

Course of neuropsychological impairment during Natalizumab associated progressive multifocal leukoencephalopathy

Running title: Neuropsychological disease course of NTZ-ass. PML

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

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Abstract

Background: Progressive multifocal leukoencephalopathy (PML) - an opportunistic infection of the central nervous system with the John Cunningham virus (JCV) - is a side-effect of Natalizumab (NTZ) treatment for relapsing remitting (RR) multiple sclerosis (MS), potentially leading to a substantial increase of physical and also mental disability. Nevertheless, data of neuropsychological impairment during NTZ-PML disease course is missing.

Objective: To evaluate the neuropsychological disease course of NTZ-PML patients and to compare neuropsychological deficits of NTZ-PML patients with two different non-PML 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 and III. post-IRIS/PML) were retrospectively analyzed and compared to those of NTZ treated RRMS or SPMS patients with and without immunotherapy.

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

Conclusion: Working-memory and visuospatial ability are the core neuropsychological deficits of NTZ-PML patients even in long-term-follow-up. Our finding should be implemented in neurorehabilitation strategies.

Introduction

Progressive multifocal leukoencephalopathy (PML), caused by an infection with the John Cunningham Virus (JCV), is a rare disease which 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 adverse event during Natalizumab (NTZ) therapy[2], an α 4-integrin inhibitor, for relapsing remitting multiple sclerosis (RRMS)[3]. By September 5th 2018, 795 NTZ treated RRMS patients have developed NTZ-PML resulting in an incidence of 4.17 per 1000 NTZ treated patients of whom 24 % died[4]. Since now 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 diagnosis of NTZ-PML[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 probably PML typical pattern of neuropsychological deterioration.

To more precisely describe neuropsychological deterioration during the course of NTZ-PML, here we aimed to investigate the course of neuropsychological impairment during NTZ-PML disease course and compare neuropsychological findings of NTZ-PML patients with two 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 SPMS control group), Hoepner et al.[9] (neuropsychological impairments at PML-diagnosis) and Hoepner et al.[6] (longitudinal clinical outcome of PML-patients); supplementary table 1) were identified by retrospective analysis of medical records. RRMS and NTZ-PML groups were matched in terms of age at MS-diagnosis, age and EDSS at first 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 neuropsychological examinations (NPE) were performed in a standardized manner as used in our clinical practice and already described in Kinner et al.[8]. The battery is composed of Multiple-Choice Vocabulary Intelligence Test as a test for crystal intelligence and linguistic skills, test d2 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 crystal 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) and Digit Span Forward and Backward (working memory) as well as Shulman Clock Drawing Test (visuospatial abilities and crystal intelligence).

RRMS patients diagnosed with NTZ-PML underwent NPE at three time points during their disease course: (I) at diagnosis ($n=21$; 9.0 ± 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 ± 47.3 days after first gadolinium enhancement in MRI) and (III) post-IRIS/PML ($n=16$; 19.0 ± 32.5 months after first gadolinium-negative MRI in patients with positive JCV PCR at last follow-up or after proof of JCV PCR negativity in cerebrospinal fluid (CSF); all PCR-analysis performed at Department of Virology, University of Düsseldorf). Four patients of this post IRIS-cohort were JCV non-eliminators as they were JCV positive in CSF at the time point of their last NPE (24 ± 31 months after NTZ-PML diagnosis and 4.5 ± 34.5 months after first gadolinium-negative MRI).

Compared to NTZ-PML patients, where NPE was performed during ongoing active encephalitis (at early PML and PML-IRIS, as well as for JCV non-eliminators 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 mitoxantrone iv (42/74; cumulative dose: $49.0 \pm 29.5\text{mg/m}^2$ body surface) or triamcinolone acetate intrathecal (32/74; 40 to 160mg every 3 to 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 (International Business Machines Corp., Armonk, New York, USA).

