Review and meta-analysis of neuropsychological findings in autoimmune limbic encephalitis with autoantibodies against LGI1, CASPR2, and GAD65 and their response to immunotherapy


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**Objectives:** It is assumed that autoimmune limbic encephalitis (ALE) demonstrates distinct neuropsychological manifestations with differential responses to immunotherapy according to which associated autoantibody (AAB), if any, is identified. Towards investigating whether this is the case, this study aims to summarize respective findings from the primary literature on ALE with AABs binding to cell surface neural antigens and ALE with AABs against intracellular neural antigens.

**Methods:** We chose ALE with AABs against leucine-rich, glioma inactivated protein 1 (LG11) and contactin-associated protein-like 2 (CASPR2) as the most frequent cell surface membrane antigens, and ALE with AABs to Embryonic Lethal, Abnormal Vision, Like 1 (ELAVL) proteins (anti-Hu) and glutamic acid decarboxylase 65 (GAD65) as the most frequent intracellular neural antigens. The PubMed and Scopus databases were searched on March 1st, 2021 for neuropsychological test and -screening data from patients with ALE of these AAB-types.

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Findings were reviewed according to AAB-type and immunotherapy status and are presented in a review section and are further statistically evaluated and presented in a meta-analysis section in this publication.

**Results:** Of the 1304 initial hits, 32 studies on ALE with AABs against LGI1, CASPR2, and GAD65 reporting cognitive screening data could be included in a review. In ALE with AABs against LGI1, CASPR2 and GAD65, memory deficits are the most frequently reported deficits. However, deficits in attention and executive functions including working memory, fluency, and psychological function have also been reported. This review shows that ALE patients with AABs against both LGI1 and CASPR2 show higher percentages of neuropsychological deficits compared to ALE patients with AABs against GAD65 before and after initiation of immunotherapy. However, the methodologies used in these studies were heterogeneous, and longitudinal studies were not comparable. Moreover, 21 studies including ALE patients with AABs against LGI1 and GAD65 were also suitable for meta-analysis. No suitable study on ALE with AABs against ELAVL proteins could be identified. Meta-Analyses could be executed for cognitive screening data and only partially, due to the small number of studies. However, in statistical analysis no consistent effect of AAB or immunotherapy on performance in cognitive screening tests could be found.

**Conclusion:** Currently, there is no definitive evidence supporting the notion that different AAB-types of ALE exhibit distinct neuropsychological manifestations and respond differently to immunotherapy. Overall, we could not identify evidence for any effect of immunotherapy on cognition in ALE. More systematic, in-depth and longitudinal neuropsychological assessments of patients with different AAB-types of ALE are required in the future to investigate these aspects.

1. **Introduction**

Autoimmune limbic encephalitis (ALE), the most common type of autoimmune encephalitis (AIE), is characterized by the rapid development of memory deficits, confusion, and mood changes. These cognitive impairments are often accompanied by epileptic seizures [1]. It primarily occurs in middle-aged adults [2]. Seropositive ALE is associated with autoantibodies (AABs) that can be classified as binding to cell surface or intracellular neural antigens [3]. However, AABs cannot be detected in all patients that fulfill the clinical and paraclinical criteria of ALE [4]. There is some empirical evidence that ALE with or without different AABs exhibit differences regarding the frequency, severity, and pattern of neuropsychological manifestations [5–8]. It is assumed that the underlying pathogenesis differs according to which AAB is driving disease. Anti-LGI1 ALE is described to be characterized by frequent facio-brachial dystonic seizures and amnesia (particularly autobiographical) [9,10]. Binks et al. cite a spousal diary of a patient “Woke and memory gone – forgotten years – only very early memories” ([11], pp. 529). Anti-CASPR2 ALE is reported to show amnesia and seizures as limbic symptoms as well [9,10], but with peripheral nerve excitability and autonomic dysfunction occurring more frequently in anti-LGI1 ALE than in anti-CASPR2 ALE [9,10]. Memory impairment is reported to predominantly affect anterograde and episodic memory [9,10]. Anti-GAD65 ALE is associated with seizures and memory loss and often cerebellar ataxia associated with type 1 diabetes mellitus [12,13], and with a wide spectrum of neuropsychological symptoms [13]. Anti-Hu ALE is described with sensory neuropathy additional to limbic symptoms [14]. While the majority of patients with anti-CASPR2 ALE appear to respond to immunotherapy, response in anti-Hu- and anti-LGI1 is reported to be poor [12,14]. AABs directed against intracellular neural antigens are associated with neuronal cell death mediated by antigen specific cytotoxic CD8+ T-cells [3]. AABs that bind to cell surface membrane neural antigens are thought to alter neurotransmission and plasticity by either activating or blocking the function of their target molecules, crosslinking and internalizing receptors impacting neural excitability, or perhaps leading to antibody-dependent cytotoxicity [3, 15–17]. The mechanisms in seronegative ALE are currently unclear [18]. The existence of subform-specific symptomatology regarding neuropsychological impairments in ALE would have implications for diagnosing ALE and discriminating it from other temporal lobe epilepsies of non-autoimmune etiology, which is already tried on the basis of neuropsychological findings (see [68]). Additionally, there is evidence that different ALE AAB-types respond differently to immunotherapy with regard to neuropsychological symptoms [6,19]. This would possibly call for AAB-specific regimens in the treatment of ALE.

AIE is diagnosed with increasing frequency [20]. Nevertheless, with a prevalence of about 2/100.000 population [21], it remains a rare disease. We here aimed to conduct a meta-analysis of the cognitive and psychological impairments of ALE associated with different AABs and their response to immunotherapy in adults. Within each group of AABs associated with ALE, we selected the most prevalent AAB types identified in adults to achieve an overview of the spectrum of ALE. Representative of AABs against intracellular proteins associated with cancer, we selected ALE with AABs against ELAVL (Hu) proteins [22]. Representative of AABs against intracellular proteins without a strong association with cancer, we selected ALE with AABs against glutamic acid decarboxylase 65 (GAD65; [23]). For ALE with AABs against cell surface proteins, we selected leucine-rich, glioma inactivated protein 1 (LGI1; [24]) and contactin-associated protein-like 2 (CASPR2; [25]). Since seronegative ALE is not yet clearly defined (as described in, e.g., [1]), we focused on AAB positive ALE subforms. ALE other than ALE, such as panencephalitis with AABs against the NMDAR, are also excluded from this review and meta-analysis.

