

Received: 16 June 2020 | Accepted: 15 October 2020

DOI: 10.1111/ene.14604

**european journal  
of neurology**  
the official journal of the european academy of neurology**ORIGINAL ARTICLE**

# Course of neuropsychological impairment during natalizumab-associated progressive multifocal leukoencephalopathy

Markus Kinner<sup>1</sup>  | Christian Prehn<sup>1</sup> | Ruth Schneider<sup>1</sup> | Christoph Schroeder<sup>1</sup> | Eva Kolb<sup>1</sup> | Ralf Gold<sup>1</sup> | Robert Hoepner<sup>1,2</sup> | Andrew Chan<sup>1,2</sup><sup>1</sup>Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany<sup>2</sup>Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland**Correspondence**Markus Kinner, Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany.  
Email: markus.kinner@rub.de**Abstract**

**Background and purpose:** Progressive multifocal leukoencephalopathy (PML), an opportunistic infection of the central nervous system from the John Cunningham virus (JCV), is a side effect of natalizumab (NTZ) treatment for relapsing–remitting multiple sclerosis (RRMS), potentially leading to a substantial increase of physical and mental disability. Nevertheless, data of neuropsychological impairment during the NTZ-PML disease course are missing. Our objective was to evaluate the neuropsychological disease course of NTZ-PML patients and to compare neuropsychological deficits of NTZ-PML patients with two different non-PML multiple sclerosis (MS) cohorts.

**Methods:** Neuropsychological examinations of 28 NTZ-PML patients performed during different phases of the disease ([i] at PML diagnosis, [ii] during immune reconstitution inflammatory syndrome [IRIS], and [iii] post-IRIS/PML) were retrospectively analyzed and compared to those of NTZ-treated RRMS or secondary progressive MS patients with and without immunotherapy.

**Results:** Compared to controls, NTZ-PML patients performed worse in neuropsychological examinations during all stages of disease, mainly affecting visuospatial ability and working memory. Furthermore, failure to eliminate the JCV from the central nervous system was associated with a prodromal decline of cognition, especially working memory.

**Conclusions:** Working memory and visuospatial abilities are the core neuropsychological deficits of NTZ-PML patients in long-term follow-up. Our findings should be implemented in neurorehabilitation strategies.

**KEYWORDS**

cognition, natalizumab, PML, progressive multifocal leukoencephalopathy, psychiatry, relapsing–remitting multiple sclerosis, Tysabri

**INTRODUCTION**

Progressive multifocal leukoencephalopathy (PML), caused by an infection with the John Cunningham Virus (JCV), is a rare disease

that in the past was mainly related to human immunodeficiency virus (HIV) infections and blood cancers like leukemia or lymphoma [1].

However, PML also occurs as an adverse event during natalizumab (NTZ) therapy [2], an  $\alpha$ 4-integrin inhibitor, for relapsing–remitting

Robert Hoepner and Andrew Chan contributed equally to this work.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *European Journal of Neurology* published by John Wiley & Sons Ltd on behalf of European Academy of Neurology

multiple sclerosis (RRMS) [3]. By 5 September 2018, 795 NTZ-treated RRMS patients developed NTZ-PML, resulting in an incidence of 4.17 per 1000 NTZ-treated patients, of whom 24% died [4]. No antiviral therapy exists, and early diagnosis to enable early discontinuation of NTZ therapy was found to positively influence NTZ-PML survival [5]. We have previously demonstrated that neuropsychological impairment, especially a deterioration of visuospatial ability and working memory, are often present at the beginning of NTZ-PML and might therefore support NTZ-PML diagnosis [6]. Interestingly, these deficits of NTZ-PML patients were also observed in an independent cohort of HIV-infected individuals with PML [7], pointing to a probable PML type pattern of neuropsychological deterioration.

To more precisely describe neuropsychological deterioration during the course of NTZ-PML, in this article we aimed to investigate the course of neuropsychological impairment during the NTZ-PML disease course and compare neuropsychological findings of NTZ-PML patients with two multiple sclerosis (MS) control groups: NTZ-treated RRMS and secondary progressive MS (SPMS) patients.

