CLINICAL/SCIENTIFIC NOTE

Memory Deficits in Cancer Patients With Serum NMDA Receptor Autoantibodies

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Abstract

Objectives

Neuronal autoantibodies are linked to cognitive impairment in neurologic diseases and can be associated with tumors. In patients with cancer, IgA/IgM N-Methyl-D-Aspartate receptor (NMDAR) autoantibodies are most common, yet their clinical relevance is unclear. We assessed cognitive function in cancer patients with serum NMDAR autoantibodies and compared the results with matched controls.

Methods

For this cross-sectional case-control study in Germany, we recruited 1,055 patients with cancer and tested for neuronal serum autoantibodies. Cognitive assessment was performed blinded to antibody status and after excluding patients with potential confounders of cognitive dysfunction. The tests included verbal memory (Rey Auditory Verbal Learning Test), visuospatial memory (Rey-Osterrieth Complex Figure), and working memory.

Results

Fifty-six patients with IgA/IgM NMDAR autoantibodies (median age 61.0 years [28.0–86.0], 35.7% female) were matched 1:1 to autoantibody-negative patients by age, sex, cancer type, and stage. Autoantibody-positive patients showed impairments in verbal memory (mean score ± SD: 9.7 ± 3.6 vs 11.4 ± 3.2; $p = 0.01$; Cohen $d = 0.49$), visuospatial memory (19.4 ± 7.0 vs 22.6 ± 5.6; $p = 0.01$; $d = 0.50$), and working memory (6.2 ± 1.9 vs 7.0 ± 2.1; $p = 0.04$; $d = 0.40$). Memory function decreased with increasing IgA NMDAR autoantibody levels. Both groups performed similarly on measures of attention, executive function, and verbal fluency.

Discussion

Serum NMDAR autoantibodies are associated with isolated memory deficits in patients with cancer and might serve as a potential biomarker for cancer-related cognitive impairment.

Introduction

Autoantibodies targeting neuronal and glial epitopes are increasingly recognized in neurologic diseases[1] and can shape brain function, leading to cognitive deficits.[2,3] Previous studies suggest autoantibody-associated autoimmunity as a potential factor in cognitive decline in patients with cancer,[4,5] dementia,[6] and stroke.[7,8] In patients with cancer, neuronal autoantibodies may arise from cross-reactivity between tumor and neuronal antigens, as seen in paraneoplastic syndromes.[1]

We previously identified a high prevalence of autoantibodies against neuronal antigens in patients with cancer, with IgA and IgM isotype autoantibodies against the N-Methyl-D-Aspartate receptor (NMDAR) being most frequent.[9] These findings complemented earlier studies that identified IgA/IgM NMDAR autoantibodies in patients with cognitive impairment and dementia.[6,10-12] In prospective cohorts of patients with melanoma (n = 157) and lung cancer (n = 167), we confirmed high seroprevalence of neuronal autoantibodies and observed

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a robust association with cognitive impairment, independent of tumor stage and treatment. However, interpretation was limited because only a subgroup had IgA/IgM NMDAR autoantibodies.[4,5]

In this study, we aimed to extend these findings by assessing the seroprevalence of IgA/IgM NMDAR autoantibodies in a larger cohort of 1,055 patients with cancer and comparing cognitive performance between patients with these autoantibodies and matched autoantibody-negative controls.

Methods

Patients

We recruited 1,055 patients with cancer at Charité–Universitätsmedizin Berlin, Germany. Demographic details and cancer types are provided in Table 1. The study was approved by the ethics committee of the Charité–Universitätsmedizin Berlin.

Neuronal Autoantibody Detection

Patient serum samples were tested for neuronal autoantibodies using commercial cell-based assays containing BIOCHIP mosaics (Euroimmun AG) (eTable 1).[4,5]

Cognitive Assessment

Cognitive testing was performed in 635 patients after exclusion of those with potential confounders of cognitive dysfunction (e.g., brain metastases, history of neurologic or psychiatric disorders, and medication with cognitive side effects). Cognitive tests measured verbal memory, visuospatial memory, working memory, executive function, general intelligence, verbal fluency, and attention (eTable 2).[4,5] In addition, patient-reported outcome measures (PROMs) were obtained (eTable 2), and functional clinical performance was

