



Hippocampal dysfunction after autoimmune encephalitis depending on the antibody type

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Abstract

Background Comprehensive neurocognitive function analyses of autoimmune encephalitis (AE) patients, especially long-term ones, are rare. This study aims to measure cognitive function in patients diagnosed with AE.

Methods This case–control study included AE patients ($n = 11$) with antibodies against NMDA receptor (NMDAR) ($n = 4$), VGKC ($n = 3$), GAD (3), and one antibody-negative patient. The control group contained 12 pneumococcal meningitis patients (PC). Subgroup analyses compared AE patients with and without NMDAR antibodies. Neurocognitive tests were performed to evaluate verbal and visual memory, face recognition, attentional capacity, incidental learning capacity, and overall cognitive function (Montreal cognitive assessment, MoCA). Limbic structural involvement was assessed through magnetic resonance imaging (MRI). Statistical analyses investigated correlations between antibody status, results of neurocognitive tests, and MRI findings.

Results Follow-up (AE vs. PC) was 33 (11–95) vs. 96 (26–132) months after diagnosis. Neurocognitive functions were normal in both AE and PC groups in all tests except face recognition, which was pathological in both groups. The overall/recognition/long-delay visual memory ($p = 0.009/0.008/0.005$) and incidental learning ($p = 0.017$) scores were significantly higher in NMDAR patients compared to non-NMDAR patients. Non-NMDAR patients with right-sided limbic MRI pathologies had significantly lower overall/recognition/long-delay visual memory ($p = 0.006/0.044/0.024$) and incidental learning ($p = 0.009$) scores compared to NMDAR patients.

Conclusions We observed mainly normal neurocognitive functions after autoimmune and bacterial encephalitis. However, compared to NMDAR patients, patients with non-NMDAR autoimmune encephalitis showed a significant and material-specific association between a right-sided hippocampal lesion and limitations in figural-mnemonic and incidental learning capacities. Neurocognitive functions in AE patients should be further evaluated prospectively and in more detail.

Keywords Autoimmune encephalitis · Neurocognition · Hippocampus · Incidental learning · RVDLT · VLMT · MoCA · NMDA · GAD · LGI1 · Caspr2

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Introduction

Medial temporal lobe abnormalities, especially involvement of hippocampal structures, are a well-described imaging finding in patients with autoimmune encephalitis (AE) contributing to the syndrome of limbic encephalitis [1, 2]. Therefore, neurocognitive deficits are well-known symptoms in AE patients [1, 3–11]. Depending on the antibody type and the time of cognitive testing after symptom onset, different cognitive impairments were described for AE patients. In one study, 64 of 75 (85%) patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis had frontal lobe impairments such as problems with attention and planning, impulsivity, and behavioural disinhibition after discharge

[3]. Chen et al. found anterograde amnesia, emotional lability, and attentional difficulties among 4 of 16 patients with NMDARs one year after diagnosis [12]. A very extensive neuropsychological assessment showed deficits in attention (4/9), working memory (4/9), episodic memory (2/9), and executive functioning (5/9) in an NMDAR group of 9 patients at a median of 43 months after disease onset [4]. The most comprehensive longitudinal neuropsychological assessment of 43 NMDAR patients showed cognitive deficits in all patients 2 years after onset, with improvement in all cognitive domains 4.9 years after onset, but with persistent deficits in memory and executive functions [10]. AE patients with voltage-gated potassium channel (VGKC) antibodies also showed significant impairment in memory, processing speed, and executive function early during disease course and prior to immunotherapy; however, at follow-up, processing speed and executive function returned to normal, while cognitive impairment was limited to memory [13]. Neurocognitive outcomes in AE patients with autoantibodies to glutamic acid decarboxylase (GAD) were studied by Frisch et al. In contrast to VGKC patients, GAD patients showed less impaired learning and memory, but no improvement of these cognitive functions with immunotherapy [14]. Data on incidental learning, which is a mixture of attention, working memory, episodic memory, and executive function, are not available for AE patients to our knowledge.

The aim of our study was to measure cognitive functions in patients after autoimmune encephalitis associated with different AE antibodies and in a comparison group of patients with bacterial meningitis. Furthermore, we aimed to compare cognitive functions and imaging findings in AE subgroups (NMDAR vs. non-NMDAR patients).

Methods

Patients

We designed a single-center, case–control study to compare AE patients with sex- and age-matched patients with pneumococcal meningo-encephalitis (PC), treated at the University Hospital Dresden between January 2002 and March 2016. Patients were selected by retrospective review of electronic databases and chart review. The inclusion and exclusion criteria for AE and PC patients are described in detail in the Supplementary Material (Supplementary Figure S1). Established diagnostic criteria for possible AE were used as proposed by Graus et al., based on positive antibody findings in serum and/or cerebrospinal fluid as well as clinical symptoms [15]. The AE group includes 4 patients with antibodies to NMDAR, 3 with antibodies to VGKC, 3 with antibodies to GAD and 1 antibody-negative patient. Antibodies to NR1/NR2B heteromers of the NMDAR were detected through

indirect immunofluorescence on NR1/NR2B transfected human embryonic kidney cells for AE patients diagnosed in 2010 and 2011 [16, 17]. For all other AE patients, the antibodies were detected by indirect immunofluorescence on commercially available mouse brain tissue and cell-based assays (Euroimmun, Lübeck, Germany) [18]. Subgroup analyses between the NMDAR group and the non-NMDAR group (VGKC, GAD, antibody-negative) were performed. At the time of the initial treatment phase of study patients, routine tests were available for anti-VGKC, but not for anti-LGI1 and anti-Caspr2 for further differentiation.