2. **General methods of review and meta-analysis**

2.1. **Study selection, inclusion and exclusion criteria**

We conducted this review and meta-analysis according to PRISM guidelines [26] by searching the Pubmed and Scopus databases on March 1st, 2021 for publications including patients diagnosed with ALE. We included studies reporting patients who were positive for AABs against LGI1, CASPR2, GAD65 or Hu and underwent standardized, psychometric examination of cognitive and psychological symptoms. Search strategies, inclusion criteria and exclusion criteria have been included in the Supplement. Of studies selected for review those were focused on AAB positive ALE subforms. AIE other than ALE, such as panencephalitis with AABs against the NMDAR, are also excluded from this review and meta-analysis.

2.2. **Statistical analysis**

2.2.1. **Review and meta-analysis**

In the primary literature selected for meta-analysis, the Montreal Cognitive Assessment (MoCA) [28] and Mini Mental State Examination (MMSE) [29] were predominantly applied and reported as raw scores. We classify a MoCA-score of 27–30 as “normal”, a score of 24–26 as “mild cognitive impairment”, a score of 17–23 as “moderate cognitive impairment” and a score below 17 as “severe cognitive impairment”,...
referring to Carson et al. [30], Freitas et al. [31] and Nasreddine et al. [30]. To classify MMSE, we applied a cut-off score of 26 or below for cognitive impairment, referring to Kukull et al. [32]. In tests without defined cut-off scores, we used a z-score < –1.0 as a cut-off, as commonly used in clinical and scientific practice (as described in e.g., [33–35]).

2.2.2. Meta-analysis

To perform meta-analyses statistics, R programming language [36] was used with the metafor package [37]. Since not all studies contain follow-up data and since neither equivalent methodology nor equivalent immunotherapy can be assumed, we analyzed data cross-sectionally. Hence, we divided the pool of studies included in the meta-analysis: We collected all subsamples of studies reporting neuropsychological screening test data before initiation of immunotherapy in one record (baseline) and subsamples of studies solely reporting neuropsychological screening test data after initiation of (1st line or 2nd line) immunotherapy in a second record (treated). Unfortunately, studies reporting follow-up measurements included diverse time intervals and different immunotherapy interventions at variable time points, and in most cases no control group. This hampered comparability of immunotherapy effects observed in these longitudinal studies. Therefore, follow-up screening test data after initiation of immunotherapy from subsamples from the baseline and treated groups were analyzed separately in a third record (follow-up).

2.2.2.1. Homogeneity for analysis of AAB-effect. We first used a random effects model to investigate between-study homogeneity among baseline, treated and follow-up subsamples. We did this for MMSE-score and MoCA-score, where possible.

2.2.2.2. Subgroup analysis for AAB-effect. Next, to investigate the possible impact of AAB-status on neuropsychological functioning, we then conducted meta-regressions for subgroup analysis of homogeneity for baseline, treated and follow-up data.

2.2.2.3. Multiple meta-regression for AAB-immunotherapy-interaction. To investigate whether ALE with different AABs responds differently to immunotherapy, we established multiple meta regressions in the combined baseline and treated records.

2.2.2.4. Overall immunotherapy effect. Finally, we investigated the homogeneity of baseline and treated subsamples to conduct a subgroup analysis investigating whether immunotherapy is a significant factor impacting cognitive status. All AAB types were included.

3. Results

The literature search in Pubmed and Scopus resulted in the identification of 1304 articles. After removing duplicates and applying the exclusion criteria, 168 studies were selected for full text screening for reported neuropsychological data. The prevalence of neuropsychological symptoms was often provided, which was based on clinical evaluation by physicians. However, only 22 studies were suitable regarding our inclusion and exclusion criteria. In total, 45 authors were contacted to request additional data. Of those 45 authors, 15 responded and 10 sent additional data. Therefore, 32 studies could be included in the review. Unfortunately, quantitative neuropsychological data on ALE are sparse and completely lacking for anti-Hu ALE. Thus, according to the available psychometric data, we performed a review on neuropsychological symptoms in ALE with AABs against LGI1, CASPR2 or GAD65, and a meta-analysis of cognition in anti-LGI1 and anti-GAD65 ALE patients.

For an overview of the tests applied in these studies, see Supplementary Table 1. For an overview of the number of ALE patients per AAB and immunotherapy-status of the studies in the review, see Supplementary Table 2.

Due to comparability of neuropsychological screening tests used, 21 studies with the same screening tests could be included for a meta-analysis. Fig. 1 depicts the flow-chart of the selection process.

3.1. Results of review

Table 1 provides a tabular overview of the neuropsychological findings in different AAB-defined ALE patient samples before and after initiation of immunotherapy. For a summary of the following description see the Supplement.

3.1.1. Immuno-therapy-naive anti-LGI1 ALE

3.1.1.1. Cognitive screening. In total, 8 studies report MMSE scores indicating a cognitive impairment in a total of 133 patients (see [38–45]) and 5 report a MMSE score in a non-pathological range in a total of 14 patients (see [46–49], Elben, n.p., 2020).

Concerning MoCA-scores, four studies present a score indicative of severe cognitive impairment in a total of 72 patients (see [41–44]). 2 studies indicate moderate cognitive impairment in a total of 43 patients (see [39,45]), 1 study reports mild cognitive impairment in a total of 4 patients ([50], with no study reporting a normal MoCA score.