Table 1 Demographic and Clinical Details of Patients

	All (n = 112), n (%) or median (range)	Antibody negative (n = 56)	IgA/IgM NMDAR positive (n = 56)
Age (y)	60.0 (28.0–86.0)	60.0 (32.0–79.0)	61.0 (28.0–86.0)
Sex			
Female	40 (35.7)	20 (35.7)	20 (35.7)
Male	72 (64.3)	36 (64.3)	36 (64.3)
Cancer type			
Melanoma	24 (21.4)	12 (21.4)	12 (21.4)
Breast cancer	22 (19.6)	11 (19.6)	11 (19.6)
Prostate cancer	22 (19.6)	11 (19.6)	11 (19.6)
Gastrointestinal cancer	20 (17.9)	10 (17.9)	10 (17.9)
Gastric/esophageal cancer	14 (12.5)	7 (12.5)	7 (12.5)
Colorectal cancer	6 (5.4)	3 (5.4)	3 (5.4)
Lung cancer	14 (12.5)	7 (12.5)	7 (12.5)
Non–small-cell lung cancer	12 (10.7)	6 (10.7)	6 (10.7)
Small-cell lung cancer	2 (1.8)	1 (1.8)	1 (1.8)
Hematologic malignancy	10 (8.9)	5 (8.9)	5 (8.9)
Hodgkin lymphoma	6 (5.4)	3 (5.4)	3 (5.4)
Non-Hodgkin lymphoma	4 (3.6)	2 (3.6)	2 (3.6)
Presence of tumor recurrence	9 (8.0)	3 (5.4)	6 (10.7)
ECOG score			
0	82 (73.2)	41 (73.2)	41 (73.2)
1	24 (21.4)	12 (21.4)	12 (21.4)
2	5 (4.5)	2 (3.6)	3 (5.4)
3	1 (0.9)	1 (1.8)	0 (0.0)
Karnofsky score	100.0 (40.0–100.0)	100.0 (40.0–100.0)	100.0 (50.0–100.0)

assessed by the Karnofsky and Eastern Cooperative Oncology Group (ECOG) scores.

Final Sample

IgA and/or IgM NMDAR autoantibodies were detected in 99 of 1,055 patients (9.4%) (eTables 3–4). Among the 635 patients with cognitive testing, a final sample of 56 were IgA/IgM NMDAR autoantibody–positive (eFigure 1). Details on age, sex, and cancer distribution for the original and final samples are presented in eTable 5 and eFigures 2–4. The final sample was matched 1:1 to autoantibody-negative patients by age, sex, cancer type, and cancer stage (Table 1).

Data Analysis

Two-group differences were assessed using the Pearson χ^2 test or Fisher exact test for categorical variables, or the Student t test for continuous variables. Multiple-group differences were assessed using permutation tests of independence with the R package "coin." Correlation analysis was performed with nonparametric Spearman rank correlation. All statistical tests were two-sided. p Values ≤0.05 were considered significant. Statistical analysis and visualization were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Data Availability

Deidentified raw data are available on reasonable request from the corresponding author.

Results

Cancer patients with IgA/IgM NMDAR autoantibodies showed significant and clinically relevant impairment in verbal long-term memory, visuospatial long-term memory, and short-term memory compared with autoantibody-negative patients (Figure 1, eTable 6). Autoantibody-positive patients performed worse on all trials of the verbal memory test (delayed recall: Cohen $d = 0.49$) and visuospatial memory test (delayed recall: $d = 0.50$). In addition, autoantibody-positive patients performed worse on the short-term/working memory task ($d = 0.40$). No relevant differences were observed in other cognitive domains or PROMs (eTable 6). Both groups were similar in education, as well as Karnofsky and ECOG scores (eTable 6, Table 1). Memory performance and group differences were similar across different cancer types (eFigures 5–7). One patient had a coexisting autoantibody (ARHGAP26, eTables 4 and 7).

Subgroup analysis revealed that memory deficits were primarily associated with IgA NMDAR autoantibodies (Figure 2, A–C, eTable 8) while IgM-positive patients showed similar trends without reaching statistical significance (Figure 2, A–C, eTable 9).

NMDAR IgA autoantibody titers correlated with reduced performance in both verbal and visuospatial memory tasks (Figure 2, D and E). IgM autoantibody levels showed a similar trend, but without a significant correlation (eFigures 8 and 9).