## METHODS

The ethics committee of Ruhr University Bochum approved this retrospective observational study (no. 4566-13). All patients (22 RRMS, 74 SPMS, 28 NTZ-PML (some patients previously published in Kinner et al. [8] (neuropsychological impairment in the SPMS control group), Hoepner et al. [9] (neuropsychological impairments at PML diagnosis), and Hoepner et al. [6] (longitudinal clinical outcome of PML patients) (Table S1)) were identified by retrospective analysis of medical records. RRMS and NTZ-PML groups were matched in terms of age at MS diagnosis, age, and Expanded Disability Status Scale (EDSS) at first neuropsychological examination (NPE), immunosuppression before NTZ start, and sex. Only duration of NTZ treatment differed significantly, with a longer duration in patients who developed NTZ-PML. Longitudinal NPEs were performed in a standardized manner as used in our clinical practice and described in Kinner et al. [8]. The battery is composed of the Multiple Choice Vocabulary Intelligence Test as a test for crystallized intelligence and linguistic skills, d2 test as a test for attention and information processing speed, German Performance Testing System subtests 3 (deductive thinking) and 7 (visuospatial abilities), Regensburg Word Fluency Test subtest lexical word fluency (linguistic skills and crystallized intelligence) and lexical category change (cognitive flexibility as a domain of executive function and linguistic skills), Verbal Learning and Memory Test A (short-term memory and linguistic skills), Wechsler Memory Scale Subtests Visual Reproduction I (visuospatial abilities and working memory), Digit Span Forward and Backward (working memory), and Shulman Clock Drawing Test (visuospatial abilities and crystal intelligence).

Relapsing–remitting multiple sclerosis patients diagnosed with NTZ-PML underwent an NPE at three time points during their disease course: (i) at diagnosis ( $n = 21$ ;  $9.0 \pm 17$  days after diagnosis), (ii) at immune reconstitution inflammatory syndrome (IRIS; defined as gadolinium enhancing PML-lesions in magnetic resonance imaging

[MRI];  $n = 10$ ;  $10.0 \pm 47.3$  days after first gadolinium enhancement in MRI), and (iii) post-IRIS/PML ( $n = 16$ ;  $19.0 \pm 32.5$  months after first gadolinium-negative MRI in patients with positive JCV polymerase chain reaction [PCR] at last follow-up or after proof of JCV PCR negativity in cerebrospinal fluid [CSF]); all PCR-analyses were performed at the Department of Virology, University of Düsseldorf). Four patients of this post-IRIS-cohort were JCV noneliminators, as they were JCV positive in CSF testing at the time of their last NPE ( $24 \pm 31$  months after NTZ-PML diagnosis and  $4.5 \pm 34.5$  months after first gadolinium-negative MRI).

Compared to NTZ-PML patients, where an NPE was performed during ongoing active encephalitis (at early PML and PML-IRIS, as well as for JCV noneliminators also at post-IRIS), in all MS controls (NTZ-RRMS and SPMS), NPEs were performed during a phase of MS disease without any acute MS exacerbation. Treatment of SPMS patients was intravenous (IV) mitoxantrone (42/74; cumulative dose:  $49.0 \pm 29.5$  mg/m<sup>2</sup> body surface) or intrathecal triamcinolone acetate (32/74; 40–160 mg every 3–4 months).

All values are presented as median  $\pm$  interquartile range. To detect differences in neuropsychological tests between PML patients and each control, Mann-Whitney *U* tests were performed using SPSS (IBM, Armonk, NY, USA).

## RESULTS

### Characteristics of study populations

Natalizumab-PML patients and control groups did not differ in age at MS diagnosis and sex. Whereas, age at NPE and disability as measured by the EDSS differed between groups, with SPMS controls being significantly older (SPMS:  $47.5 \pm 14.0$ , RRMS:  $37.5 \pm 16.8$ , and NTZ-PML:  $39.5 \pm 11.8$  years, both  $p < 0.05$ ; Table 1) and more disabled than the NTZ-PML patients and the RRMS controls (SPMS:  $6.0 \pm 1.5$ , RRMS:  $3.0 \pm 2.5$ , NTZ-PML:  $4.0 \pm 2.8$ , each  $p < 0.05$ ; Table 1). Furthermore, NTZ-PML patients had a significantly longer duration of NTZ therapy than the NTZ-treated control group (NTZ-PML:  $48.0 \pm 36.0$ , NTZ:  $25.0 \pm 26.2$  months,  $p < 0.05$ ; Table 1).

### Neuropsychological profile of NTZ-PML patients compared to MS controls

Using the Beck Depression Inventory-II, no differences in depressive symptoms were found between NTZ-PML patients and both independent MS control groups (NTZ:  $12.0 \pm 14.5$ ; SPMS:  $10.0 \pm 10.0$ ; early PML:  $10.0 \pm 9.5$ ; PML-IRIS:  $8.0 \pm 8.0$ ; post-IRIS/PML:  $8.0 \pm 8.0$ ; all  $p > 0.05$ ; Table 2).