All patients gave written informed consent. The study was approved by the ethics committee of the University of Dresden. Clinical variables and imaging data were analysed, followed by clinical follow-up between August and December 2016 for the comprehensive neurocognitive tests.

Clinical and functional variables of AE and PC patients in acute and post-acute phase

The following parameters were included: (1) demographics (sex, age), (2) clinical symptoms, (3) intensive care unit (ICU) treatment, (4) modified Rankin Scale (mRS) scale at disease onset and follow-up, (5) disease-specific treatment, (6) detection of malignancies, (7) MRI results regarding side of limbic MRI pathologies (e.g., temporomesial, temporobasal, hippocampus, and corpus amygdaloideum), (8) length of hospital stay, (9) relapses, (10) immunotherapy and antiepileptic therapy at follow-up, (11) anamnestic neurocognitive deficits at follow-up, and (12) learning capacity at follow-up.

Available cerebral MR images (FLAIR- and T2 sequences), performed for routine clinical care, were evaluated by a senior neuroradiologist. Three different MRI scanners were used (Siemens Magnetom Verio, 3.0 Tesla; Siemens Magnetom Vision, 1.5 Tesla; GE Signa HDxt, 3.0 Tesla), depending on the availability of the scanner in the clinical routine.

Neurocognitive assessment at follow-up

A cross-sectional study of recruited AE and PC patients was performed and included a neurological examination and neuropsychological testing. To characterise neurocognitive abilities, the following parameters were assessed: (1) Current anamnestic cognitive problems, (2) handedness, (3) aphasia score, and (4) Hospital Anxiety and Depression Scale (HADS). The aphasia score was used to rule out aphasia, potentially interfering with neurocognitive testing (Supplementary Figure S2). The HADS was used to exclude a possible depression or anxiety as an indication of

pseudo-dementia syndrome [19]. To assess verbal memory as a left hemispheric and left temporal function, such as verbal short-term and working memory, we used the Verbal Learning Memory Test (VLMT) [20]. Visual capacity was assessed using the Rey Visual Design Learning Test (RVDLT) and Alsterdorfer Faces Test (AFT) to assess right hemisphere functions including right temporal capacity for short and long memory [21–23]. Attentional capacity was measured using the Digit Symbol Substitution Test (DSST) as a correlate of the frontal lobe (Supplementary Material). To measure incidental learning capacity, we extended the DSST with a 2-min delay incidental learning query. The Montreal Cognitive Assessment Test (MoCA) was used to provide an overall impression of the patients' neurocognitive function and also to screen for mild cognitive impairment. [24]

Statistical analyses

The unpaired *t* test was used for metric data with a 95% confidence interval and reported as significant when $p < 0.05$. Nominal data were analysed using Fisher's exact test. The Mann–Whitney *U* test was used to analyse significant relations between pathological MRI findings and neurocognitive outcomes, the unpaired *t* test for metric data. The effect sizes for neurocognitive function were calculated using Cohen's *d*. We used the Shapiro–Wilk test due to the small sample size. The distribution results are presented in the Supplementary Material. Statistical analyses were performed using SPSS (V.23.0, IBM, Armonk, New York, USA).

Results

Clinical and functional variables in AE and PC patients in acute and post-acute phase

The median age (31 years, range 17–74) and sex distribution (8 women) of the 11 AE patients were not significantly different from the 12 PC patients (median age 41 years, range 26–52; 5 women). Of all AE patients, 8/11 had seizures, 4/11 patients extrapyramidal motoric symptoms, and 2 had pyramidal symptoms (Table 1). Furthermore, 9/11 AE patients suffered from cognitive symptoms, 5/11 from psychiatric symptoms, and 6/11 patients had autonomic dysregulations. A tumour was found in one AE patient (right amygdala and uncus gyri hippocampi) at onset and in further 3/11 patients (incidentaloma) at follow-up. ICU treatment was required in 6/11 AE patients with a median mRS of 3 points (range 2–5). Initially, 9/11 patients were treated with intravenous methylprednisolone, 4/9 patients in combination with intravenous

immunoglobulins (IVIG), and 2/9 in combination with immunoadsorption. From 4 of these 9 patients with first-line therapy, a second-line therapy with Rituximab was needed. The remaining 2/9 patients without methylprednisolone therapy were treated with antiepileptic drugs (detection of GAD antibodies was years later). The mean hospitalisation duration was 27.1 ± 15.8 days in the AE group and significant longer compared to the PC control group (15.7 ± 4.1 days, $p = 0.039$).

Initially, pathological MRI findings in limbic structures were found in 6/11 AE patients, which persisted in all available follow-up MRIs (median time of 4 months, range 1–71). Relapse was noted in 2 GAD patients. At follow-up, 4 AE patients were treated with oral prednisolone, one patient in combination with azathioprine. One AE patient was treated (repeatedly) with IVIG. Antiepileptic drug therapy was ongoing in 5 patients. Of all AE patients at the follow-up, 6/11 were fully employed, 4 patients in retirement and one got disability pension.

