Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Patients

Patients were only included and considered for the study when they were able to give informed consent to participate in the study. Patients with both SCLC and NSCLC were grouped as SCLC as this was medically and biologically considered the predominant tumor type at the time of study inclusion.

All patients who were considered for the study underwent a detailed and extensive neurological exam. In case of new neurological deficits identified as part of this exam, further diagnostic work-up including brain MRI scans were performed. Any sign of brain metastasis or new lesion identified here led to exclusion of the patient from neuropsychological evaluation.

Exclusion criteria for neuropsychological testing included presence of clinical factors with potential effect on cognitive function, age over 80 years, decreased alertness, or ECOG status of 4 and higher: 27 patients were either subjectively or objectively evaluated not fit for further testing (ECOG of 4 or higher, reduced alertness or declined further tests), and 43 patients had potential confounding factors for cognitive impairment: brain metastases (n=15), history of severe neurological or psychiatric diseases with potential effect on cognition (stroke, epilepsy, dementia, severe depression (n=13), history of cranial irradiation (n=13), and two patients were excluded due to age over 80 years. The initial exclusion criteria for time after surgery were set to <5 days. However, the actual median time from surgery to neuropsychological testing was 7 months. Only 4 patients were tested less than one month post-surgery (median 6 days (range 5-8). We did not find any associations of surgery with cognitive impairment in our sample.

All patients were tested in one session on the same day with the same test order. The number of tests and test duration is similar to that of a neuropsychological evaluation applied in the clinical routine.

eMethods 2. Neuronal Autoantibody Analysis

Antibody detection was performed using well-established commercial assays including cell-based assays (CBA) and frozen brain tissue sections using immunohistochemistry (IHC) (Institute of Experimental Immunology, Euroimmun AG, Lübeck, Germany). Briefly, neuronal antibodies were detected by indirect immunofluorescence using BIOCHIP mosaics™: BIOCHIPS contained both frozen brain tissue sections (rat hippocampus, rat cerebellum, monkey cerebellum) and different fixed recombinant HEK293-cells each expressing a single neuronal antigen (NMDAR-NR1a/NR1a, GABA-b (GABAR-B1/B2), GABA-a (GABARA1+GABARB3), AQP4, LGI1, CASPR2, GluRD2, MOG, DPPX, IgLON5, AMPA1/2, GRM1, GRM5, pre-GLRA1b, Flotilin, DNER, AT1A3, Neurochondrin, Yo, ZIC4, ARHGAP26, GAD65, GAD67, Amphiphysin, CV2, Hu, Ri, CARPVIII, ITPR1, Homer3, Recoverin, Ma2). Biochip mosaics were incubated with different dilutions of patients' serum (initial dilution 1:10), washed, and incubated with fluorescein-labelled anti–human immunoglobulin (anti-IgG, in addition anti-IgM and -IgA for NMDAR) before evaluating fluorescence comparing against empty-vector transfected cells as negative control. Immunoblot assays (EUROLINE) were additionally used to confirm CBA or IHC results for intracellular antigens (Amphiphysin, CV2, Ma2, Ri, Yo, Hu, Recoverin, SOX1, Zic4, GAD65, DNER).

eMethods 3. Neuropsychological Tests

Cognitive function was assessed status using a battery of ten standardized neuropsychological tests covering all cognitive domains: Verbal Learning and Memory Test (VLMT), a German version of the Rey Auditory-Verbal Learning Test (RAVLT) for verbal short-term and long-term memory;[1] Rey-Osterrieth Complex Figure test (ROCF) for visuospatial memory;[2] the digit span forward and backward task, a component of the Wechsler Memory Scale (WMS), for short-term and working memory; the computerized test battery for attention (Testbatterie für Aufmerksamkeit, TAP) evaluating attention (TAP alertness and TAP divided attention) and executive function (TAP Go/NoGo)[3] with the additional the Stroop color-word test. Semantic fluency was examined using the Regensburger word fluency test.[4] Fluid intelligence and abstract reasoning abilities were assessed by the subtest 3 of the Leistungsprüfungssystem (LPS)[5], a German equivalent of Raven's Progressive Matrices. Crystallized intelligence was estimated using the Mehrfachwahl-Wortschatz-Intelligenztest-A (MWT-A)[6], a German equivalent of the National Adult Reading Test (NART).

Patient-reported outcome measures (PROMs) included the FACIT Fatigue Scale (Version 4), the Short-Form-12 (SF-12) assessment scale, a brief version of the Short-Form-36 (SF-36) Health Survey Scale, evaluating physical and mental health-related quality of life, the Beck Depression Inventory-Fast Screen (BDI-FS), and a screen for subjective cognitive deficits. The Eastern Cooperative Oncology Group (ECOG) Performance Status measuring activities of daily living was completed by the investigator performing the examination.

eTable 1. Prevalence of Brain Tissue Staining in Patients With Lung Cancer: SCLC vs NSCLC

	All patients (n=167)		**SCLC patients (n=40)***		**NSCLC patients (n=127)**	
	No. *	***% **	**No. ***	***% **	**No. ***	***% **
Tissue staining positive	38	*22.8*	13	*32.5*	25	*19.7*
Negative on cell-based assay (CBA)	28	*16.8*	4	*10.0*	24	*18.9*
Tissue type						
Hippocampus (rat)	21	*12.6*	11	*27.5*	10	*7.9*
Cerebellum (rat)	31	*18.6*	11	*27.5*	20	*15.7*
Cerebellum (monkey)	34	*20.4*	12	*30.0*	22	*17.3*
Number of stained tissues†						
One	7	*4.2*	1	*2.5*	6	*4.7*
Two	14	*8.4*	3	*7.5*	11	*8.7*
Three	17	*10.2*	9	*22.5*	8	*6.3*

*Numbers do not add up due to combination of tissue staining. †Combinations of tissue staining include: One tissue: CM (n=4), CR (n=1), HR (n=2). Two tissues: CR+CM (n=12), CR+HR (n=1), CM+HR (n=1). *(CM=Cerebellum monkey, CR=Cerebellum rat, HR=Hippocampus rat).*