Natalizumab-PML patients performed significantly worse in Shulman Clock Drawing Test (SCD) at all time points than NTZ-treated RRMS patients (NTZ:  $1 \pm 0$ ; early PML:  $3 \pm 2$  [vs. NTZ  $p < 0.001$ ]; PML-IRIS:  $3 \pm 1$  [vs. NTZ  $p < 0.001$ ]; post-IRIS/PML:  $1 \pm 2$  [vs. NTZ  $p < 0.01$ ]). Compared to SPMS patients (SCD [SPMS]:  $1 \pm 1$ ),

**TABLE 1** Basic characteristics of NTZ-PML patients, RRMS, and SPMS controls

	PML	NTZ	SPMS
<i>n</i>	28	22	74
Sex, m/f	10/18	7/15	25/49
Age at first NPE, years, median [IQR]	39.5 [34.0–45.8] <sup>†</sup>	37.5 [27.5–44.3] <sup>†</sup>	47.5 [41.0–55.0]
Age at MS diagnosis, years, median [IQR]	28 [21–34] <sup>†</sup>	28 [23–35]	34.0 [27–43]
EDSS at first assessment, median [IQR]	4.0 [3.1–5.9] <sup>†</sup>	3.0 [1.5–4.0] <sup>†</sup>	6.0 [5.0–6.5]
Immunosuppression, before NTZ start, yes/no/no data	5/21/2	3/18/1	42/32/0
NTZ-duration, months, median [IQR]	48.0 [30.3–66.3] <sup>**</sup>	25.0 [13.8–40]	
PML diagnosis until first NPE, days, median [IQR]	9.0 [4.0–21.0]	<i>n</i> = 21	
IRIS (first Gd + MRI) until second NPE, days, median [IQR]	10.0 [1.5–48.8]	<i>n</i> = 10	
JCV-negative or Gd-negative until third NPE, months, median [IQR]	19.0 [0.3–32.8]	<i>n</i> = 16	
Gd-negative until third NPE if JCV-positive at third NPE, months, median [IQR]	4.5 [0.0–34.5]	<i>n</i> = 4	
JCV-negative until third NPE, months, median [IQR]	21.5 [4.0–32.8]	<i>n</i> = 12	
PLEX before IRIS, yes/no	20/7		
IA before IRIS, yes/no	17/10		
PLEX/IA cycles before IRIS, median [IQR]	5 [4–6]		
Mefloquine, yes/no	27/1		
Mirtazapine, yes/no	26/2		
Levetiracetam, yes/no	25/3		
Steroids in IRIS, yes/no/no data	24/3/1 (3/1 of continuously JCV-positive)		

Note: Mann-Whitney *U* test for continuous and Fisher exact test for dichotomous variables.

Abbreviations: EDSS, Expanded Disability Status Scale; Gd, gadolinium; IA, immunoadsorption; IQR, interquartile range; IRIS, immune reconstitution inflammatory syndrome; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; NPE, neuropsychological examination; NTZ, natalizumab; PLEX, plasmapheresis; PML, progressive multifocal leukoencephalopathy; SPMS, secondary progressive MS.

<sup>†</sup>Significant differences versus SPMS; each *p* < 0.05.

<sup>\*\*</sup>Significant differences versus NTZ.

differences were only detected shortly postdiagnosis prior to IRIS (*p* < 0.05) and during the IRIS phase (*p* < 0.01) of NTZ-PML (Table 2, Figure 1).

In addition to visuospatial ability, working memory, tested by the Digit Span Backward test (WMS-R\_DSB), was affected in NTZ-PML patients with pronounced deficits during all phases of disease compared to NTZ-treated RRMS and SPMS controls (NTZ: 7.0 ± 3.0; SPMS: 6.0 ± 2.0; early PML: 4.0 ± 3.0 (vs. NTZ: *p* < 0.001; vs. SPMS: *p* < 0.001); PML-IRIS: 3.5 ± 4.0 (vs. NTZ: *p* < 0.001; vs. SPMS: *p* < 0.05); post-IRIS/PML: 5.0 ± 2.0 (vs. NTZ: *p* < 0.001; vs. SPMS: *p* < 0.05); Table 2, Figure 2).