Neurocognitive function at follow-up in AE and PC patients

Follow-up after diagnosis was 33 (11–95) months in the AE group and 96 (26–132) months in the PC group. At follow-up, 6/11 patients with AE and 7/12 patients with PC reported cognitive problems like short- and long-term memory problems, impaired face recognition, amnesia, fears of failure, and impairment in multitasking skills ($p = 1.000$) (Table 2). All patients were right-handed except one NMDAR patient. The aphasia score, the HADS-D, and the HADS-A did not differ significantly (Supplementary Material). The overall verbal memory performance (VLMT) was in both groups (AE vs. PC) similar with a median of 52 (range 34–62) points vs. 51 (range 36–68) points ($p = 0.874$). The verbal recognition performance did not differ significantly between the AE (11 points, range 5–15) and PC group (13.5 points, range 10–15) ($p = 0.088$). The median overall visual performance (RVDLT) was not different in AEs (30 points, range 12–56) compared to PC patients (44.5 points, range 20–62), ($p = 0.193$). Furthermore, the visual recognition performance ($p = 0.378$) was not different in the AE group (11 points, range 6–15) compared to the PC group (13 points, range 8–15). The median percentage visual memory performance, using the AFT, was comparable in the AE group (55%, range 30–95) and in the PC group (65%, range 15–100) ($p = 0.830$). The median attentional capacity (DSST) was not different in the AE group (58 points, range 20–77) and in the PC group (46.5 points, range 28–64) ($p = 0.421$). Furthermore, incidental learning was comparable in both groups (AE: median score 5, range 0–9; PC: median score 7.5, range 1–9) ($p = 0.220$). Cognitive function

Table 1 Patient characteristics in AE and PC groups

	AE group	PC group	<i>p</i> value
Patients, <i>n</i>	11	12	–
Ratio female: male	8:3	5:7	<i>p</i> =0.214
Age, at diagnosis (years), median [range]	31 [17–74]	41 [26–52]	<i>p</i> =0.984
Antibodies against, <i>n</i>			
Synaptic receptors: NMDAR	4	–	–
Ion channels: VGKC (LGII, Caspr2)	3	–	–
Intracellular antigen: GAD	3	–	–
Antibody negative	1	–	–
Intensive care unit stay, <i>n</i>	6	12	<i>p</i> =0.014
mRS score, median [range]			
Acute (maximum mRS score)	3 [2–5]	5 [2–5]	<i>p</i> =0.014
Follow-up	1 [0–1]	1 [0–4]	<i>p</i> =0.236
Acute therapy, <i>n</i>			
Intravenous corticosteroids	9	12	0.217
Intravenous immunoglobulins	4	0	–
Immunoadsorption	2	0	–
Second line therapy, <i>n</i>			
Rituximab	4	0	–
Limbic MRI pathologies, <i>n</i>	6	0	<i>p</i> =0.018
Hospitalisation time (d), mean, [range]	27.1 [6–48]	15.7 [10–25]	<i>p</i> =0.039
Time from diagnosis to follow-up (mo), median, [range]	33 [11–95]	96 [26–132]	<i>p</i> =0.008
Relapse, <i>n</i>	2	0	<i>p</i> =0.217
Therapy at follow-up, <i>n</i>			
Immunotherapy	5	0	<i>p</i> =0.014
Antiepileptic drugs	5	0	<i>p</i> =0.014
Anamnestic, neurocognitive symptoms at follow-up, <i>n</i>	6	7	<i>p</i> =1.000
Fully employed, if not retired at follow-up, <i>n</i>	9	11	<i>p</i> =0.590

AE Autoimmune encephalitis; Caspr2 Contactin-associated protein-like 2; *d* Days; GAD Glutamate acid decarboxylase; HADS-D Hospital anxiety and depression scale; LGII Leucine-rich glioma inactivated 1; *mo* Months; MoCA Montreal cognitive assessment; mRS Modified Ranking Scale; *n* Number; NMDAR N-methyl-D-aspartate Receptor; PC Pneumococcal meningo-encephalitis; VGKC Voltage-gated potassium channels, *yrs* Years

Table 2 Neurocognitive function at follow-up in AE and PC groups

	AE group	PC group	<i>p</i> value	Effect size
VLMT overall, mean (SD)	49.6 (8.6)	50.3 (9.7)	<i>p</i> =0.874	<i>d</i> =−0.076
VLMT recognition, mean (SD)	11.1 (3.3)	13.0 (1.7)	<i>p</i> =0.088	<i>d</i> =−0.734
RVDLT overall, mean (SD)	33.6 (15.2)	41.3 (12.6)	<i>p</i> =0.193	<i>d</i> =−0.554
RVDLT recognition, mean (SD)	10.9 (3.3)	12.0 (2.5)	<i>p</i> =0.378	<i>d</i> =−0.378
AFT, mean (SD)	59.1 (20.8)	57.1 (23.3)	<i>p</i> =0.830	<i>d</i> =0.090
DSST, mean (SD)	52.0 (18.9)	46.6 (12.3)	<i>p</i> =0.421	<i>d</i> =0.342
DSST incidental, mean (SD)	5.1 (3.3)	6.7 (2.7)	<i>p</i> =0.220	<i>d</i> =−0.533
MoCA, mean (SD)	25.8 (3.3)	27.2 (2.6)	<i>p</i> =0.281	<i>d</i> =−0.474

AE Autoimmune encephalitis; AFT Alsterdorfer faces test; DSST Digit symbol substitution test; MoCA Montreal cognitive assessment; PC Pneumococcal meningo-encephalitis; RVDLT Rey visual design learning test; SD Standard deviation; VLMT Verbal learning memory test

according to MoCA was similar in both groups, 27 (range 17–29) points in the AE group vs. 27.5 (range 22–30) points in the PC group (*p*=0.281).