eTable 2. Demographic Characteristics of Patients by Antibody

Lung Cancer Patients (n=167)	Total (n=167)*	C- (n=107)	AICAbs (n=17)	NSAbs (n=18)	uAbs (n=28)
Age					
Median (range)	66.0 (38-88)	67.0 (38-88)	64.0 (51-80)	63.5 (47-79)	66.0 (54-79)
Sex					
Male	105 *(62.9)*	63 *(58.9)*	12 *(70.6)*	14 *(77.8)*	18 *(64.3)*
Female	62 *(37.1)*	44 *(41.1)*	5 *(29.4)*	4 *(22.2)*	10 *(35.7)*
Lung Cancer Subtype					
Small Cell Lung Cancer (SCLC)	38 *(22.8)*	20 *(18.7)*	12 *(70.6)****[1]	4 *(22.2)*	4 *(14.3)*
Non Small Cell Lung Cancer (NSCLC)					
Adenocarcinoma	61 *(36.5)*	39 *(36.4)*	3 *(17.6)*	9 *(50.0)*	11 *(39.3)*
Squamous Cell Carcinoma	43 *(25.7)*	28 *(26.2)*	2 *(11.8)*	2 *(11.1)*	11 *(39.3)*
Other[4]	22 *(13.8)*	17 *(15.9)*	0 *(0.0)*	3 *(16.7)*	2 *(7.1)*
Combined Carcinoma (SCLC+NSCLC)	3 *(1.8)*	3 *(2.8)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*
Clinical Stage (UICC 2010)					
Stage I	17 *(10.2)*	13 *(12.1)*	0 *(0.0)*	0 *(0.0)*	4 *(14.3)*
Stage II	12 *(7.2)*	5 *(4.7)*	0 *(0.0)*	1 *(5.6)*	6 *(21.4)*
Stage III	42 (25.1)	24 *(22.4)*	10 *(58.8)**[2]	6 *(33.3)*	4 *(14.3)*
Stage IV (metastases)	93 (55.7)	64 *(59.8)*	7 *(41.2)*	11 *(61.1)*	12 *(42.9)*
unknown	3 *(1.8)*	1 *(0.9)*	0 *(0.0)*	0 *(0.0)*	2 *(7.1)*
Site of metastases					
Lung / Pleura / Pericardium (M1a)	67 *(40.1)*	47 *(43.9)*	5 *(29.4)*	6 *(33.3)*	10 *(34.5)*
Brain	13 *(7.8)*	8 *(7.5)*	1 *(5.9)*	2 *(11.1)*	2 *(6.9)*
Other distant metastases (M1b)[5]	56 *(33.5)*	38 *(35.5)*	5 *(29.4)*	7 *(38.9)*	7 *(25.0)*
Treatment					
Treatment naive	45 (26.9)	31 *(29.0)*	3 *(17.6)*	3 *(16.7)*	8 *(27.6)*
Chemotherapy (prior and/or current)[6]	91 (54.5)	57 *(53.3)*	12 *(70.6)*	12 *(66.7)*	13 *(46.4)*
Radiotherapy (prior and/or current)					
Local radiation (primary tumor)	47 *(28.1)*	28 *(26.2)*	5 *(29.4)*	7 *(38.9)*	9 *(32.1)*
Brain radiation	10 *(6.0)*	7 *(6.5)*	1 *(5.9)*	1 *(5.6)*	1 *(3.6)*
Surgery of primary tumor[7]	38 (22.8)	21 *(19.6)*	4 *(23.5)*	7 *(38.9)*	7 *(24.1)*

Surgery of metastases	5 *(3.0)*	5 *(4.7)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*
Targeted Therapy [8]	8 *(4.8)*	4 *(3.7)*	0 *(0.0)*	3 *(16.7)**[3]	1 *(3.4)*
Immunotherapy (IVIGs)	3 *(1.8)*	1 *(0.9)*	1 *(5.9)*	1 *(5.6)*	0 *(0.0)*
Time since initial diagnosis (months)					
Median (range / IQR)	2.0 (0-123)	0.0 *(0-4)*	0.0 (0-2)	0.0 (0-10)	0.0 (0-7)
Other current/ prior malignancy in history					
Yes	38 *(22.8)*	25 *(23.4)*	4 *(23.5)*	5 *(27.8)*	6 *(21.4)*
Lung Cancer[9]	10 *(6.0)*	6 *(5.6)*	1 *(5.9)*	1 *(5.6)*	3 *(10.7)*
Other type of malignancy	28 *(16.8)*	19 *(17.8)*	3 *(17.6)*	4 *(22.2)*	3 *(10.7)*
Medical history					
Smoking (n=159)[10]	148 *(93.1)*	93 *(93.9)*	15 *(88.2)*	17 *(94.4)*	26 *(92.9)*
Pack years (median, range)	40 (5-100)	40 (6-100)	45 *(5-90)*	35 (20-55)	47 (5-90)
Arterial hypertension	110 (65.9)	69 *(65.5)*	11 *(64.7)*	13 *(72.2)*	19 *(67.9)*
Pulmonary disease	90 *(53.9)*	58 *(54.2)*	8 *(47.1)*	10 *(55.6)*	15 *(53.6)*
Cardiovascular disease	84 *(50.3)*	54 *(50.5)*	7 *(41.2)*	6 *(33.3)*	19 *(67.9)*
Gastrointestinal disease	51 *(30.5)*	29 *(27.1)*	5 *(29.4)*	6 *(33.3)*	11 *(39.3)*
Neurologic disease	43 (25.7)	28 *(26.2)*	8 *(47.1)*	6 *(33.3)*	3 *(10.7)*
Diabetes mellitus	42 *(25.1)*	30 *(28.0)*	5 *(29.4)*	4 *(22.2)*	5 *(17.9)*
Urologic/ Nephrologic disease	41 *(24.6)*	26 *(24.3)*	5 *(29.4)*	5 *(27.8)*	5 *(17.9)*
Thyroid disease	39 *(23.4)*	25 *(23.4)*	6 *(35.3)*	5 *(27.8)*	5 *(17.9)*
Psychiatric disease	16 *(9.6)*	10 *(9.3)*	2 *(11.8)*	1 *(5.6)*	4 *(14.3)*
Autoimmune disease	9 *(5.4)*	3 *(2.8)*	2 *(11.8)*	1 *(5.6)*	3 *(10.7)*
Rheumatic disease	6 *(3.6)*	2 *(1.9)*	1 *(5.9)*	1 *(5.6)*	2 *(7.1)*
Paraneoplastic disease	10 *(6.0)*	3 *(2.8)*	6 *(35.3)*	1 *(5.6)*	1 *(3.6)*
Antibody-related PNS	6 (3.6)	1 *(0.9)*	5 *(29.4)*	1 *(5.6)*	0 *(0.0)*
SIADH	2 *(1.2)*	1 *(0.9)*	1 *(5.9)*	0 *(0.0)*	0 *(0.0)*
Hypercalcemia	2 *(1.2)*	1 *(0.9)*	0 *(0.0)*	0 *(0.0)*	1 *(3.6)*

C-: negative control group (cell based assay and immunohistochemistry negative. AICAbs: patients positive for intracellular antibodies in cell based assay. NSAbs: patients positive for neuronal suface antibodies in cell based assay. uAbs: patients negative in cell based assay, but with positive immunohistochemistry (unidentified target antigen). Numbers do not add up due to combination of antibodies (2 patients are positive for both AICAbs and NSAbs). Significant differences between groups are marked with asteriskes (*[1] p<0.001,*[2] p=0.010,*[3] p=0.037) P-values are computed using chi-square test comparing against the C- group. [4]Large Cell Carcinoma 2 (1.2), Large Cell Neuroendocrine Carcinoma 1 (0.6), Typical Carcinoid Tumor 2 (1.2), Atypical Carcinoid Tumor 1 (1.2), NSCLC not otherwise specified 16 (9.6); [5]Other distant metastases: Liver 24 (14.4), Bone 21 (12.6), Distant lymph nodes 20 (12.0), Adrenal gland 17 (10.2), Soft tissue 7 (4.2), Pancreas 1 (0.6), Spleen 1 (0.6). [6]Current chemotherapy 58 (34.7); [7]Resection margin R0 31 (18.6), Resection margin R1 3 (1.8), unknown 4 (2.4); [8]Bevacizumab (VEGF-antibody) 3 (1.8), Nintedanib (Tyrosinkinase inhibitor) 2 (1.2), other 3 (1.8) (Erlotinib/Nivolumab; Cetuximab; Everolimus); [9]In History (cured) 6 (3.6), Synchronous Second Carcinoma 4 (2.4); [10]Data on smoking are missing for 8 patients.

eTable 3. Demographic Characteristics of Patients With Cognitive Testing Results (n = 97)

