51, https://doi.org/10.1002/ana.25120.

63. M. Saint-Martin, A. Pieters, B. Déchelotte, et al., "Impact of Anti-CASPR2 Autoantibodies From Patients With Autoimmune Encephalitis on CASPR2/TAG-1 Interaction and Kv1 Expression," *Journal of Autoimmunity* 103 (2019): 102284, https://doi.org/10.1016/j.jaut.2019.05.012.

64. M. P. Giannoccaro, D. A. Menassa, L. Jacobson, et al., "Behaviour and Neuropathology in Mice Injected With Human Contactin-Associated Protein 2 Antibodies," *Brain* 142, no. 7 (2019): 2000–2012, https://doi.org/10.1093/brain/awz119.

65. O. Varea, M. D. Martin-de-Saavedra, K. J. Kopeikina, et al., "Synaptic Abnormalities and Cytoplasmic Glutamate Receptor Aggregates in Contactin Associated Protein-Like 2/Caspr2 Knockout Neurons," *Proceedings of the National Academy of Sciences of the United States of America* 112, no. 19 (2015): 6176–6181, https://doi.org/10.1073/pnas.1423205112.

66. D. Fernandes, S. D. Santos, E. Coutinho, et al., "Disrupted AMPA Receptor Function Upon Genetic- Or Antibody-Mediated Loss of Autism-Associated CASPR2," *Cerebral Cortex* 29, no. 12 (2019): 4919–4931, https://doi.org/10.1093/cercor/bhz032.

67. L. L. Gibson, A. McKeever, E. Coutinho, C. Finke, and T. A. Pollak, "Cognitive Impact of Neuronal Antibodies: Encephalitis and Beyond," *Translational Psychiatry* 10, no. 1 (2020): 304, https://doi.org/10.1038/s41398-020-00989-x.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.