MRI findings in AE and PC patients

In 6/11 AE patients, limbic MRI pathologies were present at the time of initial hospital MRI and at all follow-up MRIs [median time 4 (range 1–71) months] (Fig. 1). The remaining 5/11 AE patients and all PC patients had no limbic MRI pathologies both in the early phase and during all follow-ups ($p=0.018$). The limbic MRI pathologies were on the right hemisphere in 5/6 patients and on the left hemisphere in one patient. Patients with limbic MRI pathologies ($n=6/19$) had a significantly worse visual figural function in the overall RVDLT (25.5 ± 13.6 , $p=0.018$) compared to the patients without limbic MRI pathologies (41.5 ± 11.8 , $n=13/19$). Furthermore, the group of patients with limbic MRI pathologies, compared to patients without MRI pathologies, had significantly lower incidental learning results in the DSST ($p=0.005$). Patients with limbic MRI pathologies had a mean incidental DSST score of $3.2 (\pm 3.1)$, the group without a score of $7.0 (\pm 2.0)$.

Clinical and functional variables in NMDAR and non-NMDAR patients in acute and post-acute phase

Patients of the NMDAR group (4/4 women, median age 19 years, range 17–29) were significantly younger at disease onset than patients of the non-NMDAR group (4/7 women, median age 58 years, range 23–74) ($p=0.006$). The median length of hospital stay was significantly different between the two groups (NMDAR vs. non-NMDAR: 42 days vs. 15 days) ($p=0.023$) (Table 3). The results of antibody testing in cerebrospinal fluid and serum in NMDAR and non-NMDAR

groups in acute and post-acute phase are reported in the Supplementary material (Supplementary Table 1).

Neurocognitive function at follow-up in NMDAR and non-NMDAR patients

Follow-up after diagnosis was 83 (20–95) months in the NMDAR group and 28 (11–85) months in the non-NMDAR group. At follow-up, 1/4 NMDAR patient reported short-term memory problems, whereas 5/7 non-NMDAR patients reported anamnestic cognitive problems in short- and long-term memory, in multitasking skills, fears of failure, and face recognition ($p=0.242$). The aphasia score and levels of HADS-A and HADS-D were not significantly different (Supplementary Material). The NMDAR group had a not significant ($p=0.073$) different overall verbal memory performance (VLMT) (median 56 points, range 53–58) compared to the non-NMDAR group (median 45 points, range 34–62). (Table 4). Furthermore, the verbal memory recognition test showed no significant difference ($p=0.098$) between the NMDAR group (median 13.5 points, range 11–15) and the non-NMDAR group (median 10.0 points, range 5–15). NMDAR patients showed a statistically significant higher median (13.5 points, range 11–15) in the long recall of the VLMT ($p=0.016$) compared to the non-NMDAR patients (median 7 points, range 5–14) (Fig. 2). In the overall visual performance (RVDLT), the NMDAR group (median 46.5 points, range 42–56) performed better than the non-NMDAR group (median 25 points, range 12–50) ($p=0.009$). Moreover, the NMDAR patients showed a significant difference ($p=0.008$) in the visual recognition performance test (median 14 points, range 13–15) compared

Fig. 1 Limbic MRI pathologies in a patient with GAD antibodies, Representative MRI findings in a patient with right-hippocampal necrosis and temporomesial space-occupying effects in the right amygdala complex, hippocampus, and nucleus accumbens. **A** T2-weighted sequence, axial; **B** FLAIR-sequence, coronary (source: University Hospital Dresden, Department of Neuro-radiology)