Results

Characteristics of study populations

NTZ-PML patients and control groups did not differ in age at MS diagnosis and gender. Whereas, age at NPE and disability as measured by Expanded Disability Status Scale (EDSS) differed between groups with SPMS controls being significantly older (SPMS: 47.5 ± 14.0 , RRMS: 37.5 ± 16.8 , NTZ-PML: 39.5 ± 11.8 , both $p < 0.05$; table 1) and more disabled than the NTZ-PML patients and the RRMS controls (SPMS: 6.0 ± 1.5 , RRMS: 3.0 ± 2.5 , NTZ-PML: 4.0 ± 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 ± 36.0 , NTZ: 25.0 ± 26.2 months, $p < 0.05$; table 1).

Neuropsychological profile of NTZ-PML patients compared to MS controls

Using BDI-II no differences in depressive symptoms were found between NTZ-PML patients and both independent MS control groups (NTZ: 12.0 ± 14.5 ; SPMS: 10.0 ± 10.0 ; early-PML: 10.0 ± 9.5 ; PML-IRIS: 8.0 ± 8.0 ; post-IRIS/PML: 8.0 ± 8.0 ; all $p > 0.05$; table 2).

NTZ-PML patients performed significantly worse in Shulman clock drawing test (SCD) at all timepoints than NTZ treated RRMS patients (NTZ: 1 ± 0 ; early PML: 3 ± 2 (vs NTZ $p < 0.001$); PML-IRIS: 3 ± 1 (vs NTZ $p < 0.001$); post-IRIS/PML: 1 ± 2 (vs NTZ $p < 0.01$)). Compared to SPMS patients (SCD (SPMS): 1 ± 1), differences were only detected shortly post diagnosis prior to IRIS ($p < 0.05$) and during the IRIS phase ($p < 0.01$) of NTZ-PML (table 2; figure 1).

In addition to visuo-spatial ability also working memory, tested by digit span backwards 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 CNS

NTZ-PML patients with and without JCV elimination from 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 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-neg.: 1 ± 1 , JCV-pos.: 5 ± 1 ; $p < 0.01$; figure 1), (II) Multiple Choice Vocabulary Test (MCVT; JCV-neg.: 30 ± 5 , JCV-pos.: 15.5 ± 7 ; $p < 0.001$; figure 3), (III) Verbal Learn and Memory Test (VLMT; 5th repetition: JCV-neg.: 14 ± 1.5 , JCV-pos.: 11 ± 6 ; $p < 0.05$; 7th repetition: JCV-neg.: 12 ± 3 , JCV-pos.: 3 ± 9 ; $p < 0.05$). Analyzing an association between the amount of JCV copy number in 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 CSF in DSB, digit span forward, VLMT (1st and 7th repetition, as well as interference round) and German Performance Test Subtest 3 (each $p < 0.05$; Pearson's correlation; supplementary table 2).

Discussion

This is the first study to describe neuropsychological dysfunction during different phases of 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 8 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 timepoint (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 CNS, 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 already published in Hoepner et al.[9]) without clear difference during PML but a worse recovery of disabilities caused by the PML. Also the previously shown core neuropsychological deficits of NTZ-PML patients (working memory and visuospatial ability)[6] were markedly affected in continuously JCV positive NTZ-PML patients. In addition, we could demonstrate a negative correlation between highest JCV copy number in CSF and working memory performance at last neuropsychological assessment post PML in all NTZ-PML patients. In our view, this provides an additional proof that JCV infection is associated with a progressing cognitive decline especially in the former mentioned core domains.[6]

As our study included a RRMS as well as a SPMS cohort, our finding of a PML related core neuropsychological deficit could be distinguished from MS related cognitive decline. In RRMS patients a decline in processing speed and in SPMS patients in frontal-executive functions has 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 timepoints 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 used neuropsychological test battery 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 first NPT 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 studies[12] so that a more severe cognitive affection of NTZ-PML patients by MS disease seems unlikely.

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 IRIS-phase high-dose corticosteroids were used to prevent an 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 demonstrates working-memory and visuospatial abilities as core neuropsychological deficits of NTZ-PML patients even in long-term follow-up. Fast JCV-elimination out of 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 work up 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 in order to support social re-integration.

Data Availability Statement

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

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Captions:

figure1: Shulman Clock Drawing Test compared to study group and phase of NTZ-PML.