### Neuropsychological profile of NTZ-PML patients with and without elimination of JCV from the central nervous system

Natalizumab-PML patients with and without JCV elimination from the CSF did not differ in steroid administration during IRIS or NTZ-PML treatment protocol (data not shown). Comparing NTZ-PML patients who successfully eliminated the JCV from the CSF with those who remained JCV positive during follow-up unmasked a

predominant decline in cognitive function in the patient population who did not eliminate the JCV in a wide range of NPEs: (i) SCD (JCV negative: 1 ± 1, JCV positive: 5 ± 1; *p* < 0.01; Figure 1), (ii) Multiple Choice Vocabulary Test (JCV-negative: 30 ± 5, JCV positive: 15.5 ± 7; *p* < 0.001; Figure 3), (iii) Verbal Learn and Memory Test (VLMT; fifth repetition: JCV negative: 14 ± 1.5, JCV positive: 11 ± 6; *p* < 0.05; seventh repetition: JCV negative: 12 ± 3, JCV positive: 3 ± 9; *p* < 0.05). Analyzing an association between the amount of JCV copy numbers in the CSF and post-IRIS/PML cognitive performance of all NTZ-PML patients demonstrated a worse cognitive outcome in those with higher JCV copy numbers in the CSF in the Digit Span Backward test, Digit Span Forward test, VLMT (first and seventh repetition, as well as interference round), and German Performance Test subtest 3 (each *p* < 0.05; Pearson correlation; Table 2).

### DISCUSSION

This is the first study to describe neuropsychological dysfunction during different phases of the NTZ-PML disease course using a standardized test battery in the largest NTZ-PML cohort treated in a single center. As previously demonstrated in a smaller cohort of

TABLE 2 Neuropsychological test data of all three cohorts

Scales	Median (IQR)														
	n	NTZ, n	SPMS, n	Early PML, n	PML-IRIS, n	Post-IRIS, n	JCV-negative, n	JCV-positive, n	NTZ	SPMS	Early PML	PML-IRIS	Post-IRIS/PML	JCV-negative = post-PML	JCV-positive = post-IRIS
SCD	22	72	18	18	9	17	14	3	1 (0)	1 (1)	3 (2) <sup>***#</sup>	3 (1) <sup>***##</sup>	1 (2) <sup>**</sup>	1 (1) <sup>***</sup>	5 (1)
WMS-R_DSB	22	71	18	18	10	18	15	3	7 (3)	6 (2)	4 (3) <sup>***###</sup>	3.5 (4) <sup>***#</sup>	5 (2) <sup>***#</sup>	5 (2)	4 (2)
WMS-R_DSF	22	72	18	18	10	18	15	3	8.5 (3)	7 (2)	6.5 (2) <sup>***</sup>	6 (2) <sup>**</sup>	6 (3) <sup>**</sup>	6 (3)	5 (6)
MCVT	22	62	17	17	6	15	11	4	29 (7)	28.5 (6)	27 (4)	26.5 (12)	27 (8)	30 (5) <sup>***</sup>	15.5 (7)
GPT3	22	67	12	12	6	12	11	1	24.5 (7)	19 (8)	21 (9.5) <sup>*</sup>	19.5 (3) <sup>**</sup>	20.5 (9)	21 (9)	14
d2_OA	20	54	9	9	5	10	10	0	400 (177)	320 (125)	371 (133)	356 (65)	381 (120)	381 (120)	
d2_ER	20	54	9	9	5	10	10	0	3.3 (4.2)	2.0 (3.9)	7 (6.8)	8.8 (9.9) <sup>***##</sup>	2.6 (6.8)	2.6 (6.8)	
d2_OA-F	20	54	9	9	5	10	10	0	385 (176)	316.5 (108)	354 (197)	274 (53)	338 (242)	338 (242)	
d2_CP	20	55	9	9	5	10	10	0	153 (63.5)	126 (38)	138 (89)	109 (44) <sup>#</sup>	130 (100)	130 (100)	
RWT_WFL	22	65	14	14	9	14	13	1	11 (7)	9 (4)	9 (9)	8 (10)	12 (10)	12 (10)	7
RWT_CG	22	64	14	14	8	14	13	1	12 (6)	12 (6)	6.5 (8) <sup>*</sup>	6.5 (9) <sup>*</sup>	12 (9)	12 (9)	12
VLMT_1	22	72	15	15	9	15	12	3	7 (2)	5.5 (3)	6 (3)	6 (3) <sup>*</sup>	6 (2) <sup>*</sup>	6 (2)	4 (3)
VLMT_5	22	72	14	14	9	15	12	3	14 (2)	13 (4)	12.5 (5) <sup>*</sup>	9 (7)	14 (2)	14 (1.5) <sup>†</sup>	11 (6)
VLMT_1	22	72	14	14	9	15	12	3	7 (3)	5 (2.5)	6 (3)	5 (3)	7 (5)	7 (4)	5 (2)
VLMT_6	22	71	14	14	9	15	12	3	12.5 (3)	10 (7)	8.5 (9) <sup>**</sup>	6 (11) <sup>*</sup>	10 (6) <sup>*</sup>	11.5 (5)	2 (9)
VLMT_7	22	71	14	14	9	15	12	3	13.5 (3)	10 (6)	9.5 (6) <sup>**</sup>	8 (11) <sup>**</sup>	12 (6)	12 (3) <sup>†</sup>	3 (9)
VLMT_Wf	17	62	13	13	7	12	9	3	15 (1)	13 (4)	13 (3) <sup>*</sup>	12 (18) <sup>*</sup>	15 (4.5)	15 (3)	11 (5)
WMS-R_VR	20	55	12	12	7	12	11	1	38.5 (5.5)	35 (6)	35.5 (8.5)	31 (31) <sup>**</sup>	34 (7.5) <sup>*</sup>	36 (7)	16
GPT7	22	66	13	13	6	12	11	1	20.5 (9)	13 (7)	14 (76) <sup>*</sup>	12 (10)	15 (7.5) <sup>**</sup>	15 (8)	0
BDI	22	67	15	15	5	13	12	1	12 (14.5)	10 (10)	10 (9.5)	8 (8)	8 (8)	8 (7.5)	3