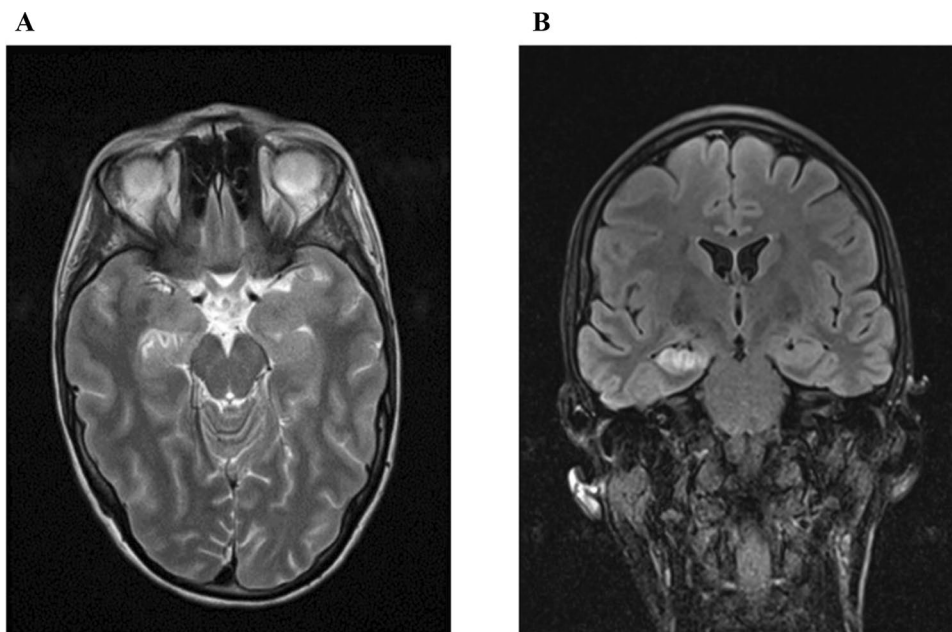


Table 3 Patient characteristics in NMDAR and non-NMDAR groups

	NMDAR patients	non-NMDAR patients	p value
Patients, n	4	7	–
Ratio female: male	4: 0	4: 3	$p=0.236$
Age, at diagnosis (years), median [range]	19 [17–29]	58 [23–74]	$p=0.006$
Clinical symptoms, n			
Seizure	3	5	$p=1.000$
Extra pyramidal motoric symptoms	3	1	$p=0.088$
Pyramidal symptoms	0	2	$p=0.491$
Cognitive symptoms	4	5	$p=0.491$
Psychiatric symptoms	3	2	$p=0.242$
Autonomic dysregulation	2	4	$p=1.000$
Tumour, n	1	3	$p=1.000$
Intensive care unit stay, n	4	2	$p=0.061$
mRS score, median [range]			
Acute (maximum mRS score)	3 [3–5]	2 [2–4]	$p=0.166$
Follow-up	0 [0–1]	1 [0–1]	$p=0.166$
Acute therapy, n			
Intravenous corticosteroids	4	5	$p=0.491$
Intravenous immunoglobulins	3	1	$p=0.088$
Immunoadsorption	0	2	$p=0.491$
Second line therapy, n			
Rituximab	3	1	$p=0.088$
Limbic MRI pathologies, n			
Right side: left side	0	5: 1	$p=0.015$
Hospitalisation time (d), mean, [range]	40.5 [33–45]	19.4 [6–48]	$p=0.023$
Time from diagnosis to follow-up (mo), median, [range]	83 [20–95]	28 [11–85]	$p=0.121$
Relapse, n	0	2	$p=0.491$
Therapy at follow-up, n			
Immunotherapy	0	5	$p=0.061$
Antiepileptic drugs	0	5	$p=0.061$
Anamnestic, neurocognitive symptoms at follow-up, n	1	5	$p=0.242$
Fully employed, if not retired at follow-up, n	3	6	$p=1.000$

Caspr2 Contactin-associated protein-like 2; *d* days; *GAD* Glutamate acid decarboxylase; *HADS-D* Hospital anxiety and depression scale; *LGII* Leucine-rich glioma inactivated 1; *mo* Months; *MoCA MONTREAL* cognitive assessment; *mRS* Modified ranking scale; *n* Number; *NMDAR* *N*-methyl-*D*-aspartate Receptor; *non-NMDAR* Without *N*-methyl-*D*-aspartate Receptor; *PC* Pneumococcal meningo-encephalitis; *VGKC* Voltage-gated potassium channels; *yrs* Years

to the non-NMDAR patients (median 9 points, range 6–14). Also, NMDAR patients had a significantly higher median (13.5, range 9–15) in the long-recall RVDLT ($p=0.005$) compared to the non-NMDAR patients (median 5 points, range 3–12). The visual performance, measured by the AFT, was not significantly different between the NMDAR patients with a median of 67.5 points (range 35–95) compared to the non-NMDAR patients who scored a median of 55 points (range 30–80) ($p=0.418$) (Fig. 3). Thereof, only 2/4 of the NMDAR patients and 1/7 of non-NMDAR patients achieved a normal AFT result. There were no significant differences ($p=0.090$) in the DSST scores between the NMDAR group (median 64 points, range 58–73) and the non-NMDAR group (median 37 points, range 20–77). The incidental

learning was significantly better in the NMDAR group (median 8.5 points, range 6–9) than in the non-NMDAR group (median 3 points, range 0–9) ($p=0.017$). The MoCA results were similar in both groups with 27.5 (range 26–28) points in the NMDAR group vs. 26 (range 17–29) points in the non-NMDAR group ($p=0.292$).