Discussion

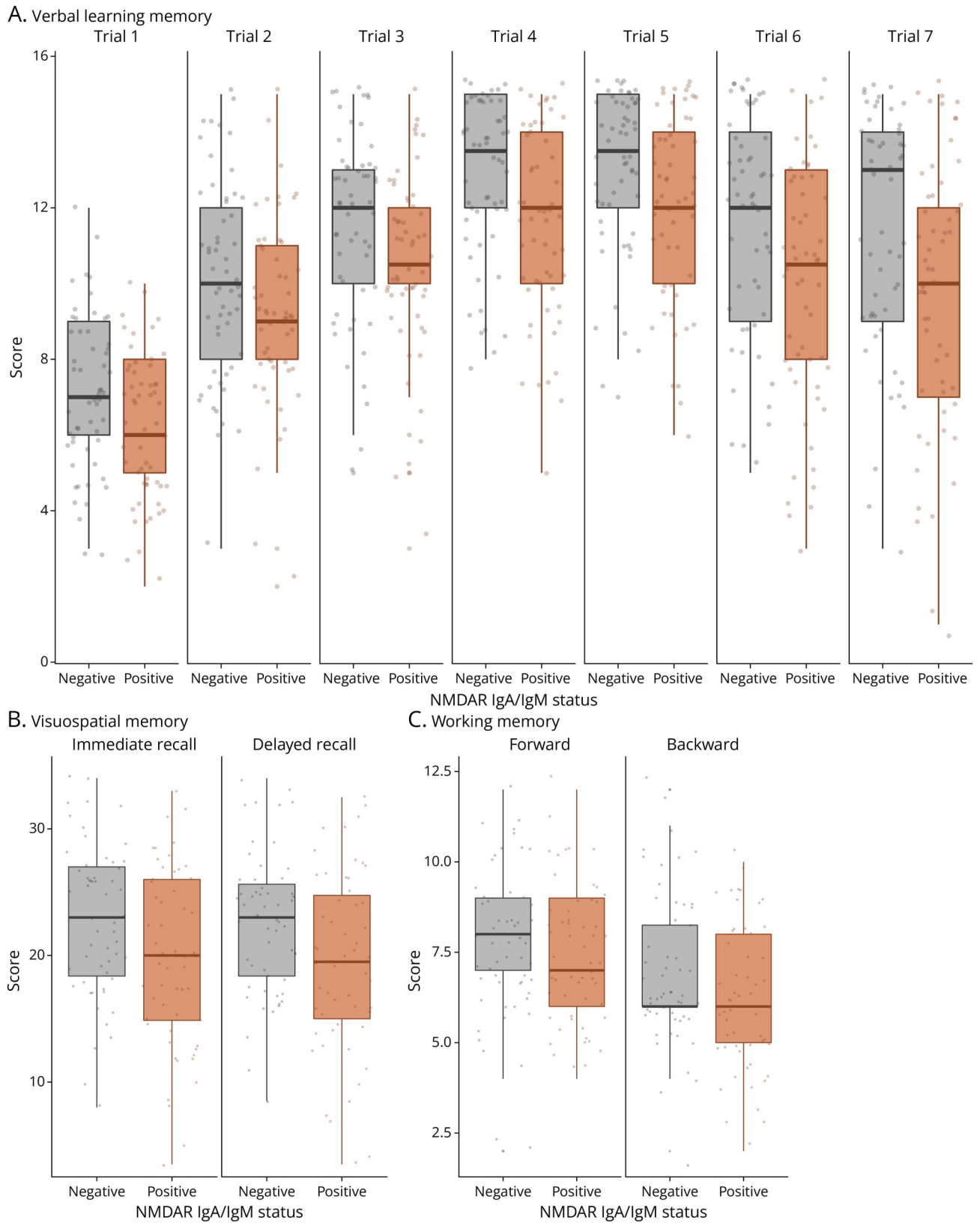
We show that serum IgA and IgM NMDAR antibodies are associated with memory impairment in patients with cancer, with higher IgA NMDAR antibody titers correlating with more severe memory deficits.