	SCLC (n=26)	NSCLC (n=71)
	No. (%)	**No. (%)**
Age (years)		
Mean *(SD)*	63.0 (8.1)	63.5 (9.2)
Sex		
Male	16 (61.5)	40 (56.3)
Ethnicity		
Caucasian	25 (96.2)	71 (100)
African	1 (3.8)	0 (0.0)
Non-Small Cell Lung Cancer Subtype		
Adenocarcinoma		37 (52.1)
Squamous Cell Carcinoma		21 (29.6)
Typical Carcinoid Tumor		2 (2.8)
Atypical Carcinoid Tumor		1 (1.4)
NSCLC not otherwise specified		10 (14.1)
Clinical Stage (UICC 2010)		
Stage I	0 (0.0)	13 (18.3)
Stage II	1 (3.8)	7 (9.9)
Stage III	13 (50.0)	14 (19.7)
Stage IV (non-cerebral metastases)	11 (42.3)	36 (50.7)
Lung or pleural metastases (M1a)	4 (15.4)	20 (28.2)
Other distant metastases (M1b)	7 (26.9)	16 (22.5)
unknown	1 (3.8)	1 (1.4)
Treatment		
Treatment naive	11 (42.3)	26 (36.6)
Chemotherapy	15 (57.7)	19 (26.8)
Radiotherapy (radiation of primary tumor)	8 (30.8)	18 (25.4)
Surgery of primary tumor	0 (0.0)	25 (35.2)
Targeted Therapy[1]	0 (0.0)	3 (4.2)
Immunotherapy	1 (3.8)	1 (1.4)
Time since initial diagnosis (mth)		
Mean (SD)	1.9 (2.4)	6.5 (18.5)
Medical history		

Smoking[2]	23 (88.5)	61 (85.9)
Arterial hypertension	14 (53.8)	47 (66.2)
Pulmonary disease	10 (38.5)	40 (56.3)
Cardiovascular disease	6 (23.1)	36 (50.7)
Diabetes mellitus[3]	5 (19.2)	20 (28.2)
Thyroid disease	9 (34.6)	16 (22.5)
Neurologic disease	9 (34.6)	11 (15.5)
Other malignancy (current/prior)	5 (19.2)	12 (16.9)
Psychiatric disease	5 (19.2)	7 (9.9)
Paraneoplastic disease[4]	6 (23.1)	1 (1.4)
Autoimmune disease	2 (7.7)	3 (4.2)
Sedating Medication at time of examination		
Yes	9 (34.6)	31 (43.7)
Opioid analgesics	5 (19.2)	24 (33.8)
Antidepressants	1 (3.8)	8 (11.3)
Sleeping drugs	2 (7.7)	6 (8.5)
Anticonvulsant drugs (co-analgesics)	2 (7.7)	1 (1.4)
ECOG Performance status		
0	17 (65.4)	45 (63.4)
1	6 (23.1)	14 (19.7)
2	3 (11.5)	9 (12.7)
3	0 (0.0)	3 (4.2)
FACIT Fatigue Score		
Mean (SD)	36.4 (10.1)	34.0 (11.6)
BDI-FS Depression Score		
Mean (SD)	2.0 (2.2)	2.3 (3.0)
SF-12 Physical Health Score		
Mean (SD)	39.4 (10.2)	36.3 (10.6)
SF-12 Mental Health Score		
Mean (SD)	44.6 (12.6)	48.4 (11.6)
Years of education		
Mean (SD)	12.7 (2.1)	12.7 (2.3)
IQ (derived by MWT-A test score)		
Mean (SD)	103.2 (15.2)	107.9 (13.1)

[1]One patient underwent targeted therapy against other tumor than lung cancer
[2]Data on smoking are missing for five patients (1 SCLC/4 NSCLC). Eight patients (2 SCLC/6 NSCLC) are non-smokers
[3]DM Type 2 (N=22) (5 SCLC/17 NSCLC), DM Type 1 (N=2), DM Type 3 (N=1)
[4]Paraneoplastic diseases include antibody-related PNS (N=4), SIADH (N=2) (all SCLC); Hypercalcemia (N=1) (NSCLC)

eTable 4. Demographic Characteristics of Tested Patients by Antibody (n = 97)

Tested Lung Cancer Patients (n=97)	Total (n=97)*	C- (n=60)	AICAbs (n=11)	NSAbs (n=10)	uAbs (n=17)
Age					
Median (range)	64.0 (38-88)	64.5 (38-78)	62.0 (51-80)	62.5 (47-72)	65.0 (59-79)
Sex					
Male	56 (57.7)	33 (55.0)	7 (63.3)	7 (70.0)	10 (58.8)
Female	41 (42.3)	27 (45.0)	4 (36.4)	3 (30.0)	7 (41.2)
Lung Cancer Subtype					
Small Cell Lung Cancer (SCLC)	24 (24.7)	11 (18.3)	8 (72.7)***[1]	2 (20.0)	4 (23.5)
Non Small Cell Lung Cancer (NSCLC)					
Adenocarcinoma	37 (38.1)	25 (41.7)	3 (27.3)	4 (40.0)	5 (29.4)
Squamous Cell Carcinoma	21 (21.6)	12 (20.0)	0 (0.0)	2 (20.0)	7 (41.2)
Other[10]	13 (13.4)	10 (16.7)	0 (0.0)	2 (20.0)	1 (5.9)
Combined Carcinoma (SCLC+NSCLC)	2 (2.1)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical Stage (UICC 2010)					
Stage I	13 (13.4)	9 (15.0)	0 (0.0)	0 (0.0)	4 (23.5)
Stage II	8 (8.2)	3 (5.0)	0 (0.0)	1 (10.0)	4 (23.5)
Stage III	27 (27.8)	13 (21.7)	8 (72.7)**[2]	5 (50.0)	2 (11.8)
Stage IV (metastases)	47 (48.5)	34 (56.7)	3 (27.3)	4 (40.0)	6 (35.3)
unknown	2 (2.1)	1 (1.7)	0 (0.0)	0 (0.0)	1 (5.9)
Site of metastases					
Lung / Pleura / Pericardium (M1a)	36 (37.1)	26 (43.3)	3 (27.3)	3 (30.0)	4 (23.5)
Brain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other distant metastases (M1b)[11]	25 (25.8)	20 (33.3)	1 (9.1)	2 (20.0)	2 (11.8)
Treatment					
Treatment naive	37 (38.1)	25 (41.7)	3 (27.3)	2 (20.0)	7 (41.2)

Chemotherapy (prior and/or current)[12]	34 (35.1)	19 (31.7)	6 (54.5)	6 (60.0)	4 (23.5)
Radiotherapy (radiation of primary tumor)	26 (26.8)	16 (26.7)	3 (27.3)	3 (30.0)	5 (29.4)
Surgery of primary tumor[13]	25 (25.8)	12 (20.0)	3 (27.3)	4 (40.0)	6 (35.3)
Surgery of metastases	4 (4.1)	4 (44.4)	0 (0.0)	0 (0.0)	0 (0.0)
Targeted Therapy [14]	3 (3.1)	1 (1.7)	0 (0.0)	2 (20.0)**[7]	0 (0.0)
Immunotherapy (IVIGs)	2 (2.1)	0 (0.0)	1 (9.1)*[3]	1 (10.0)*[8]	0 (0.0)
Time since initial diagnosis (months)					
Median (range / IQR)	1 (0-123 / 0-4)	1 (0-25 / 0-3)	2 (0-25 / 0-5)	2 (0-123 / 0-3)	1 (0-91/ 0-8)
Other current/ prior malignancy in history					
Yes	17 (17.5)	8 (13.3)	2 (18.2)	3 (30.0)	5 (29.4)
Lung Cancer[15]	3 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (17.6)
Other type of malignancy	14 (14.4)	8 (13.3)	2 (18.2)	3 (30.0)	2 (11.8)
Medical history					
Smoking (n=92)[16]	84 (91.3)	51 (91.0)	9 (81.8)	9 (90.0)	16 (94.1)
Pack years (median, range)	40 (5-100)	40 (6-100)	40 (5-90)	30 (20-46)	45 (5-70)
Arterial hypertension	61 (62.9)	35 (58.3)	8 (72.2)	6 (60.0)	13 (76.5)
Pulmonary disease	50 (51.5)	31 (51.7)	4 (36.4)	5 (50.0)	10 (58.8)
Cardiovascular disease	42 (42.3)	25 (41.7)	5 (45.5)	3 (30.0)	9 (52.9)
Gastrointestinal disease	30 (30.9)	16 (26.7)	4 (36.4)	3 (30.0)	7 (41.2)
Neurologic disease	20 (20.6)	12 (20.0)	5 (45.5)	4 (40.0)	0 (0.0)
Diabetes mellitus	25 (25.8)	18 (30.0)	2 (18.2)	2 (20.0)	3 (17.6)
Urologic/ Nephrologic disease	23 (23.7)	14 (23.3)	4 (36.4)	3 (30.0)	2 (11.8)
Thyroid disease	25 (25.8)	17 (28.3)	5 (45.5)	2 (20.0)	2 (11.8)
Psychiatric disease	12 (12.4)	7 (11.7)	2 (18.2)	1 (10.0)	3 (17.6)
Autoimmune disease	5 (5.2)	1 (1.7)	2 (18.2)*[4]	1 (10.0)	1 (5.9)
Rheumatic disease	3 (3.1)	0 (0.0)	1 (9.1)*[5]	1 (10.0)*[9]	1 (5.9)
Paraneoplastic disease	7 (7.2)	2 (3.3)	5 (45.5)***[6]	1 (10.0)	0 (0.0)