Statistic: Mann Whitney U test: #: NTZ-PML vs SPMS: #: $p < 0.05$; ##: $p < 0.01$; *: NTZ-PML vs NTZ: **: $p < 0.01$, ***: $p < 0.001$; +: NTZ-PML JCV-neg. vs NTZ-PML JCV-pos: ++: $p < 0.01$.

Abbreviations of study-groups: NTZ=Natalizumab; PML=progressive multifocal leukoencephalopathy; IRIS=immune reconstitution inflammatory syndrome; SPMS=secondary progressive multiple sclerosis; JCV=John-Cunningham-Virus

figure2: Wechsler-Memory Scale – Digit Span Backwards Test compared to study group and phase of NTZ-PML.

Statistic: Mann Whitney U test: #: NTZ-PML vs SPMS: #: $p < 0.05$; ##: $p < 0.001$; *: NTZ-PML vs NTZ: ***: $p < 0.001$.

Abbreviations of study-groups: NTZ=Natalizumab; PML=progressive multifocal leukoencephalopathy; IRIS=immune reconstitution inflammatory syndrome; SPMS=secondary progressive multiple sclerosis; JCV=John-Cunningham-Virus

figure 3: Multiple Choice Vocabulary Test compared to study group and phase of NTZ-PML.

Statistic: Mann Whitney U test: +: NTZ-PML JCV-neg. vs NTZ-PML JCV-pos: +++: $p < 0.001$.

Abbreviations of study-groups: NTZ=Natalizumab; PML=progressive multifocal leukoencephalopathy; IRIS=immune reconstitution inflammatory syndrome; SPMS=secondary progressive multiple sclerosis; JCV=John-Cunningham-Virus

table 1: Basic characteristics of NTZ-PML patients, RRMS and SPMS controls.

Statistic: Man-Whitney-U-Test for continuous and Fisher's-Exact-Test for dichotomous variables. * significant differences vs NTZ; # significant differences vs SPMS; each $p < 0.05$.

Abbreviations: Gd=Gadolinium, PML=progressive multifocal leukoencephalopathy; NTZ=Natalizumab; NPE=Neuropsychological examination; MS=multiple sclerosis; SPMS=secondary progressive MS; EDSS=Expanded disability status scale; IQR=Interquartile range, IRIS=immune reconstitution inflammatory syndrome; JCV=John Cunningham virus in cerebrospinal fluid; PLEX=plasmapheresis; IA=immunoadsorption

table 2: Neuropsychological test data of all three cohorts

Statistic: All data is 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 #

($p < 0.05$; ## = $p < 0.01$; ### = $p < 0.001$) and JCV pos. + ($p < 0.05$; ++ = $p < 0.01$; +++ = $p < 0.001$)

Abbreviations: NTZ = Natalizumab; SPMS = secondary progressive multiple sclerosis; PML =

progressive multifocal leukoencephalopathy; IRIS = immune reconstitution inflammatory

syndrome; JCV = John-Cunningham-Virus PCR in cerebrospinal fluid at post IRIS timepoint;

IQR = interquartile range); SCD = Shulman Clock Drawing Test; WMS-R = Wechsler Memory

Scale - Revised; DSB/F = subtest digit span backwards/forwards; VR = subtest visual

reproduction; MCVT = multiple choice vocabulary test; GPT3/7 = German performance

measuring system subtest 3/7; d2_OA/ER/OA-F/CP = test d2 overall/error ratio/overall less

false/concentration performance; RWT_WFL/CG = Regensburg word fluency test subtest

word fluency/category change; VLMT_1/5/6/7/Wf/I = verbal learning and memory test

first/5th/6th/7th repetition/retrieval less false/interference; BDI = Beck depression