NMDAR IgG autoantibodies are associated with anti-NMDAR encephalitis.[13] These patients exhibit cognitive and memory deficits,[14] which specifically persist long-term.[3,15] By contrast, IgA and IgM are not associated with anti-NMDAR encephalitis. However, previous studies have described IgA NMDAR antibodies in patients with slowly progressing cognitive impairment[12] and IgA and IgM NMDAR antibodies in a subgroup of patients with dementia.[6]

In patients with cancer, IgA and IgM NMDAR antibodies are the most frequent class of neuronal autoantibodies.[9] We previously identified neuronal autoantibodies (including NMDAR IgA/IgM) as a potential pathogenic factor in the development of cancer-related cognitive impairment (CRCI).[4,5] CRCI occurs independently of chemotherapy and represents an important complication that is of increasing significance and prevalence.[e1,e2] Building on our previous studies linking neuronal antibodies to CRCI, we now demonstrate that IgA/IgM NMDAR antibodies specifically correlate with memory impairment in patients with cancer, with IgA titers proportional to deficit severity. This suggests autoantibody-associated autoimmunity as a potential factor in CRCI pathophysiology, particularly affecting memory. Moreover, an association of NMDAR antibodies with memory impairments is highly plausible on pathophysiologic grounds: NMDARs are a key molecular mechanism for learning and memory,[e3] and the hippocampus—the key brain structure for memory—contains the highest density of NMDARs.[e4] Consequently, NMDAR dysfunction—whether from antagonists or autoantibodies—is linked to memory impairment.[e5,e6] It is important to note that promising results from immunosuppression in patients with IgA NMDAR autoantibodies suggest potential benefits of immunomodulatory therapy for these patients.[2,12]

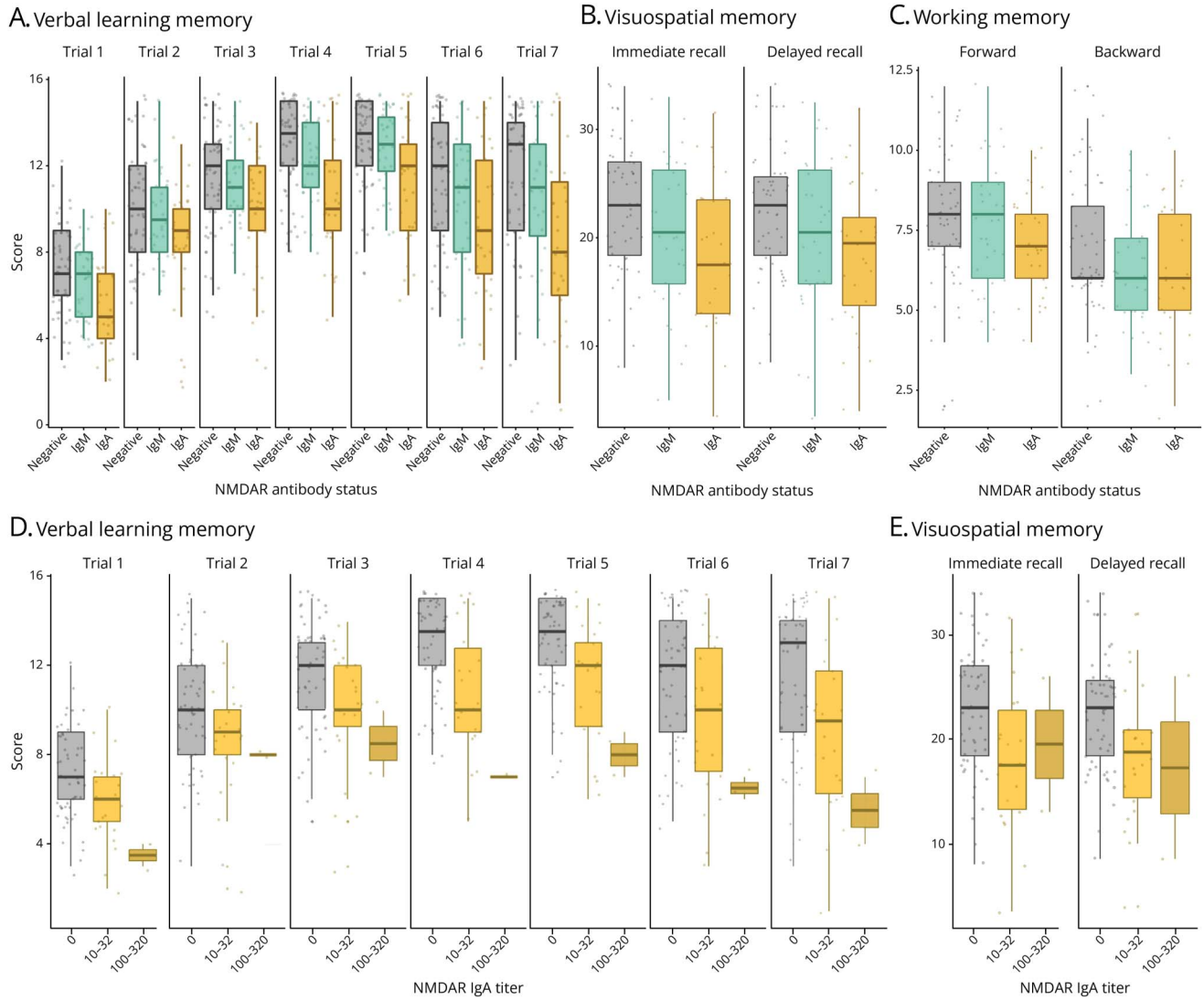
While the effects of NMDAR autoantibodies of IgG isotype have been clearly demonstrated,[e7] there is also good evidence showing molecular and electrophysiologic effects of the IgA and IgM isotypes: these autoantibodies were similarly shown to bind and downregulate the NMDAR, with subsequent electrophysiologic effects similar to IgG NMDAR antibodies.[10-12] However, another study using a different methodology could not confirm these results.[e8] Our data here link IgA/IgM NMDAR autoantibodies to memory dysfunction, warranting further investigations on their mechanistic role. Of interest, a recent study showed a similar association in a large