Antibody-related PNS	4 (4.1)	0 (0.0)	4 (36.4)	0 (0.0)	0 (0.0)
SIADH	2 (2.1)	1 (1.7)	1 (9.1)	0 (0.0)	0 (0.0)
Hypercalcemia	1 (1.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)

C-: negative control group (cell based assay and immunohistochemistry negative. AICAbs: patients positive for intracellular antibodies in cell based assay. NSAbs: patients positive for neuronal suface antibodies in cell based assay. uAbs: patients negative in cell based assay, but with positive immunohistochemistry (unidentified target antigen). Numbers do not add up due to combination of antibodies (1 patient is positive for both AICAbs and NSAbs). Significant differences between groups are marked with asteriskes (***[1] p<0.001,**[2] p=0.008,*[3] p=0.019, *[4] p=0.012, *[5] p=0.019, *[6] p<0.001, **[7] p=0.002, *[8] p=0.014, *[9] p=0.014). P-values are computed using chi-square test comparing against the C- group. Only significant p-values are displayed. [10]Typical Carcinoid Tumor 2 (2.1), Atypical Carcinoid Tumor 1 (1.0), NSCLC not otherwise specified 10 (10.3); [11]Current chemotherapy 24 (24.7); [12]Resection margin R0 19 (19.6), Resection margin R1 3 (3.1), unknown 3 (3.1); [13]Bevacizumab (VEGF-antibody) 1 (1.0), Cetuximab 1 (1.0), Everolimus 1 (1.0); [14]In History (cured) 3 (3.1). [15]Data on smoking are missing for 5 patients.

eTable 5. Demographic Characteristics of Patients by Cognitive Impairment

	No Cognitive Impairment (n=32)	Cognitive Impairment (n=65)	Total (n=97)
Lung cancer subtype			
SCLC	10 (31.2%)	16 (24.6%)	26 (26.8%)
NSCLC	22 (68.8%)	49 (75.4%)	71 (73.2%)
Sex			
Male	17 (53.1%)	39 (60.0%)	56 (57.7%)
Female	15 (46.9%)	26 (40.0%)	41 (42.3%)
Age			
Median (IQR)	58.00 (51.00, 65.25)	66.00 (62.00, 72.00)	64.00 (58.00, 69.00)
Treatment with opioids			
No	23 (71.9%)	45 (69.2%)	68 (70.1%)
Yes	9 (28.1%)	20 (30.8%)	29 (29.9%)
MWTA Test IQ			
Median (IQR)	111.00 (99.50, 123.00)	108.00 (98.00, 115.00)	108.00 (98.00, 115.00)
Missing	0 (0%)	2 (3.08%)	2 (2.06%)
SF-12 physical health (score)			
Median (IQR)	41.92 (30.99, 50.66)	35.09 (25.98, 41.59)	36.59 (29.29, 44.66)
Missing	2 (6.25%)	1 (1.54%)	3 (3.09%)
SF-12 mental health (score)			
Median (IQR)	48.62 (40.94, 56.08)	46.83 (38.98, 59.42)	46.88 (39.19, 57.79)
Missing	2 (6.25%)	1 (1.54%)	3 (3.09%)
BDI-FS Score			
Median (IQR)	1.00 (0.00, 2.75)	2.00 (0.00, 3.00)	2.00 (0.00, 3.00)
Missing	2 (6.25%)	1 (1.54%)	3 (3.09%)

Chemotherapy			
No	18 (56.2%)	45 (69.2%)	63 (64.9%)
Yes	14 (43.8%)	20 (30.8%)	34 (35.1%)
Radiotherapy			
No	24 (75.0%)	47 (72.3%)	71 (73.2%)
Yes	8 (25.0%)	18 (27.7%)	26 (26.8%)
Surgery			
No	21 (65.6%)	51 (78.5%)	72 (74.2%)
Yes	11 (34.4%)	14 (21.5%)	25 (25.8%)
Stage of Lung Cancer (I-IV)			
Stage I	3 (9.4%)	10 (15.9%)	13 (13.7%)
Stage II	1 (3.1%)	7 (11.1%)	8 (8.4%)
Stage III	13 (40.6%)	14 (22.2%)	27 (28.4%)
Stage IV	15 (46.9%)	32 (50.8%)	47 (49.5%)
Unknown	0 (0%)	2 (3.08%)	2 (2.06%)

eTable 6. Cognitive Test Scores of Patients With SCLC: AIC Antibodies vs No Antibodies

		AICAb patients mean t-score	SEM	p
Overall cognition	**Composite cognitive score**	-0.97	0.31	**0.002**
Verbal memory	**Immediate memory**	-0.19	0.42	0.713
	Learning	-2.55	1.04	0.057
	Sum Score	-1.72	0.69	**0.012**
	Susceptibility to interference	-1.34	0.71	**0.046**
	Delayed recall	-2.26	0.71	**0.002**
Visuospatial memory	**ROCF immediate recall**	-0.16	0.51	0.795
	ROCF delayed recall	-0.34	0.56	0.544
Working memory	**Digit span forward**	-0.46	0.43	0.398
	Digit span backward	-0.07	0.11	0.872
Attention	**Tonic alertness (time)**	-2.88	0.82	**0.015**
	Tonic alertness (SD)	-2.87	1.07	**0.043**
	Phasic alertness (time)	-2.01	0.73	**0.039**
	Phasic alertness (SD)	-1.64	0.76	**0.022**
	Divided attention (auditive)	-0.46	0.60	0.488

	Divided attention (visual)	-0.94	0.57	0.120
	Divided attention (errors)	0.88	0.29	0.073
	Divided attention (omissions)	-2.42	1.41	0.149
Executive function	**Go/No Go (time)**	-0.25	0.39	0.631
	Go/No Go (errors)	0.01	0.42	0.980
	Go/No Go (omissions)	0.27	0.30	0.570
	Stroop (time)	-0.47	0.36	0.324
	Verbal fluency	-0.78	0.53	0.176

Significant differences in mean t-values were computed using t-test. Mean t-value of negative control group for all tests = 0 (SD = ±1.0). Significant p-values are marked in bold. AICAbs: patients positive for intracellular antibodies in cell based assay. Neg. patients: negative control group (cell based assay and immunohistochemistry negative). SEM: Standard error of the mean.

eTable 7. Cognitive Test Scores of Patients With NSCLC: VLMT IgA NMDAR Antibodies vs No Antibodies