inventory

	PML	NTZ	SPMS
n	28	22	74
Sex (m/f)	10/18	7/15	25/49
Age at (first) NPE (median [IQR])	39.5 [34.0; 45.8]#	37.5 [27.5;44.3]#	47.5 [41.0;55.0]
Age at MS diagnosis (median [IQR])	28 [21; 34]#	28 [23;35]	34.0 [27; 43]
EDSS at (first) assessment (median [IQR])	4.0 [3.1; 5.9]#	3.0 [1.5; 4.0]#	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 in months (median [IQR])	48.0 [30.3;66.3]*	25.0 [13.8; 40]	
PML diagnosis till 1st NPE (in days, median [IQR])	9.0 [4.0;21.0]	(n=21)	
IRIS (first Gd+ MR) till 2nd NPE (in days, median [IQR])	10.0 [1.5;48.8]	(n=10)	
JCV-neg or Gd-neg till 3rd NPE (in months, median [IQR])	19.0 [0.3;32.8]	(n=16)	
Gd-neg till 3rd NPT if JCV-pos at 3rd NPE (in months, median [IQR])	4.5 [0.0;34.5]	(n=4)	
JCV-neg till 3rd NPT (in months, median [IQR])	21.5 [4.0;32.8]	(n=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)		

Table 1: Basic characteristics of NTZ-PML patients, RRMS and SPMS controls.

Statistic: Man-Whitney-U-Test for continuous and Fisher's-Exact-Test for dichotomous variables. * significant differences vs NTZ; # significant differences vs SPMS; each $p < 0.05$.

Abbreviations: Gd=Gadolinium, PML=progressive multifocal leukoencephalopathy; NTZ=Natalizumab;

NPE=Neuropsychological examination; MS=multiple sclerosis; SPMS=secondary progressive MS; EDSS=Expanded disability status scale; IQR=Interquartile range, IRIS=immune reconstitution inflammatory syndrome; JCV=John Cunningham virus in cerebrospinal fluid; PLEX=plasmapheresis; IA=immunoadsorption

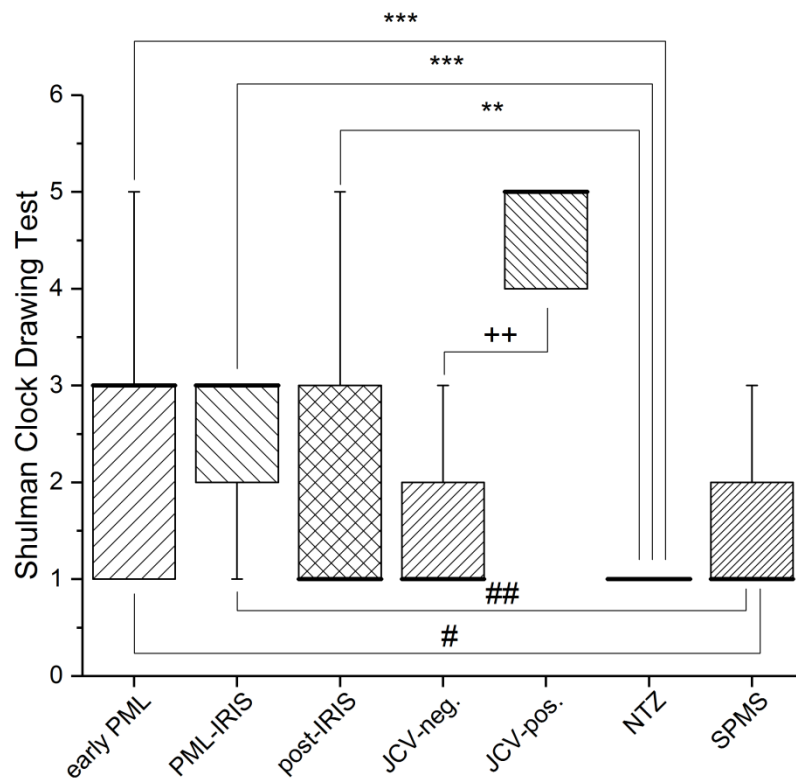
Scales	n							Median (IQR)						
	NTZ	SPMS	early PML	PML IRIS	post IRIS	JCV neg.	JCV pos.	NTZ	SPMS	early PML	PML IRIS	post-IRIS/PML	JCV neg. =post-PML	JCV pos. =post-IRIS
	(n)	(n)	(n)	(n)	(n)	(n)	(n)							
SCD	22	72	18	9	17	14	3	1 (0)	1 (1)	3 (2)***#	3 (1)***##	1 (2)**	1 (1)++	5 (1)
WMS-R_DSB	22	71	18	10	18	15	3	7 (3)	6 (2)	4 (3)***###	3.5 (4)***#	5 (2)***#	5 (2)	4 (2)
WMS-R_DSF	22	72	18	10	18	15	3	8.5 (3)	7 (2)	6.5 (2)***	6 (2)**	6 (3)**	6 (3)	5 (6)
MCVT	22	62	17	6	15	11	4	29 (7)	28.5 (6)	27 (4)	26.5 (12)	27 (8)	30 (5)+++	15.5 (7)
GPT3	22	67	12	6	12	11	1	24.5 (7)	19 (8)	21 (9.5)*	19.5 (3)**	20.5 (9)	21 (9)	14
d2_OA	20	54	9	5	10	10	0	400 (177)	320 (125)	371 (133)	356 (65)	381 (120)	381 (120)	
d2_ER	20	54	9	5	10	10	0	3.3 (4.2)	2.0 (3.9)	7 (6.8)	8.8 (9.9)**###	2.6 (6.8)	2.6 (6.8)	
d2_OA-F	20	54	9	5	10	10	0	385 (176)	316.5 (108)	354 (197)	274 (53)	338 (242)	338 (242)	
d2_CP	20	55	9	5	10	10	0	153 (63.5)	126 (38)	138 (89)	109 (44)*#	130 (100)	130 (100)	
RWT_WFL	22	65	14	9	14	13	1	11 (7)	9 (4)	9 (9)	8 (10)	12 (10)	12 (10)	7
RWT_CG	22	64	14	8	14	13	1	12 (6)	12 (6)	6.5 (8)*	6.5 (9)*	12 (9)	12 (9)	12
VLMT_1	22	72	15	9	15	12	3	7 (2)	5.5 (3)	6 (3)	6 (3)*	6 (2)*	6 (2)	4 (3)
VLMT_5	22	72	14	9	15	12	3	14 (2)	13 (4)	12.5 (5)*	9 (7)	14 (2)	14 (1.5)+	11 (6)
VLMT_I	22	72	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	9	15	12	3	12.5 (3)	10 (7)	8.5 (9)**	6 (11)*	10 (6)*	11.5 (5)	2 (9)
VLMT_7	22	71	14	9	15	12	3	13.5 (3)	10 (6)	9.5 (6)**	8 (11)**	12 (6)	12 (3)+	3 (9)
VLMT_Wf	17	62	13	7	12	9	3	15 (1)	13 (4)	13 (3)*	12 (18)*	15 (4.5)	15 (3)	11 (5)