Note: All data are expressed as median and interquartile range. Mann-Whitney U test. Significantly worse compared to NTZ (\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ), SPMS (<sup>#</sup> $p < 0.05$ , <sup>##</sup> $p < 0.01$ , <sup>###</sup> $p < 0.001$ ), and JCV-positive (<sup>†</sup> $p < 0.05$ , <sup>††</sup> $p < 0.01$ , <sup>†††</sup> $p < 0.001$ ).

Abbreviations: BDI, Beck Depression Inventory; d2\_OA/ER/OA-F/CP, d2 test overall/error ratio/overall less false/concentration performance; DSB/F, subtest Digit Span Backward/Forward; GPT3/7, German Performance Measuring System subtest 3/7; IQR, interquartile range; IRIS, immune reconstitution inflammatory syndrome; JCV, John Cunningham virus polymerase chain reaction in cerebrospinal fluid at post-IRIS timepoint; MCVT, Multiple Choice Vocabulary Test; NTZ, natalizumab; PML, progressive multifocal leukoencephalopathy; RWT\_WFL/CG, Regensburg Word Fluency Test subtest word fluency/category change; SCD, Shulman Clock Drawing Test; SPMS, secondary progressive multiple sclerosis; VLMT\_1/5/6/7/Wf/1 = verbal learning and memory test first/fifth/sixth/seventh repetition/retrieval less false/interference; VR = subtest visual reproduction; WMS-R = Wechsler Memory Scale-Revised.

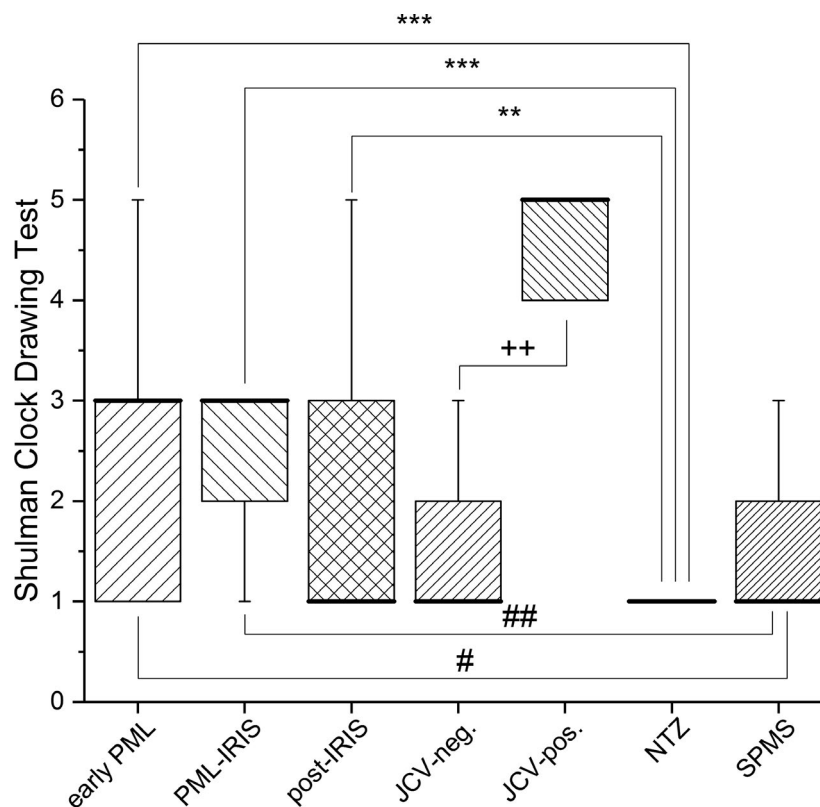
eight NTZ-PML patients [6] and again validated by our study, all NTZ-PML patients had neuropsychological abnormalities in formal testing, highlighting the relevance of this symptom in NTZ-PML patients.