NSCLC-patients: Cognitive test results NMDAR-IgA-Ab+ vs. Ab-negative						
		NMDAR-IgA-Ab+ (n=3)		**Neg. patients (n=47)**		**p**
		Mean raw score	**SEM**	**Mean raw score**	**SEM**	
Verbal memory	**VLMT Score Trial 1 (immediate memory)**	5.00	1.16	6.19	0.31	0.347
	VLMT Score Trial 2	5.00	1.73	8.79	0.37	**0.017**
	VLMT Score Trial 3	6.67	1.67	10.62	0.40	**0.019**
	VLMT Score Trial 4	8.67	0.88	11.26	0.42	0.128
	VLMT Score Trial 5 (best learning)	9.33	1.45	11.89	0.37	0.093
	VLMT Sum Score (Trial 1-5)	34.67	5.81	48.74	1.64	**0.041***
	VLMT Score Trial 6 (susceptibility to interference)	7.33	1.76	9.72	0.50	0.246
	VLMT Score Trial 7 (Delayed recall)	4.33	1.67	9.66	0.49	**0.011**
	VLMT Score Recognition	4.33	4.91	12.30	0.42	0.246

Significant differences between mean raw scores were computed using T-test. Significant p-values are marked in bold. NMDAR-IgA-Ab+ = NMDAR-IgA antibody positive patients; Neg. patients = Antibody negative patients (in cell-based assay and immunohistochemistry). *Sum score value not shown in figure 3A. SEM: standard error of the mean.

eTable 8. Cognitive Test Scores of All Patients With Lung Cancer: Unknown Antibodies vs No Antibodies

		uAbs patients mean t-score	SE	p
Overall cognition	**Composite cognitive score**	-0.44	0.16	**0.019**
Verbal memory	**Immediate memory**	-0.65	0.18	**0.014**
	Learning	-0.35	0.28	0.226
	Sum Score	-0.58	0.25	**0.039**
	Susceptibility to interference	-0.17	0.19	0.518
	Delayed recall	-0.19	0.27	0.499
Visuospatial memory	**ROCF immediate recall**	-0.29	0.24	0.289
	ROCF delayed recall	-0.34	0.23	0.212
Working memory	**Digit span forward**	-0.28	0.31	0.337
	Digit span backward	-0.35	0.23	0.195
Attention	**Tonic alertness (time)**	-0.39	0.34	0.197
	Tonic alertness (SD)	-0.57	0.28	0.051
	Phasic alertness (time)	-0.23	0.28	0.417
	Phasic alertness (SD)	-0.39	0.33	0.192

	Divided attention (auditive)	0.13	0.19	0.565
	Divided attention (visual)	-0.60	0.25	**0.045**
	Divided attention (errors)	-0.56	0.30	0.057
	Divided attention (omissions)	-0.47	0.25	0.099
Executive function	**Go/No Go (time)**	-0.49	0.25	0.086
	Go/No Go (errors)	-0.08	0.27	0.776
	Go/No Go (omissions)	-1.22	0.60	0.064
	Stroop (time)	-0.64	0.34	**0.038**
	Verbal fluency	-0.60	0.24	**0.031**

Significant differences between mean t-scores were computed using T-test. Mean t-value of negative control group for all tests = 0 (SD = ±1.0). Significant p-values are marked in bold. uAbs=Patients with serum autoantibodies against brain tissue and yet unidentified target epitopes; Neg. patients = Antibody negative patients (in cell-based assay and immunohistochemistry). *Sum score value not shown in figure 3A. SE: standard error of the mean, SD: standard deviation.

eTable 9. Model Adjusted for Opioid Therapy

		Model 1	Model 2
		OR (95% Credibility Interval)	OR (95% Credibility Interval)
Any antibody	SCLC	11.00 (1.16-103.78)	14.45 (1.35-154.40)
	NSCLC	1.29 (0.38-4.39)	1.32 (0.37-4.63)
AICABs	SCLC	8.30 (0.74-92.44)	8.59 (0.77-96.94)
NMDA IgA	SCLC	2.89 (0.10-80.21)	5.12 (0.16-166.27)
	NSCLC	15.72 (0.55-449.81)	16.44 (0.56-480.26)
uAbs	SCLC	8.51 (0.65-111.40)	13.10 (0.77-224.39)
	NSCLC	2.62 (0.43-16.06)	2.79 (0.43-17.96)

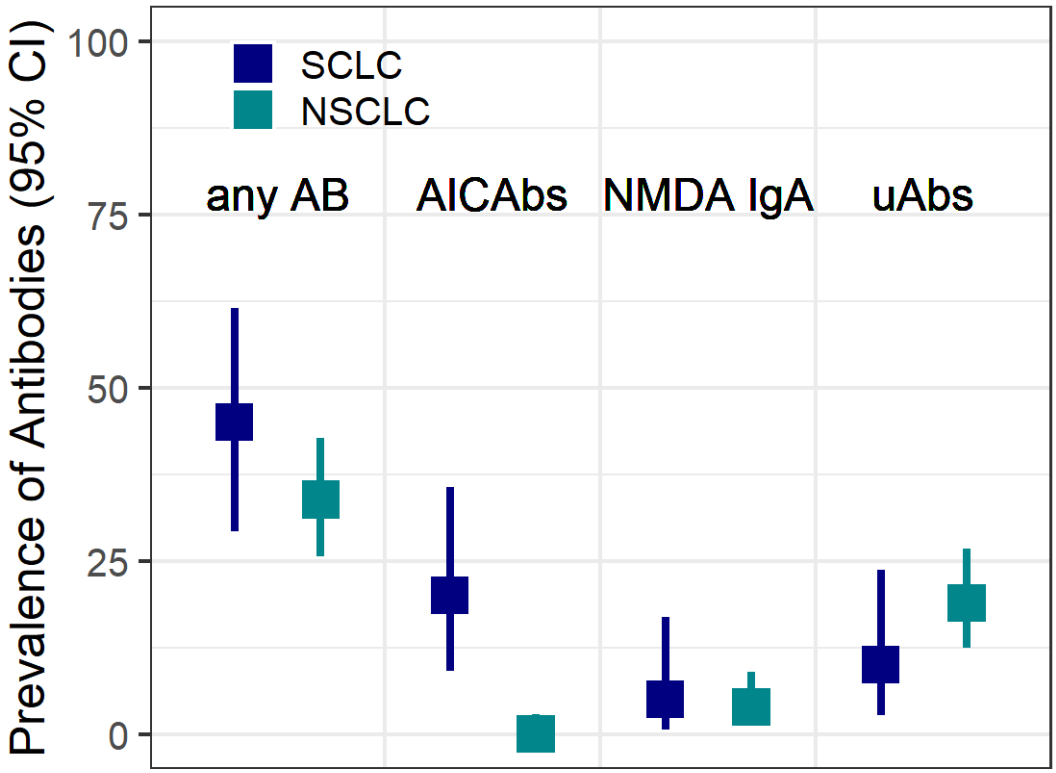
Bayesian logistic regression models without (Model 1) and with adjustment (Model 2) for opioid analgesics: These analyses show that the additional adjustment for treatment with opioid analgesics did not relevantly alter our results and did not drive the observed association between neuronal autoantibodies and cognitive impairment.

eTable 10. Neuronal Autoantibodies and Neurological Deficits in Patients With Lung Cancer (n = 96)