MRI findings in NMDAR and non-NMDAR patients

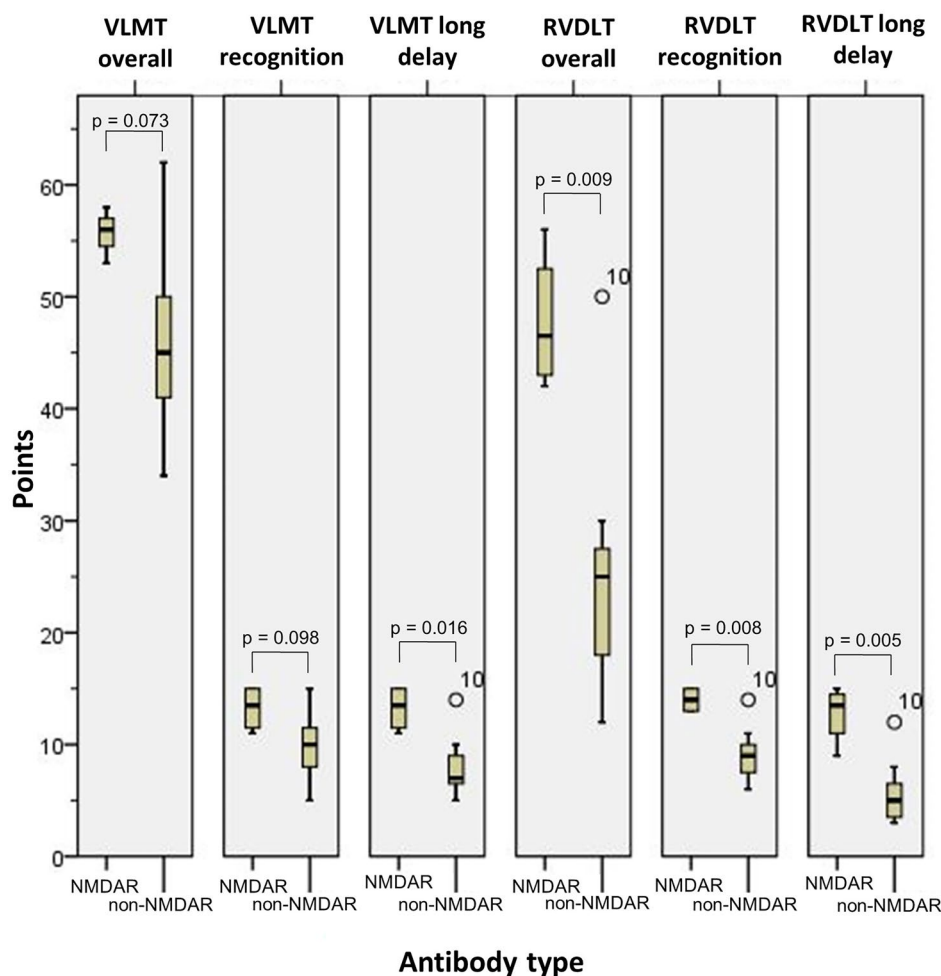
In contrast to 6 out of 7 patients in the non-NMDAR group, none of the 4 NMDAR patients exhibited limbic MRI pathologies at the onset of the disease or in any follow-up MRIs [mean follow-up time of 13.3 (± 21.7) months; $p=0.015$]. Patients with a limbic MRI pathology

Table 4 Neurocognitive function in NMDAR and non-NMDAR groups

	NMDAR group	non-NMDAR group	p value	Effect size
VLMT overall, mean (SD)	55.8 (2.1)	46.1 (9.1)	$p=0.073$	$d=1.289$
VLMT recognition, mean (SD)	13.3 (2.1)	9.9 (3.3)	$p=0.098$	$d=1.151$
VLMT long delay, mean (SD)	13.3 (2.1)	8.1 (3.0)	$p=0.016$	$d=1.903$
RVDLT overall, mean (SD)	47.8 (6.2)	25.4 (12.4)	$p=0.009$	$d=2.086$
RVDLT recognition, mean (SD)	14.0 (1.2)	9.1 (2.7)	$p=0.008$	$d=2.120$
RVDLT long delay, mean (SD)	12.8 (2.6)	5.7 (3.3)	$p=0.005$	$d=2.302$
AFT, mean (SD)	66.3 (26.6)	55.0 (17.8)	$p=0.418$	$d=0.534$
DSST, mean (SD)	64.8 (7.4)	44.7 (20.0)	$p=0.090$	$d=1.191$
DSST incidental, mean (SD)	8.0 (1.4)	3.4 (2.9)	$p=0.017$	$d=1.839$
MoCA, mean (SD)	27.3 (1.9)	25.0 (3.9)	$p=0.292$	$d=0.683$

AFT Alsterdorfer Faces Test; DSST Digit symbol substitution test; MoCA Montreal cognitive assessment; NMDAR N-methyl-D-aspartate Receptor; non-NMDAR Without N-methyl-D-aspartate Receptor; RVDLT Rey visual design learning test; SD Standard deviation; VLMT Verbal learning memory test