First, our NTZ-PML cohort demonstrated a deterioration in all tests during the IRIS phase, with a trend to recovery at the last time point (Table 2) if JCV was eliminated from the CSF. In contrast, in NTZ-PML patients who were not able to eliminate the virus from the central nervous system, a pronounced deterioration of neuropsychological function was seen, which also matches the clinical course of these patients (clinical course excluding neuropsychological findings of all patients as reported in Hoepner et al. [9]) without clear difference during PML but a worse recovery of disabilities caused by PML. Also, the previously shown core neuropsychological deficits of NTZ-PML patients (working memory and visuospatial abilities) [6] were markedly affected in continuously JCV-positive NTZ-PML patients. In addition, we could demonstrate a negative correlation between the highest JCV copy number in the CSF and working memory performance at last neuropsychological assessment post-PML in all NTZ-PML patients. In our view, this provides additional proof that JCV infection is associated with progressing cognitive decline, especially in the previously mentioned core domains [6].

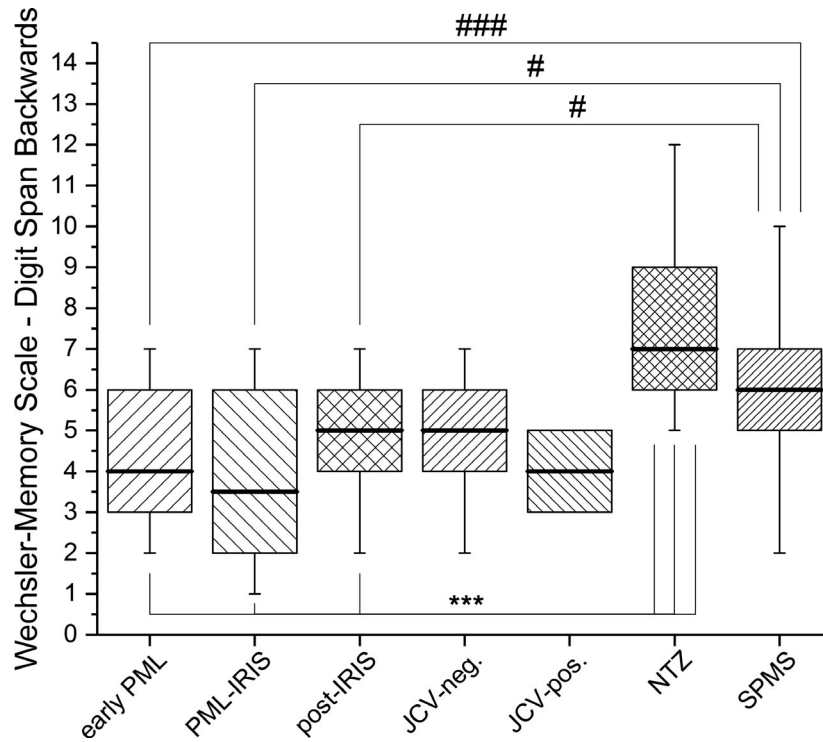
As our study included an RRMS as well as a SPMS cohort, our finding of a PML-related core neuropsychological deficit could be

distinguished from MS-related cognitive decline. A decline in processing speed in RRMS patients and a decline in frontal executive functions in SPMS patients have been previously demonstrated as core neuropsychological deficits [10,11]. In SPMS, as a model for the neurodegenerative and chronic progressive phase of MS, affected cognitive fields also differed from NTZ-PML, which pronounces the distinction of NTZ-PML core cognitive deficits.