Neurological examination	Total (n=96)	CBA- IHc- (n=59)	CBA + (n=20)*	p	NSAbs (n=10)*	p	AICAbs (n=11)*	p	CBA- IHC+ (n=17)	p
Abnormal neurological examination	61 *(63.5)*	33 *(55.9)*	15 *(75.0)*	0.131	7 *(70.0)*	0.405	9 *(81.8)*	0.108	13 *(76.5)*	0.127
Cranial nerves										
Abnormal oculomotor function†	3 *(3.1)*	0 (0.0)	3 (15.0)	**0.002**	0 *(0.0)*	.	3 (27.3)	**<0.001**	0 *(0.0)*	.
Trigeminal hypesthesia	3 *(3.1)*	1 *(1.7)*	2 *(10.0)*	0.093	0 *(0.0)*	0.678	2 *(18.2)*	**0.013**	0 *(0.0)*	0.589
Uni/bilateral hypacusis	23 *(23.7)*	15 *(25.4)*	5 *(25.0)*	0.970	4 *(40.0)*	0.340	2 *(18.2)*	0.607	3 *(17.6)*	0.506
Motor function										
Reduced muscle strength/paresis	2 *(2.2)*	0 *(0.0)*	2 *(10.0)*	**0.026**	1 *(10.0)*	**0.037**	2 *(18.2)*	**0.003**	0 *(0.0)*	.
Abnormal muscle tone (rigor/spasticity)	3 *(3.1)*	2 *(3.4)*	1 *(5.0)*	0.745	0 *(0.0)*	0.555	1 *(9.1)*	0.391	0 (0.0)	0.442
Asymmetric reflexes	8 *(8.2)*	5 *(8.5)*	2 *(10.0)*	0.836	1 *(10.0)*	0.874	1 *(9.1)*	0.947	1 *(5.9)*	0.727
Missing reflexes	24 *(24.7)*	16 *(27.1)*	6 *(30.0)*	0.804	4 *(40.0)*	0.406	3 *(27.3)*	0.992	2 *(11.8)*	0.109
Babinski positive	1 *(1.0)*	0 *(0.0)*	1 *(5.0)*	0.084	0 *(0.0)*	.	1 *(9.1)*	**0.020**	0 *(0.0)*	.
Sensory function										
Pallhypaesthesia	33 *(34.0)*	17 *(28.8)*	9 *(45.0)*	0.183	2 *(25.0)*	0.822	6 *(54.5)*	0.095	12 *(48.0)*	0.091
Hypaesthesia upper/lower limb	13 *(13.4)*	6 *(10.0)*	5 *(25.0)*	0.092	1 *(10.0)*	1.000	4 *(36.4)*	**0.021**	2 *(11.8)*	0.833
Polyneuropathic symptoms§	22 *(22.7)*	11 *(18.3)*	9 *(45.0)*	**0.017**	3 *(30.0)*	0.393	6 *(54.5)*	**0.010**	2 *(11.8)*	0.523
Coordination										
Dysmetria in finger-nose-test	13 *(13.4)*	7 *(11.7)*	4 *(20.0)*	0.349	0 *(0.0)*	0.255	4 *(36.4)*	**0.037**	2 *(11.8)*	0.991
Balancing insecurity	30 *(30.9)*	19 *(34.5)*	6 (30.0)	0.925	3 *(33.3)*	0.943	3 (27.3)	0.943	5 *(29.4)*	0.692
Romberg trial positive	4 *(4.1)*	3 *(5.2)*	1 *(5.0)*	0.701	0 *(0.0)*	0.682	1 *(9.1)*	0.732	0 *(0.0)*	0.456
Cerebellar symptoms‡	36 *(37.1)*	21 *(35.0)*	8 *(40.0)*	0.687	3 *(30.0)*	0.758	5 *(45.5)*	0.508	7 *(41.2)*	0.640

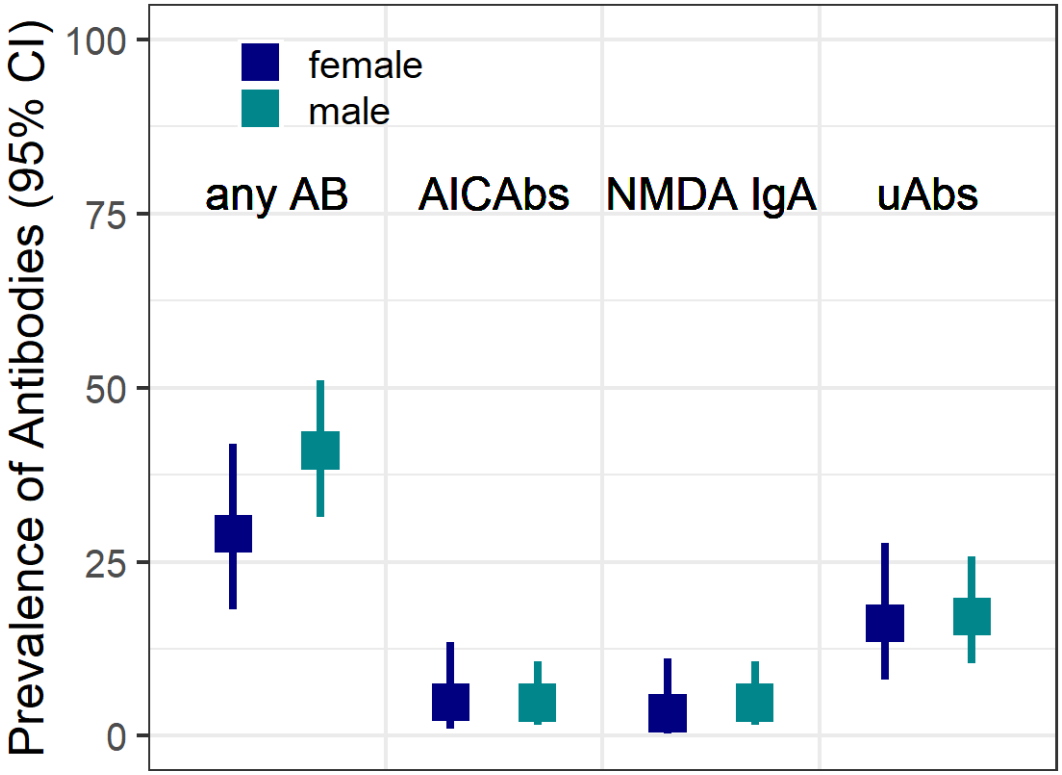
Abbreviations: CBA- IHC-: cell based assay negative and immunohistochemistry negative (= control group). CBA+: cell based assay positive (independent of IHC result). NSAbs: neuronal surface antibodies in CBA positive. AICAbs: Intracellular antibodies in CBA positive. CBA- IHC+: Cell based assay negative, immunohistochemistry positive (unidentified antigen). *Numbers do not add up due to combination of antibodies (of the ten NSAb-positive patients, one patient is additionaly AICAb-positive). Bold numbers represent a significant effect. P-values are computed with chi-square test. †: includes: saccaded pursuit movements, diplopia or combinations. §: includes: PNP diagnosis, pallhypaesthesia, distal symmetric hypaesthesia or combinations. ‡: includes: dysmetria, dysdiadochokinesia, Romberg trial positive, balancing insecurity or combinations