Spots et al. report an Addenbrookes Cognitive Examination (ACE-R) test score of 61/100 for one of their 2 patients, reflecting a severe cognitive deficit [49].

3.1.1.2. Memory. Extensive neuropsychological testing in 2 immunotherapy-naive anti-LGI1 ALE patients was reported by Dodich et al. [47]. Amongst other parameters, they assessed verbal short-term memory with a resulting score of z = –0.7 (range –1.6 to 0.2), a verbal working memory score of z = 0.4 (range –1.3 to 2.1), a nonverbal short-term and working memory score of z = –1.9 (range –2.4 to (–1.4)) and a delayed free memory recall of z = –2.7 (range –4.4 to (–1.1)).

Holtmann et al., report an ALE sample with mixed AABs at baseline and two follow-up examinations [51]. In their 4 patients with anti-LGI1 AABS they found an unimpaired performance in working memory z = –0.4 (range –1.3 to 0.2) in verbal learning z = –0.6 (range –1.8 to 0.3), verbal forgetting z = –0.6 (range –1.3 to 0.3), and visual memory z = –0.4 (range –1.1 to 0.1) [51].

3.1.1.3. Attention and executive functions. Dodich et al., additionally assessed a reasoning score of z = 0.4 (range –0.5 to 1.2), a semantic word fluency score of z = –0.3 (range –1.4 to 0.8), and a global score of socio-emotional skills of z = 0.7 (range –1.6 to 0.3), with the worst performance observed in the rating of disgusting and fearful faces [47]. Holtmann et al. found processing speed z = –0.1 (range –0.8 to 0.5), set-shifting z = 0.1 (range –0.1 to 0.4)) and phonemic fluency z = –0.4 (range –0.9 to 0.2) also to be not impaired according to their cut-off score of z < –1.5 [51]. One study applied the Frontal Assessment Battery (FAB) and found a mean score of 15.3 (range 13–28 [50]), which is above the cut-off score, thus not indicative for a dysexecutive syndrome.

3.1.1.4. Psychological symptoms. Wang et al. used the Brief Psychiatric Rating Scale (BPRS) and found an abnormal score of 56.3 (range 57–79) in their 13 patients [52].

Quality of sleep, as measured with Pittsburgh Sleep Quality Index (PSQI), and daytime sleepiness (Epworth Sleepiness Scale (ESS)) were within normal range in a subsample of 2 patients [53].

3.1.2. Anti-LGI1 ALE after initiation of immunotherapy

3.1.2.1. Cognitive screening. MMSE-scores were in pathological range in 4 studies [38,40,42,54] in a total of 13 patients and within normal range
in 2 studies [48,55] in a total of 11 patients. A MoCA score indicating a moderate cognitive impairment was reported in 4 studies in a total of 21 patients (see [42,54,56,57], with Hébert et al. presenting 2 follow-up measurements after immunotherapy).

Brown et al. reported 2 patients who had a mean raw score on the ACE-R of 80 (range 78–82) [58], which indicates cognitive impairment. Dong et al. report cognitive functioning as per the Glasgow Coma Scale (GCS) after initiation of immunotherapy (corticosteroids, intravenous immunoglobulin) with a mean score of 14 for 7 patients, with a range of 7–15, which reflects severely impaired consciousness to a normal, conscious state [59]. Day et al. depict raw scores using the Clinical Dementia Rating (CDR) after initiation of immunotherapy (corticosteroids, immunoglobulins, rituximab), resulting in a mean score of 0.8 in 4 patients [46], which is above the cut-off score of 0.7 for early symptomatic Alzheimer’s Disease.

3.1.2.2. Memory. Finke et al. investigated 30 anti-LGI1 ALE patients after initiation of immunotherapy consisting of corticosteroids, immunoglobulins or long-term immunosuppression [57]. In their neuropsychological examination, they investigated several cognitive functions and applied different tests in a different number of patients (11–26 patients) per test [57]. They provide the raw scores of these tests and illustrate that patients performed significantly worse than healthy controls in verbal learning, in recall of an interference list and in delayed recall and recognition of learned verbal material [57]. In addition, they scored significantly worse than controls in visuospatial memory and in verbal short-term and working memory [57].

Onugoren et al. report memory function in three anti-LGI1 ALE patients among other ALE patients [60]. They used the Verbal Lern- und Merkfähigkeitstest (VLMT), the Diagnosticon für Cerebralschädigung (DCS), and the Rey Complex Figure Test (RCFT) to present an average memory performance [60]. After an average of 6.3 days (range 4–9) following immunoadsorption, the mean memory score was z = −1.1 (range (−1.7 to −0.3)). After an average of 3.7 months (range 3.2–4.1) after initiation of immunoadsorption, memory performances resulted in a mean score of z = −0.5 (range (−1.8 to −0.5)). The authors conclude that there was no recovery of memory performance [60]. Bauer et al. also used the VLMT and DCS, but they report mean scores, composed of subscores, transformed on a scale with a mean score of 100 and a SD of 10 in comparison to 488 healthy controls. In their study linking white matter characteristics, AAB-status, and clinical features, they include anti-LGI1, anti-CASPR2 and anti-GAD65 ALE patients [61]. For their 4 anti-LGI1 ALE patients, they report a VLMT score of 83.6 (range 70–108) and a DCS score of 77.5 (range 61–99) [61], which are both below average.

Findings by Holtmann et al. at first follow up of 2 remaining anti-LGI1 ALE patients after initiation of immunotherapy result in a z-score of the VLMT learning scale z = 0.0 (range (−0.3 to 0.3), a long term forgetting rate of z = −0.4 (range (−0.9 to (−0.2)), a DCS learning efficiency index z = −0.8 (range (−1.7 to 0.0) and a digit span forwards z = −0.2 (range (−0.6 to 0.3) [51]. Thus, they found performances were within the normal range in these patients.