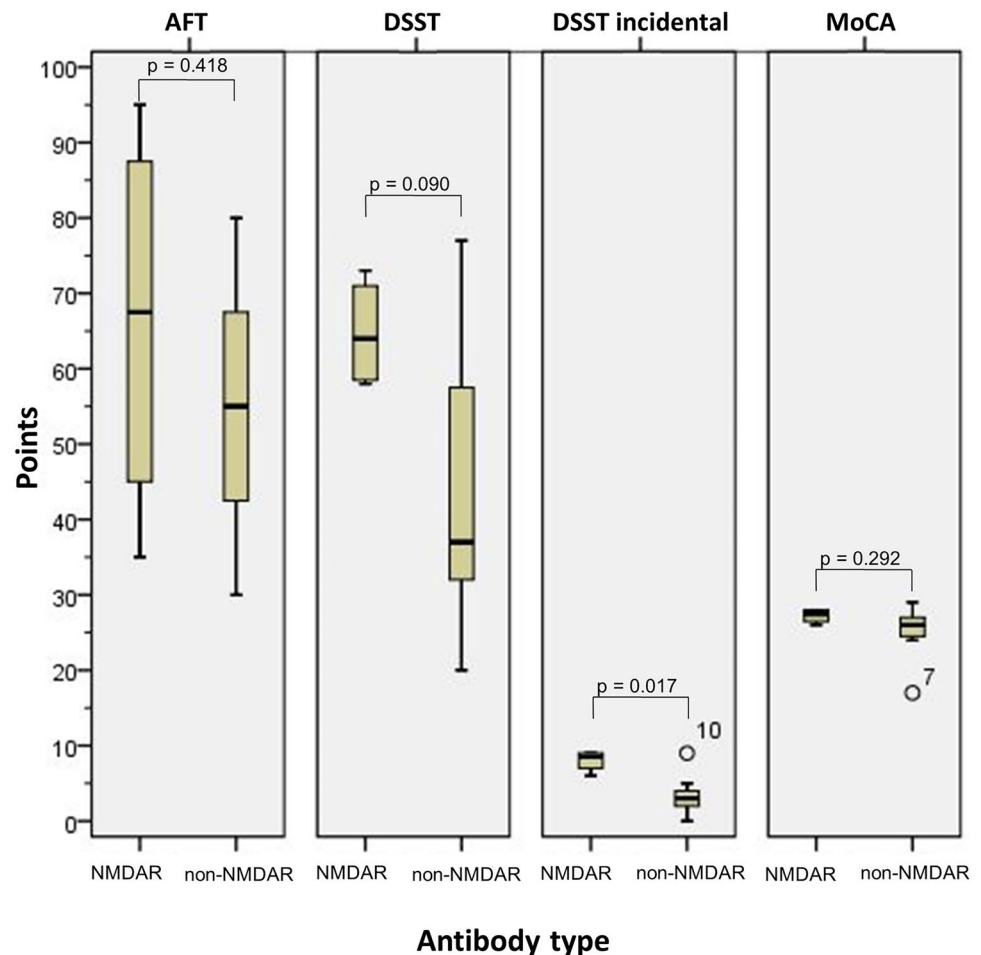
Fig. 2 VLMT overall, recognition and long delay, RVDLT overall, recognition, and long delay in NMDAR and non-NMDAR patients NMDAR N-methyl-D-aspartate Receptor; non-NMDAR without N-methyl-D-aspartate Receptor; RVDLT Rey visual design learning test; VLMT Verbal learning memory test



on the right side ($n=5$) compared to those without limbic MRI pathologies ($n=5$) had significant worse results in the overall RVDLT [mean 20.6 (± 7.1) vs. 43.2 (± 11.5), $p=0.006$], recognition RVDLT [mean 8.6 (± 1.8) vs. 12.6 (± 3.3), $p=0.044$], long-delay RVDLT [mean 4.8 (± 2.0)

vs. 11.0 (± 4.5), $p=0.024$], long-delay VLMT [mean 7.2 (± 1.9) vs. 12.0 (± 3.3), $p=0.023$], and incidental DSST [mean 2.0 (± 1.2) vs. 7.4 (± 1.8), $p=0.001$]. The median duration between the last MRI and neurocognitive test for

Fig. 3 AFT, DSST overall and incidental and MoCA in NMDAR and non-NMDAR patients *AFT* Alsterdorfer faces test; *DSST*, Digit symbol substitution test; *MoCA* Montreal cognitive assessment; *NMDAR* N-methyl-D-aspartate Receptor; *non-NMDAR* without N-methyl-D-aspartate Receptor



the five patients with limbic pathologies on the right hemisphere was 25 (range 11–69) months.

Discussion

Neuropsychiatric symptoms and prolonged neurocognitive deficits in AE patients and its relationship especially with impaired limbic functions were described in several studies [1, 3–11]. In addition to these studies, we were able to show a predominant right-hippocampal dysfunction and impaired incidental learning after autoimmune encephalitis, depending on the AE antibody type. Overall cognitive performance at long-term follow-up was normal in the AE group, except for the visual capacity assessed using the Alsterdorfer Faces Test. However, in subgroup analyses, the NMDAR group performed numerically better than the non-NMDAR group on almost all neurocognitive tests and significantly better on right-hippocampal functions (RVDLT) and incidental learning (DSST). Additional analyses showed that AE patients with right-sided limbic MRI pathologies had significantly worse results on the overall/recognition/long-delay RVDLT

and worse incidental learning skills (DSST) compared to those without limbic MRI pathologies. To our knowledge, these findings were not previously reported in AE patients.

Several aspects of our findings need to be discussed. First, NMDAR patients may experience greater neurocognitive improvement following AE in comparison to non-NMDAR patients, potentially attributable to differing pathophysiological pathways in these AE subgroups. Due to antibody-mediated capping and internalisation of NMDARs from the cell surface, NMDAR antibodies cause a reversible and selective decrease of NMDARs [25]. This leads to a higher chance of lack of structural damage to neurons, that NMDAR patients potentially respond well to early immunosuppressive treatment, depending on the length and peculiarity of antibody exposure [26]. In the previous studies, the longest median follow-up to date was 4.9 years, with improvement in all cognitive domains but persistent deficits in memory and executive function in 43 NMDAR patients [10]. In contrast, our NMDAR cohort was assessed at a median of 6.9 years after symptom onset and showed no neurocognitive impairment other than pathological AFT. This may indicate that neurocognitive recovery may

be more substantial in the long-term than was previously assumed. However, a “good” functional outcome does not always guarantee complete recovery, as long-term cognitive impairments and fatigue may occur [7]. However, for patients with VGKC antibodies targeting ion channels and those with GAD antibodies targeting intracellular antigens, a less effective response to immunotherapy was described [13, 27]. These different group results between the NMDAR and non-NMDAR group, depending on the antibody type, were also seen in olfactory function/impairment, while both cognition and olfaction are related to hippocampal structures [28]. Particularly, the non-NMDAR group had significant lower odour discrimination values compared to the NMDAR group, considering that odour discrimination is related as a higher cognitive function. [28, 29]