eFigure 1. Antibody Prevalence



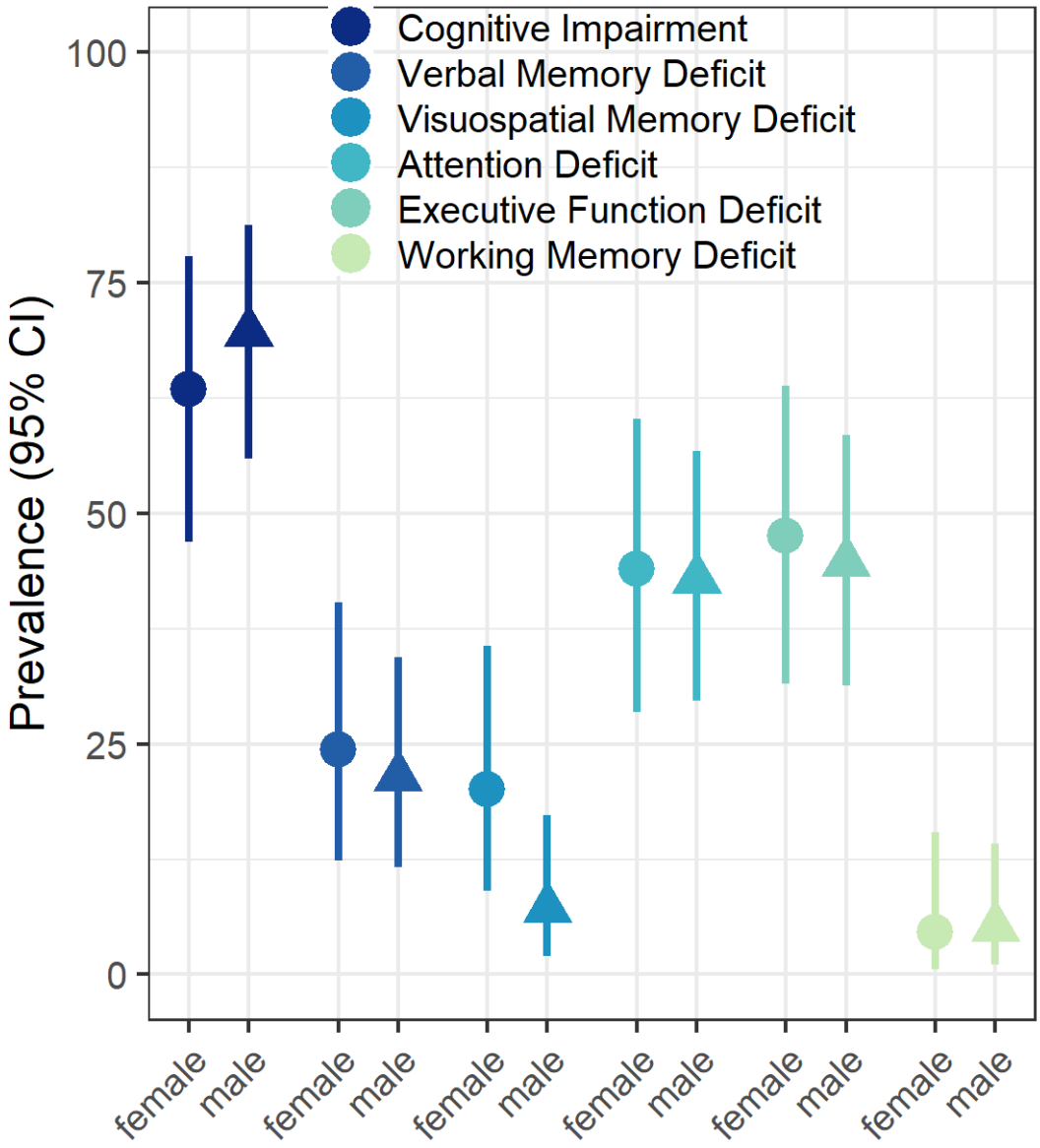
Antibody prevalence with 95% confidence intervals (95%CI) derived based on Clopper and Pearson.

eFigure 2. Antibody Prevalence by Sex



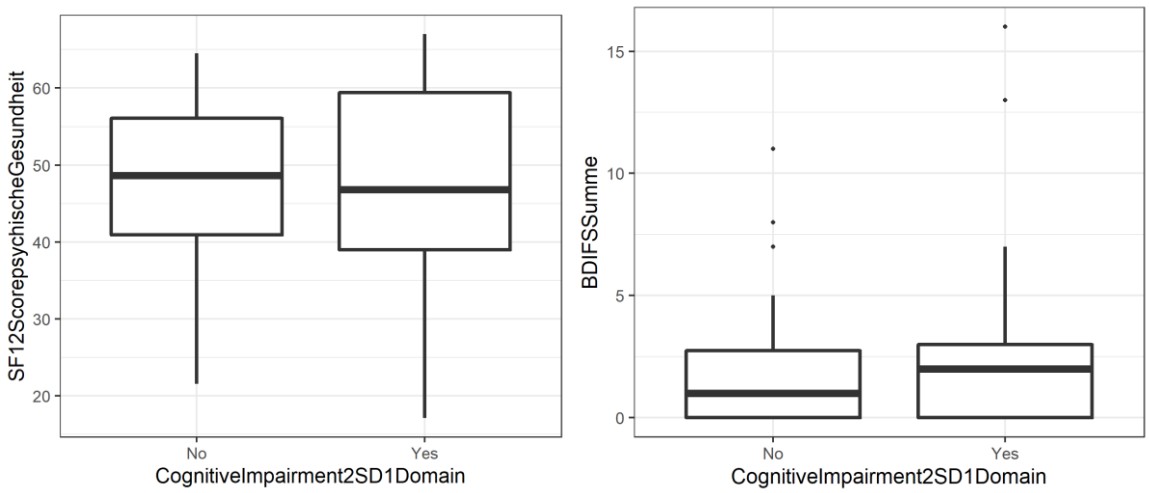
Antibody prevalence with 95% confidence intervals (95%CI) derived based on Clopper and Pearson.

eFigure 3. Cognitive Impairment by Sex

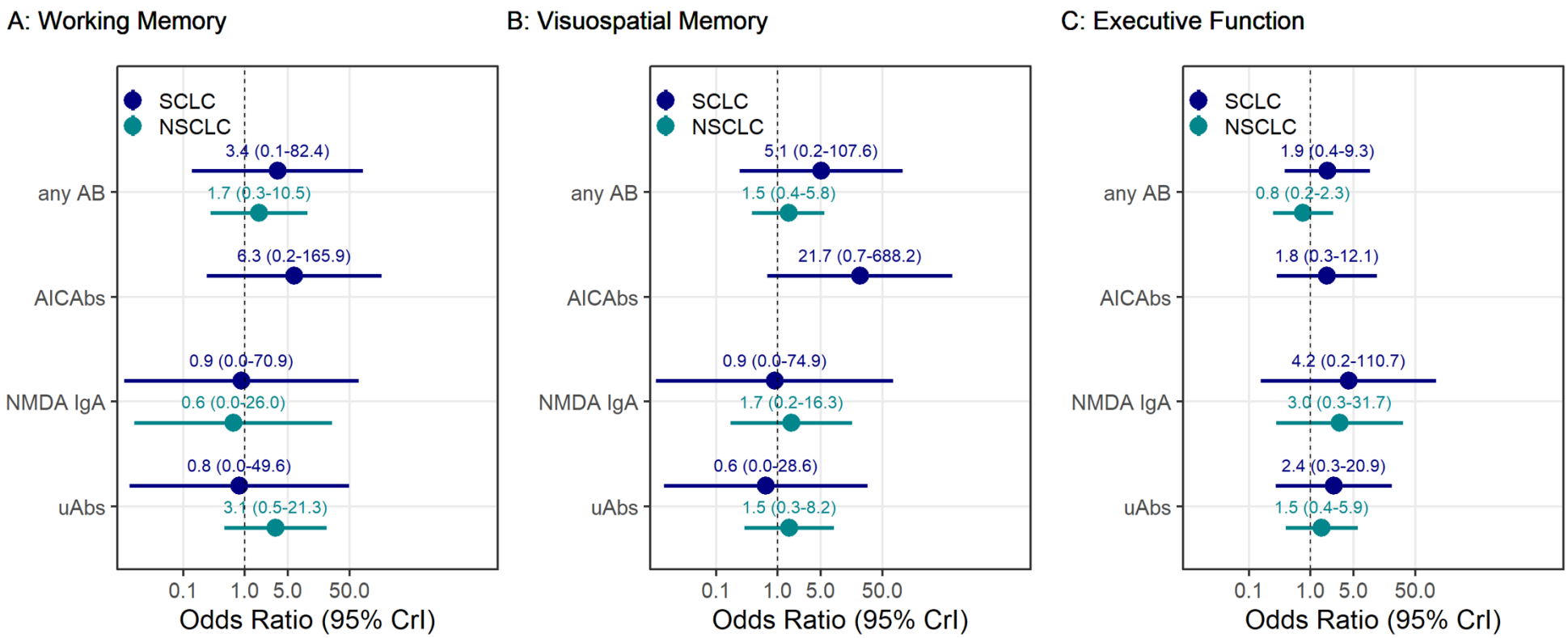


Prevalence of cognitive impairment and cognitive domain deficits with 95% confidence intervals (95%CI) derived based on Clopper and Pearson.