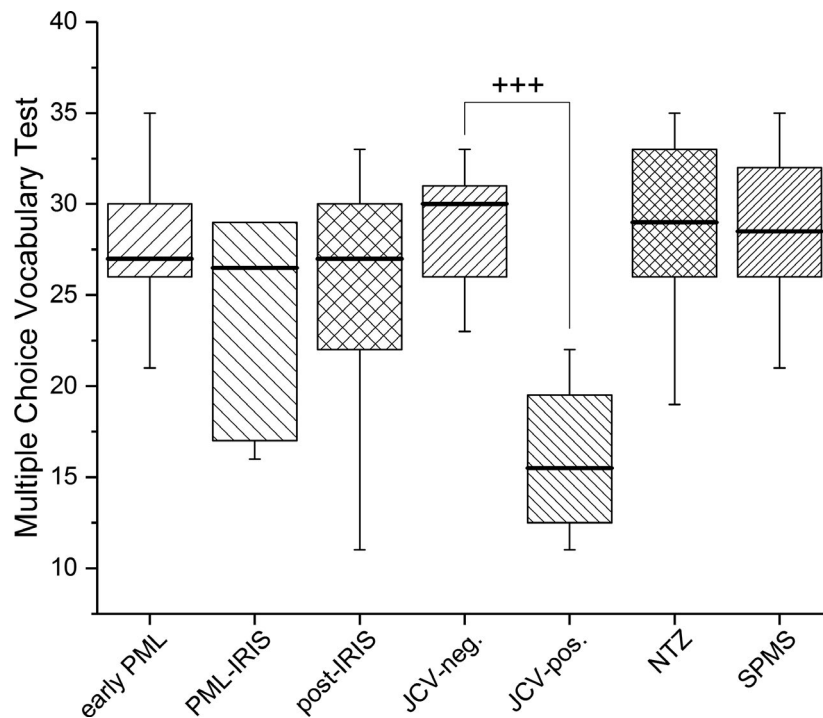
The main limitation of our retrospective study is the missing data at several time points of NTZ-PML. These missing values were caused by the retrospective nature of our study, which prohibits a direct intraindividual comparison of NPEs at different phases of NTZ-PML. The neuropsychological test battery used is adjusted to scan for neuropsychological deficits in our clinical routine. Therefore, some cognitive domains (especially executive functions) might be underrepresented. Overall, the NTZ-PML and RRMS groups are well matched. However, it should be noted that the NTZ-PML group has a longer NTZ therapy duration than the RRMS group. Matching based on MRI was not possible due to missing MRI data in the RRMS group. As EDSS at the first NPE does not differ, we do not think that this is due to a higher disease activity before starting NTZ. In contrast, NTZ therapy is associated with cognitive stability or even improvement in some studies [12], so that a more severe cognitive effect of NTZ-PML patients by MS disease seems unlikely.



**FIGURE 1** Shulman Clock Drawing Test compared to study group and phase of NTZ-PML. Mann-Whitney *U* test. #NTZ-PML versus SPMS,  $p < 0.05$ ; ## $p < 0.01$ ; \*NTZ-PML versus JCV-neg.,  $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ; ++NTZ-PML JCV-negative versus NTZ-PML JCV-positive;  $p < 0.01$ . IRIS, immune reconstitution inflammatory syndrome; JCV, John Cunningham virus; neg., negative; NTZ, natalizumab; PML, progressive multifocal leukoencephalopathy; pos., positive; SPMS, secondary progressive multiple sclerosis



**FIGURE 2** Wechsler Memory Scale–Digit Span Backward Test compared to the study group and phase of NTZ-PML. Mann-Whitney *U* test. #NTZ-PML versus SPMS,  $p < 0.05$ ; ### $p < 0.001$ ; \*\*\*NTZ-PML versus NTZ;  $p < 0.001$ . IRIS, immune reconstitution inflammatory syndrome; JCV, John Cunningham virus; neg., negative; NTZ, natalizumab; PML, progressive multifocal leukoencephalopathy; pos., positive; SPMS, secondary progressive multiple sclerosis



**FIGURE 3** Multiple Choice Vocabulary Test compared to the study group and phase of NTZ-PML. Mann-Whitney *U* test. +++NTZ-PML JCV-negative versus NTZ-PML JCV-positive;  $p < 0.001$ . IRIS, immune reconstitution inflammatory syndrome; JCV, John Cunningham virus; NTZ, natalizumab; PML, progressive multifocal leukoencephalopathy; SPMS, secondary progressive multiple sclerosis

In addition to the limitations of the retrospective design, the NTZ-PML treatment, which can also affect cognition, must be highlighted. Our NTZ-PML patients were treated in a standardized fashion (Wenning et al.) [13], which included plasma exchange and immunoadsorption, mefloquine [14], mirtazapine [15], and prophylactic antiepileptic medication with levetiracetam [16]. In addition, during the IRIS phase, high-dose corticosteroids were used to prevent overshooting immunological damage. However, as the same qualitative profile of neurocognitive findings was also demonstrated after elimination of JCV, when medications for NTZ-PML treatment had already been withdrawn, a confounding effect of this treatment regime appears to be minor.