Second, patients without limbic MRI pathologies had significant better results in visual figural functions and incidental learning compared to those with limbic MRI pathologies. Moreover, if the limbic MRI pathology was on the right hemisphere, both the visual figural function and the incidental learning capabilities were significantly lower compared to patients with normal MRI. This was observed in the complete AE group and the subgroup analyses. The significant better results in the NMDAR group may be attributable to a lesser extent of limbic damage, as discussed before. Finke and colleagues reported a correlation between verbal memory performance and total left hippocampal volume as well as presubiculum in 40 NMDAR patients. However, no significant correlations between hippocampal volumes and visuospatial memory performance were found in this and another previous study [1, 5]. Correspondingly, Wagner et al. could show a predominant affection of the amygdala in the early disease stage of VGKC- and GAD-associated AE, which resolved during the later course of disease [30]. Persisting MRI abnormalities have been observed following VGKC- and GAD-antibody positive encephalitides; however, no correlations between MRI laterality and neuropsychological outcomes were reported in an earlier study [14]. Of note, Wagner et al. found a negative correlation of diffusivity parameters with figural memory performance located mainly in the right temporal lobe in GAD patients in 2015 [2]. It is therefore a new finding of our study that abnormalities in the right hippocampus, particularly in GAD and VGKC patients, are associated with poorer performance on the RVDLT and incidental learning.

Third, we would like to discuss the RVDLT as a tool for right-hippocampal damage. Currently, there is a lack of neuropsychological tests to assess right temporal lobe memory function in patients with temporal lobe epilepsy (TLE) [23]. Typically, the Wechsler Memory Scale or the Rey Complex Figure Test is used for non-verbal memory function; however, these tests are considered inadequate for lateralising the epileptic focus in epilepsy surgery candidates with unilateral

right TLE [23, 31, 32]. As discussed by Benger et al., a number of studies have failed to find differences, e.g., in face memory between left and right TLE patients and in pre- and postoperative face recognition after right temporal lobectomy. We suggest that the RVDLT may be used as a tool to detect right-hippocampal dysfunction, analogous to the AFT established by Benger et al. in 2009, as it is known that the right temporal lobe represents face recognition memory and the RVDLT correlates with white matter structure [23, 33–35]. In 14 healthy subjects, Bègrè et al. were able to show a significant and direct relationship between 11 clusters of intervoxel coherence using diffusion tensor imaging in the left and right dorsal hippocampal commissure, posterior cingulate, right medial orbitofrontal regions, and other limbic brain areas with visual memory performance. [35]

In relation to the aforementioned findings, we acknowledge the various methodological limitations of this study. The most significant limitation concerns the small sample size and the heterogeneity of different antibody types, which affects the interpretation of our findings. For upcoming studies, neurocognitive sequelae after AE should be assessed prospectively in larger prospective multi-centre, case–control studies with sufficiently large subgroups defined by AE antibodies [36]. To improve understanding of neurocognitive function after AE, it is advisable to assess the neurocognitive battery not only in the long term, but also in the early treatment phase. Furthermore, sequential MRI studies should be performed between disease onset and follow-up to characterise limbic changes over time and in more detail. In our study, we did not distinguish between patients with anti-LGI1 and anti-Caspr2 among our cohort of VGKC-positive patients, although this is meanwhile established [37]. We have added one antibody-negative patient with AE to the non-NMDAR group as we focussed on characterising NMDAR and non-NMDAR subgroups. However, it is possible that autoimmune encephalitis in seronegative patients is mediated by NMDAR-like or other unknown cell surface AE antibodies, potentially resulting in effects on neurocognitive function comparable to NMDAR patients. Another limitation is the significant higher age of the non-NMDAR group compared to the NMDAR group. The higher age might affect neurocognitive function negatively [38–40]. We did not apply age correction and sensitivity analyses due to the small sample size. Moreover, as there have been no previous measurements of incidental learning levels in the Digit Symbol Substitution Test, there are no values to compare. Currently, it is recommended to validate the results of incidental learning in the DSST using healthy cohort. Finally, the selection of our comparison group of bacterial meningitis is debatable. As alternative, patients with Herpes simplex virus (HSV) encephalitis could serve as an appropriate control population [41, 42]. However, due to the known higher mortality rate compared to AE and its very low incidence, we were concerned that we would not be able to recruit enough control

subjects [41–43]. In future, larger studies on cognitive functions in AE patients, patients affected by HSV encephalitis may also serve as a control group.

Conclusion

The results of our study show mainly normal neurocognitive functions after NMDAR encephalitis in the long term. However, patients with non-NMDAR autoimmune encephalitis have impaired right-hippocampal neurocognitive functions and reduced incidental learning capacities, most likely due to structural damages of the limbic system. Additionally, we propose the RVDLT as a novel tool for detecting right-hippocampal dysfunction.

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Data availability The data used in this article were provided by the Department of Neurology, University Hospital Dresden, Dresden, Germany. Anonymized data are available on reasonable request.

Declarations

Conflicts of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval The ethical approval was given by the Ethics Committee of the University of Dresden [EK 104032016, EK 125042012]. The study was performed by the Declaration of Helsinki (1964). All patients gave written informed consent.

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