eFigure 4. Mental Health and Depression Scale Scores and Cognitive Impairment

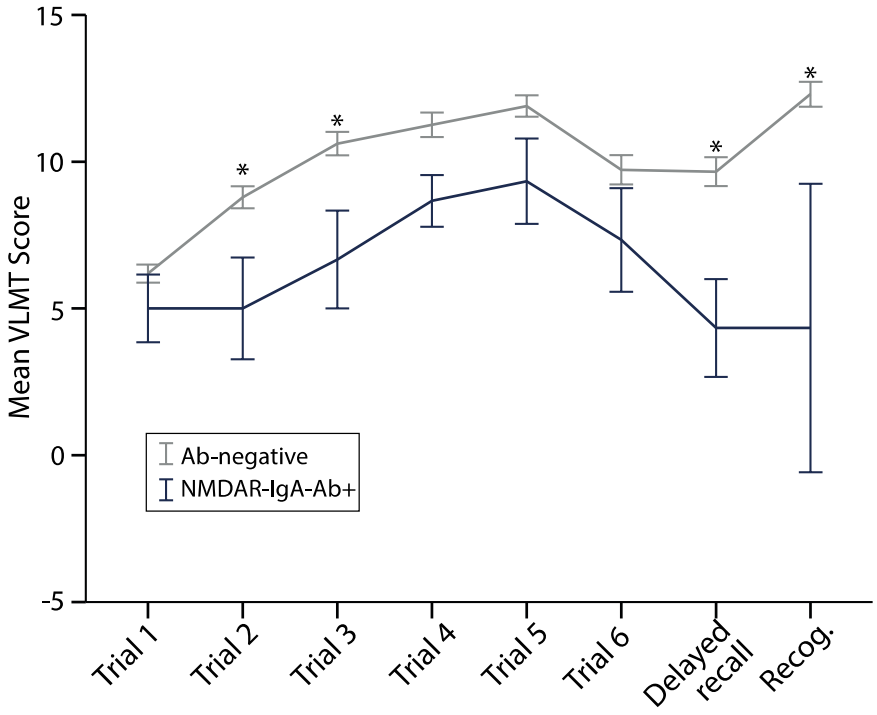


eFigure 5. Cognitive Domain Deficits: Working Memory, Visuospatial Memory, and Executive Function



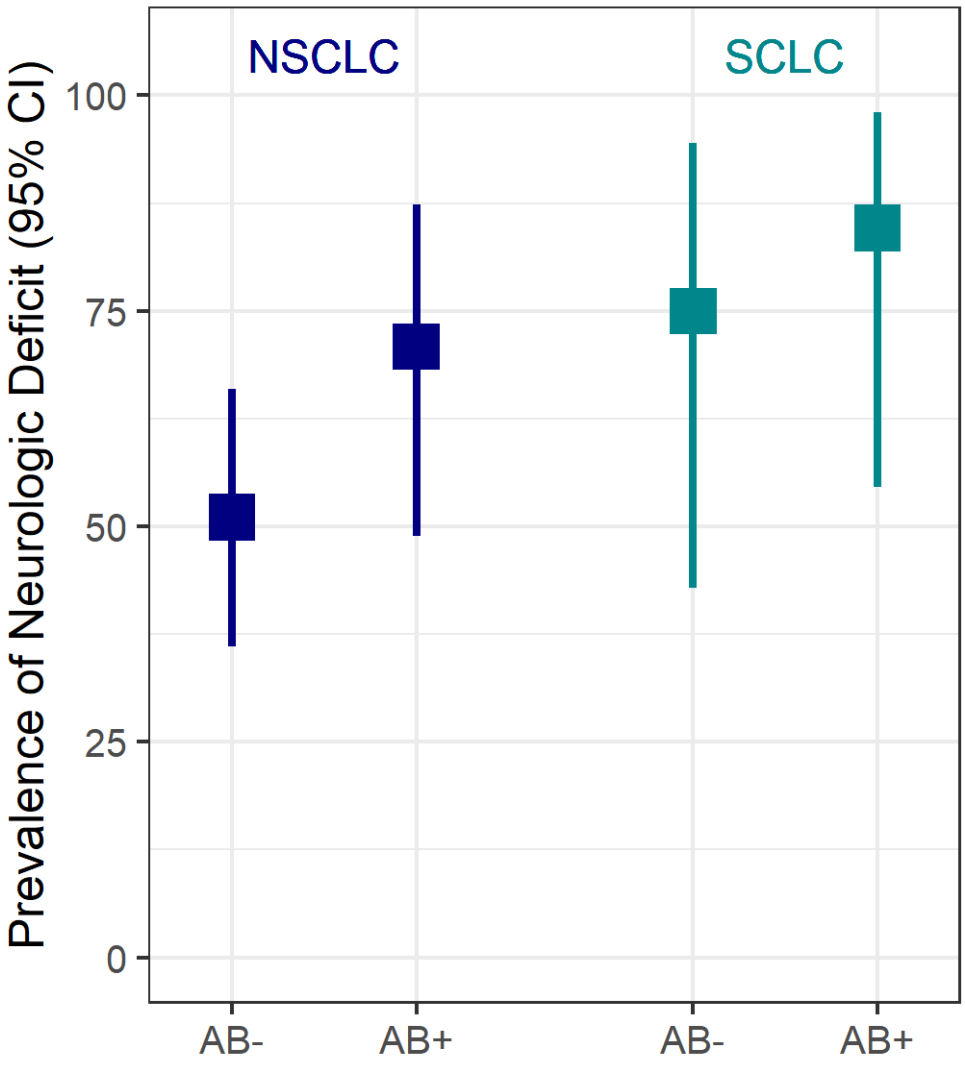
Odds ratio estimates with 95% credible intervals (CrI) based on Bayesian logistic regression models. Displayed are the derived estimates for the respective autoantibody compared to antibody-negative patients, where each model is adjusted for sex, age, and neurologic deficit. Outcome variables are the binary measures of **A)** Working Memory Deficit, **B)** Visuospatial Memory Deficit, and **C)** Executive Function Deficit.

eFigure 6. Verbal Memory Performance in Patients With IgA NMDAR Antibodies



Comparison of verbal memory performance. Test raw scores of verbal learning memory task (VLMT) subtests are shown comparing patients with NMDAR IgA antibodies (n=3) vs. antibody-negative patients (n=47).
Abbreviations: Mean VLMT Score = Mean score in the Verbal Learning and Memory Test; NMDAR-IgA-Ab+ = NMDAR-IgA antibody positive patients; Ab-negative = Antibody negative patients; Recog. = Recognition test score.

eFigure 7. Neurological Deficits



Prevalence of neurological deficits with 95% confidence intervals (95%CI) derived based on Clopper and Pearson.

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