In conclusion, our data demonstrate working memory and visuospatial abilities as core neuropsychological deficits of NTZ-PML patients even in long-term follow-up. Fast JCV elimination from the CSF seems to protect against ongoing neuropsychological deterioration caused by NTZ-PML. Thus, our findings argue for a prompt and consequent treatment of NTZ-PML. As neuropsychological abnormalities were already present during early disease stages, NPE should be integrated in the diagnostic workup of suspected NTZ-PML. Finally, the description of the residual post-PML neuropsychological deficit should stimulate the development of rehabilitation programs tailored to the needs of NTZ-PML patients to support social reintegration.

## ACKNOWLEDGMENT

Open access funding enabled and organized by Projekt DEAL.

## DISCLOSURE OF CONFLICTS OF INTEREST

The authors declare no financial or other conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

Markus Kinner  <https://orcid.org/0000-0001-5790-4164>

## REFERENCES

- Astrom KE, Mancall EL, Richardson EP. Progressive multifocal leuko-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. *Brain* 1958;81:93-111.
- Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005;353:375-81.
- Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899-910.
- Biogen. Medical Information: TYSABRI® (natalizumab): PML in Patients Receiving TYSABRI (USA TYSABRI PML Update). [https://www.tysabri.de/de\\_de/home/dcsecure/welcome.html](https://www.tysabri.de/de_de/home/dcsecure/welcome.html) (accessed 06/03/2019).
- Clifford DB. Progressive multifocal leukoencephalopathy therapy. *J Neurovirol* 2015;21:632-636.
- Hoepner R, Klotz P, Faissner S, et al. Neuropsychological impairment in natalizumab-associated progressive multifocal leukoencephalopathy: implications for early diagnosis. *J Neurol Neurosurg Psychiatry* 2016;87:224-226.
- Zucchella C, Sinforiani E, Tavazzi E, et al. Neuropsychological evaluation and follow up in jcv- and non-jcv-related leukoencephalopathies in HIV infection. *Neurol Sci* 2011;32:833-839.
- Kinner M, Hoepner R, Klotz P, et al. Immunotherapy improves cognitive function in secondary progressive multiple sclerosis. *CNS Neurosci Ther* 2016;22:1019-1022.
- Hoepner R, Kolb EM, Dahlhaus S, et al. Predictors of severity and functional outcome in natalizumab-associated progressive multifocal leukoencephalopathy. *Mult Scler* 2017;23:830-835.
- Leavitt VM, Tosto G, Riley CS. Cognitive phenotypes in multiple sclerosis. *J Neurol* 2018;265:562-566.
- Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008;7:1139-1151.
- Mattioli F, Stampatori C, Bellomi F, Scarpazza C, Capra R. Natalizumab significantly improves cognitive impairment over three years in MS: pattern of disability progression and preliminary MRI findings. *PLoS One* 2015;10:e0131803.
- Wenning W, Haghikia A, Laubenberger J, et al. Treatment of progressive multifocal leukoencephalopathy associated with natalizumab. *N Engl J Med* 2009;361:1075-1080.
- Brickelmaier M, Lugovskoy A, Kartikeyan R, et al. Identification and characterization of mefloquine efficacy against JC virus in vitro. *Antimicrob Agents Chemother* 2009;53:1840-1849.
- O'Hara BA, Atwood WJ. Interferon beta1-a and selective anti-5HT(2a) receptor antagonists inhibit infection of human glial cells by JC virus. *Virus Res* 2008;132:97-103.
- Hoepner R, Dahlhaus S, Kollar S, et al. Prophylactic antiepileptic treatment reduces seizure frequency in natalizumab-associated progressive multifocal leukoencephalopathy. *Ther Adv Neurol Disord* 2014;7:3-6.

## SUPPORTING INFORMATION

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

**How to cite this article:** Kinner M, Prehn C, Schneider R, et al. Course of neuropsychological impairment during natalizumab-associated progressive multifocal leukoencephalopathy. *Eur J Neurol*. 2020;00:1-7. <https://doi.org/10.1111/ene.14604>

# THE IMPORTANCE OF GREY AND WHITE MATTER

In Multiple Sclerosis



Visit [GreyAndWhiteMS.com](https://www.GreyAndWhiteMS.com) for more information.