Van Sonderen et al., using the Cambridge Neuropsychological Test Automated Battery (CANTAB), report persistently impaired spatial
recognition memory in their anti-LGI1 ALE patients (n = 10–11) in a follow-up period of 44 months (range 25–95) after immunotherapy [53]. Verbal memory was in the unimpaired range upon follow-up [53].

3.1.2.3. Attention and executive functions. Finke et al. report that their patients showed impairments in executive function as well as in word fluency and attention [57]. Holtmann et al., however, observed performances in normal range in processing speed $z = 0.4$ (range 0.3–0.6), set-shifting $z = -0.2$ (range –0.8 to 0.4), and phonemic word fluency $z = -0.3$ (range –0.8 to 0.2) [51]. Likewise, Van Sonderen et al. found executive functions and attention to be in the normal range upon follow-up [53].

3.1.2.4. Psychological symptoms. Psychiatric symptom score 2 months after initial examination and immunotherapy was 24.9 (range 16–37) on BPRS [52], reflecting a reduction by 31.4 to a normal score, according to the authors [52]. That is, 85% returned to normal psychiatric status [52]. The most common remaining symptom was apathy [52].

Sleep quality, as measured by the PSQI, was normal with a mean score of 4.6 (range 1–10) and daytime sleepiness was not elevated (ESS mean score = 1.8 (range 0–6) in 11 patients upon follow-up) [53].

3.1.3. Immunotherapy-naive anti-CASPR2 ALE

3.1.3.1. Cognitive screening. No data using cognitive screening are reported.

3.1.3.2. Memory. The sample of Onugoren et al., contains neuropsychological data of a total of two immunotherapy-naive anti-CASPR2 ALE patients. Their mean memory score was in the deficit range ($z = -1.05$ (range –1.4 to –0.7); [60]).

3.1.3.3. Attention and executive functions. No data regarding attention and executive function are reported.

3.1.3.4. Psychological symptoms. No data regarding psychological symptoms are reported.

3.1.4. Anti-CASPR2 ALE after initiation of immunotherapy

3.1.4.1. Cognitive screening. No data from cognitive screening are reported.

3.1.4.2. Memory. Onugoren et al., also report early follow-up data with a mean memory score of $z = -1.9$ (range –2.2 to (–1.8)) after an average of 19.5 days following immunoadsorption in 3 patients and a score of $z = -1.8$ (range –2.2 to (–0.9)) at an average of 4.2 (range 3–5) months after immunoadsorption in 4 patients [60]. The authors conclude that despite a good early overall recovery, there was no recovery of memory performance in patients with anti-CASPR2 ALE [60].

In five 5 anti-CASPR2 ALE patients of their study, Bauer et al. report a mean VLMT raw score of 88.8 (range 78–92) and a mean DCS raw score of 91.9 (range 81–107) after corticosteroid treatment. Scores are averaged over subscales and transformed on a scale with a mean score of 100 and a SD of 10 in comparison to healthy controls [61]. In the mean values this reflects a deficit in verbal memory and an average performance in figural memory.

3.1.4.3. Attention and executive functions. No data regarding attention and executive functions are reported.

3.1.4.4. Psychological symptoms. No data regarding psychological symptoms are reported.
mean MMSE score of 17 (SD = 7.1) [63]. Joubert et al. studied temporal lobe epilepsy with anti-GAD65 antibodies [64]. Of their 35 patients, 22 fulfilled the criteria of a definite or probable autoimmune encephalitis [64]. Nine patients were assessed prior to initiation of immunotherapy [64]. Of those, 6 with a limbic syndrome had a mean MMSE-score of 23.3 (18–26) [64]. Hence, referring to the mean score, in all 3 studies using the MMSE, a cognitive impairment was found.

### 3.1.5.2. Memory.

In all 3 immunotherapy-naïve anti-GAD65 ALE patients in the subsample from Helmsaetdter et al. accelerated long-term forgetting of verbal material was observed [7]. The mean DCS learning efficiency index, assessed in two of these 3 patients, was $z = -0.6$ (range = 2.5 to 0.9) [7].

Hansen et al. applied the VLMT, DCS to assess verbal memory and figural memory in anti-GAD65 ALE [65]. They used subscores of these tests to assign individual rating scores based on the mean and standard deviation of normative data for each patient. Eleven patients with anti-GAD65 ALE reported therein reached an average mean rating of 2.4 (SD = 0.3) in verbal memory and 2.00 (SD = 0.3) in figural memory [65]. A mean rating of 3 reflects performances between 1 SD below and 1 SD above the mean. A mean rating of 2 reflects a performance below 1 SD of the mean of the normative group. They consider rating scores $\leq 2$ as “impaired” and rating scores $\geq 3$ as “normal”. They do not clearly define values between 2 and 3 but used the value 2 as cut-off score. Expressed in prevalences, verbal memory was impaired in 45 % and figural memory was impaired in 64 % [65] of cases.

### 3.1.5.3. Attention and executive functions.

No impairment in executive functions was found on the Batterie Rapide d’Éfficacité Frontale (BREF), with a mean score of 17/18 (15–18) in 5 patients [64]. Helmsaetdter et al. also did not report a deficit in attention and executive function in their sample [7]. They found an EpiTrack-score of 38.5 (range 38–39) in 2 of their patients [7]. Likewise, 11 patients with anti-GAD65 ALE reported by Hansen et al. reached an average mean rating of 2.5 (SD = 0.3) in attention and executive functions in EpiTrack, 2.4 (SD = 0.3) and 2.3 (SD = 0.3) in verbal fluency, which is above their cut-off score [65]. However, they report that 27 % of their sample demonstrated impaired attention and 45 % of cases impaired verbal fluency [65].

### 3.1.5.4. Psychological symptoms.

Hansen et al. evaluated mood relying on patients records and the BDI-I and applied the same scoring as for cognition. [65]. Their immunotherapy-naive anti-GAD65 ALE patients received a mean rating of 2.5 (SD = 0.2), according to their Supplementary material, thus a value above their applied cut-off score [65].