Figure 1 Seroprevalence of Anti-NMDAR IgA or IgM Autoantibodies Correlates With Deficits in Memory



(A) Verbal Learning Memory Test (VLMT) scores for Trials 1–7 in patients with NMDAR IgA or IgM vs autoantibody-negative patients. (B) Rey-Osterrieth Complex Figure (ROCF) test scores for the immediate and delayed recall trials in patients with NMDAR IgA or IgM vs autoantibody-negative patients. (C) Digit span scores for forward and backward trials in patients with NMDAR IgA or IgM vs autoantibody-negative patients.

Figure 2 Comparison Between Anti-NMDAR IgA and IgM Autoantibodies (A–C) and Titer Correlation of IgA Autoantibodies With Cognitive Deficits (D–E)



(A) Verbal Learning Memory Test (VLMT) scores for Trials 1–7 in patients with either NMDAR IgA or IgM compared with autoantibody-negative patients. (B) Rey-Osterrieth Complex Figure (ROCF) test scores for the immediate and delayed recall trials. (C) Digit span scores for forward and backward trials. (D) VLMT scores for Trials 1–7 in patients with NMDAR IgA plotted by titer level. (E) ROCF scores for the immediate and delayed recall trials in patients with NMDAR IgA plotted by titer level.

cohort of poststroke patients.[8] Together, these observations suggest a potential second-hit hypothesis, where autoantibody seroprevalence with either cancer or stroke might increase the risk of memory impairment. Indeed, we and others previously described a potential role of blood-brain barrier (BBB) damage that might increase the risk of cognitive impairment in patients with these serum autoantibodies.[9,e9] In patients with cancer, systemic inflammation with increased levels of proinflammatory cytokines (e.g., IL-6 and TNF-alpha) could compromise the BBB integrity. The stronger cognitive impact of IgA autoantibodies could be due to their smaller size facilitating brain entry across a damaged BBB, as well as their more specific, affinity-matured nature, in contrast to the larger IgM antibodies that reflect an earlier and less-targeted immune response.

Our study has several limitations. First, the cohort included diverse cancer entities with different cognitive risk profiles. Second, our rigorous exclusion criteria, applied to eliminate potential confounders of cognitive dysfunction, resulted in a final sample that was small and slightly younger compared with the original cohort. A key limitation is the study's cross-sectional design, which precluded any analysis of the long-term dynamics, progression, or reversibility of cognitive deficits in relation to the clinical course or cancer treatment. Finally, the absence of CSF and quantitative neuroimaging data prevented the direct investigation of intrathecal antibody synthesis and underlying structural brain changes.

In summary, our data show a titer-dependent association between serum IgA/IgM NMDAR autoantibodies and

memory deficits in patients with cancer. Future research should explore this effect in noncancer populations, potentially identifying a biomarker or pathogenic factor in memory disorders that could benefit from immunotherapy.

Author Contributions

F. Bartels: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A. Tapuc: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K. Rentzsch: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S.L. Duong: drafting/revision of the manuscript for content, including medical writing for content. H. Prüss: drafting/revision of the manuscript for content, including medical writing for content. C. Finke: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Disclosure

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