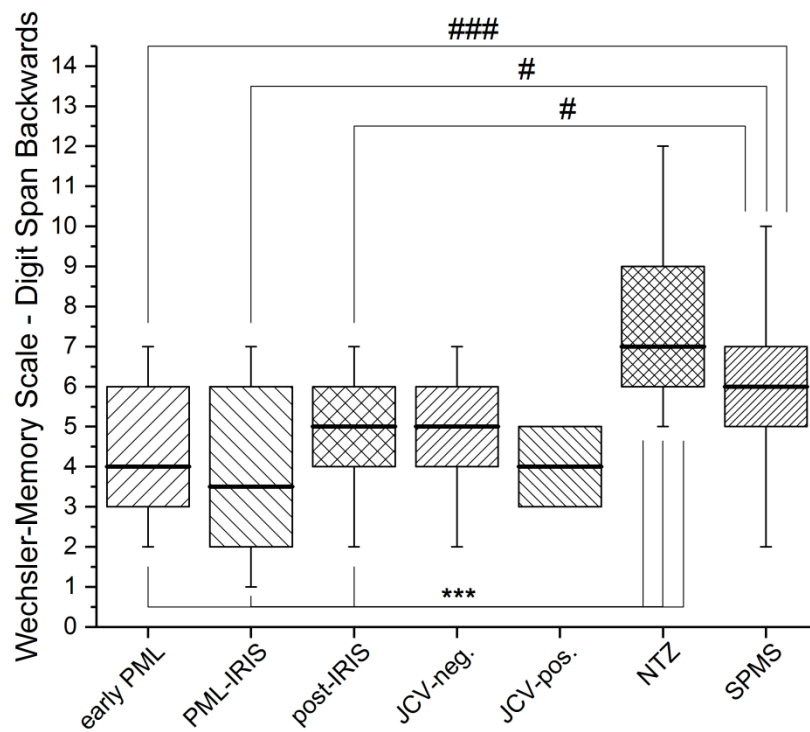
WMS-R_VR	20	55	12	7	12	11	1	38.5 (5.5)	35 (6)	35.5 (8.5)	31 (31)**	34 (7.5)*	36 (7)	16
GPT7	22	66	13	6	12	11	1	20.5 (9)	13 (7)	14 (76)*	12 (10)	15 (7.5)**	15 (8)	0
BDI	22	67	15	5	13	12	1	12 (14.5)	10 (10)	10 (9.5)	8 (8)	8 (8)	8 (7.5)	3