Helmsaetdter et al. found a BDI-I score of 23.5 (range 23–24) according to additional data, indicating a moderate depression referring to the scoring criteria [7].

### 3.1.6. Anti-GAD65 ALE after initiation of immunotherapy


Regarding the sample of Joubert et al., 11 of their patients with anti-GAD65 AABs, a definite or probable autoimmune encephalitis and a limbic syndrome underwent cognitive examination after or during treatment with corticosteroids, immunoglobulin or rituximab [64]. The MMSE mean score of 24.2 (range 18–29, 5 patients) was in the deficit bracket [64].

Notably, Zhang et al. report that their 3 patients were negative for anti-GAD65 AABs in the early disease stage, but were positive 43 days and 79 days after disease onset, respectively [62]. Thus, they demonstrate that production of anti-GAD65 may have a certain latency period, and that AAB-status usually is negative at the time of disease onset [62]. Zhu et al. state that the course of anti-GAD 65 ALE is longer than that of the other forms of AIE [63].

MoCA scores of 5 anti-GAD65 ALE patients demonstrated a mean score of 21.8 (SD = 1.5) [66], reflecting a moderate impairment.

#### 3.1.6.2. Memory.

After methylprednisolone therapy, 11 patients reported by Hansen et al. had a mean rating of 2.5 (SEM = 0.3) on verbal memory and 2.0 (SEM = 0.3) on figural memory, which is above their defined cut-off score [65]. In terms of prevalence they report an impairment of verbal memory in 36 % and of figural memory in 64 % of cases [65]. Compared to naive status, 18 % deteriorated in verbal memory as measured by change in rating score from unimpaired to impaired, and 0 % had a change in figural memory in their rating score [65].

Wagner, together with Hansen et al., described individual verbal and figural memory scores of 14 anti-GAD65 ALE patients after initial immunotherapy with either methylprednisolone, immunoglobulin or azathioprine [67]. They used 1) verbal learning, 2) loss of words after retention, and 3) error-corrected recognition of words using the VLMT to calculate a verbal memory score. Moreover, they employed 4) correctly learned designs over learning trials, 5) final learning performance, and 6) error-corrected recognition performance, using the DCS to calculate figural memory [67]. Mean verbal memory score was 100.1 (range 85–109) and mean figural memory was 90.6 (range 66–108) in standard values, with a mean of 100 and a standard deviation of 10 [67]. Thus, these patients showed average memory performances.

Bauer, in collaboration with Wagner et al., gives a mean score for verbal memory of 96.7 (range 71–108) and a mean score for figural memory of 88.5 (range 65–108) in their subsample of 19 anti-GAD65 ALE patients after initial immunotherapy with either methylprednisolone, immunoglobulin or azathioprine [61]. This represents an average verbal memory performance and a below average figural memory performance.

#### 3.1.6.3. Attention and executive functions.

After methylprednisolone therapy, 11 patients reported by Hansen et al. had a mean rating of 2.7 (standard error of the men (SEM) = 0.1) for attention and executive function and 2.1 (SEM = 0.2) on verbal fluency [65]. These are ratings above their applied cut-off score of 2. In terms of prevalence, they report an impairment of attention in 27 % and an impairment of verbal fluency in 63 % of cases [65].

#### 3.1.6.4. Psychological symptoms.

Hansen et al. report a burden of symptoms of depression (determined by patients’ records and the (BDI-II)) that does not fall within their defined critical range [65]. They assigned a mean score of 2.2 (SEM = 0.2) to these patients [65]. It had improved after immunotherapy in 9 % of 11 patients [65], therefore in 1 patient.

#### 3.1.7. Anti-Hu ALE

No study reporting neuropsychological data in anti-Hu ALE could be included in this review, as no study was found with at least two Hu patients, data reflecting neuropsychological test scores, and immunotherapy status.

### 3.2. Results of Meta-analysis

Raw scores of the screening tests MMSE and MoCA were reported in more than four studies and thus selected for meta-analysis. In total, we could include 21 studies in this meta-analysis (see Table 2). The studies comprised of anti-LGI1 ALE patients and anti-GAD65 ALE patients. There were no publications on anti-CASPR2 ALE and anti-Hu ALE reporting MMSE or MoCA scores. We conducted meta-analyses using these cognitive screening tests to investigate whether there are AAB-specific neuropsychological phenotypes in ALE and whether they respond differently well to immunotherapy. We therefore analyzed homogeneity and subgroups of AABs in the three subsamples baseline, treated and follow-up (for subsample definition see Section 2.1), where
3.2.1. Homogeneity for analysis of AAB-effect

The baseline subsamples were heterogeneous regarding the MMSE (I² = 98 %, p < .01) and MoCA (I² = 88 %, p < .01) score. In the treated subsamples, MMSE data are not available. Concerning MoCA score, the baseline and treated subsamples are homogenous (I² = 35 %, p = .21). In follow-up studies, data are heterogenous regarding the MMSE (I² = 89 %, p < .01) score, but homogenous regarding MoCA score (I² = 58 %, p = .07).

3.2.2. Subgroup analysis for AAB-effect

The studies demonstrate that the heterogeneity in immunotherapy-naive ALE patients at baseline regarding the MMSE score is not due to a significant systematic difference between anti-LGI1 and anti-GAD65 ALE (Q = 2.29, df = 13, p = .13). The mean MMSE score was 23.0 (95 % CI: 20.7–25.2) in anti-LGI1 ALE and 18.5 (95 % CI: 6.6–30.4) (note: this is a hypothetical range. A maximum score of 30.0 is possible for the MMSE) in anti-GAD65 ALE.

The heterogeneity in ALE patients at baseline regarding the MoCA score was due to a significant systematic difference between anti-LGI1 and anti-GAD65 ALE (Q = 4.04, df = 1, p = .04). The mean MoCA score was 19.0 (95 % CI 15.9–22.0) in anti-LGI1 patients and 21.80 (95 % CI 20.5–23.1) in anti-GAD65 ALE patients.

Subgroup analyses of the heterogeneity of ALE patients in the treated subsamples could not be performed, since no such study reported MMSE scores in both ALE groups and the studies reported MoCA scores in anti-LGI1 ALE patients only. These patients showed a mean MoCA score of 22.6 (CI: 2.6–42.5). Subgroup analysis of heterogeneity in ALE patients in the follow-up subsamples regarding the MMSE score showed no significant difference (Q = 1.27, df = 1, p = .26) between anti-LGI1 and anti-GAD65 ALE patients. For the anti-LGI1 ALE group, the mean MMSE score was 26.5 (95 % CI 24.4–28.7) and for the anti-GAD65 ALE group it was 24.2 (95 % CI 20.5–27.9) in one study. Concerning the MoCA score in follow-up subsamples, there were only four studies on anti-LGI1 ALE, with a mean score of 22.6 (95 % CI 18.50–26.80).

### Table 2

Overview of studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>AAB</th>
<th>Disease duration (months)</th>
<th>n study/subsample</th>
<th>MMSE (SD)</th>
<th>MoCA (SD)</th>
<th>Age f/m</th>
<th>Nationality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LGI1</td>
<td>0.1</td>
<td>3</td>
<td>22.0 (0.8)</td>
<td>16.0 (1.6)</td>
<td>2/1</td>
<td>China</td>
</tr>
<tr>
<td></td>
<td>LGI1</td>
<td>onset</td>
<td>2</td>
<td>28.0 (0.0)</td>
<td>22.5 (2.5)</td>
<td>0/2</td>
<td>USA</td>
</tr>
<tr>
<td>[54]</td>
<td>LGI1</td>
<td>5.0</td>
<td>2</td>
<td>27.0 (2.5)</td>
<td>1/1</td>
<td>66.0 (0)</td>
<td>Italy</td>
</tr>
<tr>
<td>[45]</td>
<td>LGI1</td>
<td>0.5</td>
<td>2</td>
<td>27.5 (0.5)</td>
<td>1/1</td>
<td>42.0 (2.0)</td>
<td>Germany</td>
</tr>
<tr>
<td>[46]</td>
<td>LGI1</td>
<td>1.5</td>
<td>21</td>
<td>21.2 (3.5)</td>
<td>19.0 (4.4)</td>
<td>8/13</td>
<td>China</td>
</tr>
<tr>
<td>[48]</td>
<td>LGI1</td>
<td>NA</td>
<td>4</td>
<td>26.8 (2.6)</td>
<td>2/2</td>
<td>63.5[30–76]</td>
<td>Italy</td>
</tr>
<tr>
<td>[64]</td>
<td>GAD65</td>
<td>35.0</td>
<td>6</td>
<td>23.3 (2.6)</td>
<td>5/1</td>
<td>30.5 (NA)</td>
<td>France</td>
</tr>
<tr>
<td>[66]</td>
<td>GAD65</td>
<td>NA</td>
<td>5</td>
<td>21.8 (1.5)</td>
<td>0/5</td>
<td>34.7[27–49]</td>
<td>China</td>
</tr>
<tr>
<td>[51]</td>
<td>LGI1</td>
<td>NA</td>
<td>8</td>
<td>19.3 (3.7)</td>
<td>3/5</td>
<td>62.4 (NA)</td>
<td>China</td>
</tr>
<tr>
<td>[44]</td>
<td>LGI1</td>
<td>NA</td>
<td>15</td>
<td>22.1 (4.0)</td>
<td>13.6 (5.9)</td>
<td>6/9</td>
<td>China</td>
</tr>
<tr>
<td>[39]</td>
<td>LGI1</td>
<td>3.4</td>
<td>14</td>
<td>22.1 (5.9)</td>
<td>18.3 (5.5)</td>
<td>3/11</td>
<td>China</td>
</tr>
<tr>
<td>[43]</td>
<td>LGI1</td>
<td>NA</td>
<td>41</td>
<td>20.1 (6.6)</td>
<td>16.6 (6.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[49]</td>
<td>LGI1</td>
<td>4.0</td>
<td>4</td>
<td>27.5 (0.5)</td>
<td>0/2</td>
<td>49.0 (1.0)</td>
<td>Hungary</td>
</tr>
<tr>
<td>[50]</td>
<td>LGI1</td>
<td>3.0</td>
<td>4</td>
<td>24.8 (2.9)</td>
<td>1/3</td>
<td>55.8[44–75]</td>
<td>Chile</td>
</tr>
<tr>
<td>[41]</td>
<td>LGI1</td>
<td>NA</td>
<td>24</td>
<td>21.3 (4.6)</td>
<td>NA</td>
<td>NA (NA)</td>
<td>China</td>
</tr>
<tr>
<td>[41]</td>
<td>LGI1</td>
<td>NA</td>
<td>13</td>
<td>16.2 (7.2)</td>
<td>NA</td>
<td>NA (NA)</td>
<td>China</td>
</tr>
<tr>
<td>[38]</td>
<td>LGI1</td>
<td>1.7</td>
<td>4</td>
<td>17.0 (3.0)</td>
<td>2/2</td>
<td>54.0[41–75]</td>
<td>China</td>
</tr>
<tr>
<td>[62]</td>
<td>GAD65</td>
<td>NA</td>
<td>3</td>
<td>14.7 (1.7)</td>
<td>3</td>
<td>32.3[26–44]</td>
<td>China</td>
</tr>
<tr>
<td>[40]</td>
<td>LGI1</td>
<td>0.6</td>
<td>3</td>
<td>16.5 (5.5)</td>
<td>2/1</td>
<td>54.0 (NA)</td>
<td>China</td>
</tr>
<tr>
<td>[63]</td>
<td>GAD65</td>
<td>NA</td>
<td>3</td>
<td>17.0 (7.0)</td>
<td>3/0</td>
<td>46.7 (NA)</td>
<td>China</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>22.0</td>
<td></td>
<td>19.0</td>
<td>42/59</td>
<td>50.0[20–76]</td>
</tr>
<tr>
<td>Follow-up subsamples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[57]</td>
<td>LGI1</td>
<td>23.3</td>
<td>11</td>
<td>22.4 (1.2)</td>
<td>NA</td>
<td>NA (NA)</td>
<td>China</td>
</tr>
<tr>
<td>[56]</td>
<td>LGI1</td>
<td>32.4</td>
<td>4</td>
<td>19.5 (6.2)</td>
<td>1/3</td>
<td>58.0 (NA)</td>
<td>Canada</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>27.9</td>
<td></td>
<td>21.5</td>
<td>58.0</td>
<td></td>
</tr>
</tbody>
</table>