Table 2: Neuropsychological test data of all three cohorts

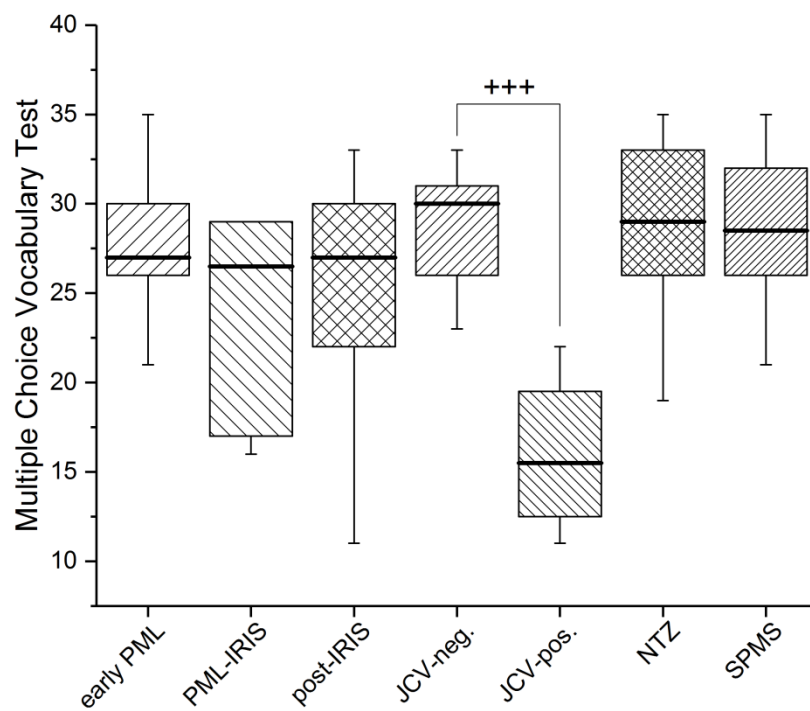
Statistic: All data is expressed as median and interquartile range. Mann Whitney U test; significantly worse compared to NTZ * ($p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$), SPMS # ($p < 0.05$; ## = $p < 0.01$; ### = $p < 0.001$) and JCV pos. + ($p < 0.05$; ++ = $p < 0.01$; +++ = $p < 0.001$)

Abbreviations: NTZ = Natalizumab; SPMS = secondary progressive multiple sclerosis; PML = progressive multifocal leukoencephalopathy; IRIS = immune reconstitution inflammatory syndrome; JCV = John-Cunningham-Virus PCR in cerebrospinal fluid at post IRIS timepoint; IQR = interquartile range); SCD = Shulman Clock Drawing Test; WMS-R = Wechsler Memory Scale - Revised; DSB/F = subtest digit span backwards/forwards; VR = subtest visual reproduction; MCVT = multiple choice vocabulary test; GPT3/7 = German performance measuring system subtest 3/7; d2_OA/ER/OA-F/CP = test d2 overall/error ratio/overall less false/concentration performance; RWT_WFL/CG = Regensburg word fluency test subtest word fluency/category change; VLMT_1/5/6/7/Wf/I = verbal learning and memory test first/5th/6th/7th repetition/retrieval less false/interference; BDI = Beck depression inventory





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ene_14604_f3.tif

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