Note. Baseline subsamples are immunotherapy-naive patients from studies that only contain cognitive screening data from before initiation of immunotherapy (bi) and immunotherapy-naive patients from follow-up studies. Treated subsamples contain patients that only have cognitive screening data after initiation of immunotherapy (ai). Follow-up subsamples represent patients of the baseline subsamples and treated subsamples at later follow-up examination timepoints, after the initiation of immunotherapy (ai). NA = information not available, n = number of patients.
just account for a heterogeneity variance of $R^2 = 4.46\%$. An interaction effect was not significant ($F_{2,7} = 0.93, p = .44$).

3.2.4. Overall immunotherapy effect

Homogeneity was not calculated for MMSE in the combined subsample containing baseline and treated subsamples, since there are no subsamples of treated patients who underwent examination with the MMSE screening test. Concerning MoCA score, the combined baseline and treated subsamples are heterogeneous ($I^2 = 92\%, p < .01$). Subgroup analysis of the impact of immunotherapy in the combined subsample containing all AABs investigated here demonstrates no significant impact on MoCA score ($Q = 2.73, df = 1, p = .10$).

4. General discussion of the review and meta-analysis

We included a total of 32 studies on neuropsychological symptoms in ALE associated with AABs against the most frequently reported cell surface (LGII and CASPR2) and intracellular (GAD65) neural antigens in a review. Unfortunately, we could not identify a suitable study including patients with anti-Hu ALE. Of note, only five to six of the included studies have a clear neuropsychological focus, whereas the other studies report data from less intensive neuropsychological testing. In the majority of studies, short screening instruments of cognitive functioning were applied. Given that impaired neuropsychological function is considered a core clinical symptom in ALE, this finding illustrates the so far unmet need for extensive detailed neuropsychological investigations in particular including psychometric data on psychological symptoms. Moreover, overall sample sizes are still very small.

Nevertheless, this review reveals that patients with ALE and AAB against LGII, CASPR2 and GAD65 show impairments in several aspects of cognitive functions and psychological health. Mostly, memory deficits are reported, but attention and executive functions including working memory and fluency, and psychological functions have also been observed in the abnormal range. This is in line with earlier reviews of ALE associated with LGII AABs and GAD65 AABs (see [10,13]).

4.1. Does AAB-status matter?

Comparing the different AAB-associated ALE subtypes, anti-LGII and anti-CASPR2 patients both show higher percentages of reported neuropsychological deficits than anti-GAD65 ALE patients before and after initiation of immunotherapy in the studies of this review. However, in our own cohort, Mueller et al. found no significant differences between AAB-defined subtypes in a large ALE patient cohort [69]. Considering the different methodological approaches employed in these primary studies, this does not definitively prove that anti-GAD65 ALE patients experience a lower prevalence of neuropsychological deficits. Moreover, it cannot be ruled out that impairments in anti-GAD65 ALE patients are equally prevalent but not severe enough to reach the cut-off score of $z < -1$ used here to identify a deficit.

In fact, this is supported by the results of the subgroup analysis of our meta-analysis of immunotherapy-naive ALE patients at baseline, which show a significantly worse MoCA score in anti-LGII ALE patients (18.96) compared to anti-GAD65 ALE patients (21.80). However, both groups are classified as moderately impaired. Further, this subgroup analysis is based on 8 studies with a total of 100 anti-LGII ALE patients and only 1 study with a total of five anti-GAD65 ALE patients (see Table 2). In a multiple meta-regression analysis combining baseline and treated subsamples, no effect for AAB was found for MoCA score. There is high chance that, due to variance within the population, these small subgroups may be not representative and therefore are less reliable than larger subgroups. This could also be the reason why we could not detect a significant difference between AAB-defined ALE subgroups at baseline using the MMSE score from the extracted data as the sample sizes were 146 anti-LGII ALE patients reported in a total of 14 studies and only 12 anti-GAD65 ALE patients reported in a total of 3 studies. Furthermore, the significant difference could also be derived from different sample mean ages of 55.86 [51.1–65.9] years in the anti-LGII ALE and 34.7 [27–49] years in the anti-GAD65 ALE sample (see Table 2). Since there are no detailed data reported in the studies, we could not analyze disease duration together with neuropsychological testing and so it is also possible that temporal differences in disease course contribute to the significant group difference here (see e.g.[70,71]). Thus, based on the currently available research, it is not possible to give patients a prognosis regarding their symptoms based on their AAB type. However, generalizability of our findings is limited by the fact that the meta-analysis could only include two AAB types.

4.2. Does immunotherapy exert an effect on neuropsychological symptoms?

Strikingly, as this review and meta-analysis show, neuropsychological deficits are reported in ALE before immunotherapy and after initiation of immunotherapy (see Table 1). Unfortunately, the primary studies do not permit an evaluation of psychological symptoms in our meta-analysis.

Concerning cognition, the meta-analysis resulted in a mean MMSE score of 23.00 (95 % CI: 20.74–25.21) from immunotherapy-naive anti-LGII ALE patients at baseline, while it was 26.53 (95 % CI 24.36–28.70) after initiation of immunotherapy in the follow-up subsamples. The mean MoCA score in anti-LGII ALE patients at baseline was 18.96, while it was 22.55 (CI: 2.62–42.49) in the treated subsamples and 22.63 (95 % CI 18.50–26.75) in the follow-up subsamples, which indicates a moderate impairment across all subsamples.

While anti-GAD65 ALE patients at baseline reached a MMSE score of 18.52 (95 % CI 6.64–30.40), it was 24.20 [95 % CI 20.54–27.86] in one reported subsample of anti-GAD65 ALE patients at follow-up.

Although highly suggestive, it cannot be proved that these differences are significant. Additionally, there is no definitive evidence that they could be attributed to immunotherapy. In fact, spontaneous improvements are reported in anti-LGII ALE patients in the natural course of the disease (see [49]). Irrespective of the underlying cause of the improvement, these data indicate persistent cognitive deficits despite immunotherapy, considering that mean MMSE score of anti-LGII ALE patients after initiation of immunotherapy is just above the pathological cut-off score, and that of anti-GAD65 ALE patients is still in the pathological range. The immunotherapy outcome as measured by the MoCA score in anti-LGII ALE patients at follow-up even indicates a persisting moderate cognitive impairment. Patients and clinicians should be aware that cognitive impairment may persist. There is not sufficient evidence to suggest a different prognosis depending on AAB type or immunotherapy.

Vrillon et al. support the persistence of cognitive impairment by reporting that in anti-GAD65 ALE patients, memory function outcome is generally poor after 1st line and even 2nd line immunotherapy [72]. In anti-LGII ALE, however, a good overall clinical outcome is reported. Importantly, Day in his comment stresses that physicians and researchers may overlook functional measures, such as the return to baseline cognitive capacity or resumption of gainful employment [73]. This is supported by Gibson et al., who state that cognitive impairment in anti-LGII ALE patients is generally poor after 1st line and even 2nd line immunotherapy [72]. In anti-LGII ALE, however, a good overall clinical outcome is reported. Importantly, Day in his comment stresses that physicians and researchers may overlook functional measures, such as the return to baseline cognitive capacity or resumption of gainful employment [73]. This is supported by Gibson et al., who state that cognitive impairment in anti-LGII ALE patients is generally poor after 1st line and even 2nd line immunotherapy [72]. In anti-LGII ALE, however, a good overall clinical outcome is reported. Importantly, Day in his comment stresses that physicians and researchers may overlook functional measures, such as the return to baseline cognitive capacity or resumption of gainful employment [73]. This is supported by Gibson et al., who state that cognitive impairment in anti-LGII ALE patients is generally poor after 1st line and even 2nd line immunotherapy [72]. In anti-LGII ALE, however, a good overall clinical outcome is reported. Importantly, Day in his comment stresses that physicians and researchers may overlook functional measures, such as the return to baseline cognitive capacity or resumption of gainful employment [73]. This is supported by Gibson et al., who state that cognitive impairment in anti-LGII ALE patients is generally poor after 1st line and even 2nd line immunotherapy [72]. In anti-LGII ALE, however, a good overall clinical outcome is reported. Importantly, Day in his comment stresses that physicians and researchers may overlook functional measures, such as the return to baseline cognitive capacity or resumption of gainful employment [73]. This is supported by Gibson et al., who state that cognitive impairment in anti-LGII ALE patients is generally poor after 1st line and even 2nd line immunotherapy [72]. In anti-LGII ALE, however, a good overall clinical outcome is reported. Importantly, Day in his comment stresses that physicians and researchers may overlook functional measures, such as the return to baseline cognitive capacity or resumption of gainful employment [73]. This is supported by Gibson et al., who state that cognitive impairment in anti-LGII ALE patients is generally poor after 1st line and even 2nd line immunotherapy [72]. In anti-LGII ALE, however, a good overall clinical outcome is reported. Importantly, Day in his comment stresses that physicians and researchers may overlook functional measures, such as the return to baseline cognitive capacity or resumption of gainful employment [73].
4.3. General limitations of the review and meta-analysis

There is some evidence from the literature that anti-LGI1 ALE patients experience a higher prevalence and severity of cognitive impairment compared to anti-GAD65 ALE patients as assessed by the MoCA score, whereas such evidence is lacking for the MMSE score. Cognitive symptoms appear to be milder at later points of time after initiation of immunotherapy as compared to earlier points of time prior to immunotherapy, but whether this can be attributed to immunotherapy itself or to the natural history of the disease remains unclear. Moreover, it remains unclear whether ALE with different AABs as associated with distinct cognitive impairments and whether they respond differently to immunotherapy.

To investigate these issues in ALE, more comprehensive psychometric test data including psychological symptoms with matched control groups obtained at predefined points in time during the disease course in longitudinal trials is required.

CRediT authorship contribution statement

Christoph Mueller: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. Sascha Elben: Data curation, Investigation, Methodology, Software, Visualization, Writing – review & editing. Gregory S. Day: Data curation, Investigation, Writing – review & editing. Pedro Alves: Data curation, Investigation, Writing – review & editing. Julien Hebert: Data curation, Investigation, Writing – review & editing. David F. Tang-Wai: Data curation, Investigation, Writing – review & editing. Olga Holtmann: Data curation, Investigation, Writing – review & editing. Raffaele Iorio: Data curation, Investigation, Writing – review & editing. Niels Hansen: Data curation, Investigation, Writing – review & editing. Thorsten Bartsch: Data curation, Investigation, Writing – review & editing. Andreas Johnen: Data curation, Methodology, Resources, Software, Writing – review & editing. Alice G. Willison: Data curation, Investigation, Writing – review & editing. Heinz Wiendl: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing. Sven G. Meuth: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing. Jens Bölte: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. Nico Melzer: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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Competing interests

The authors have no competing interests to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2022.107559.

References


