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Nonverbal memory tests revisited: Neuroanatomical correlates and differential influence of biasing cognitive functions

Nadia Mock [a,b,c,*], *Christian Balzer* [a], *Klemens Gutbrod* [d,e], *Lutz Jäncke* [b], *Jasmin Wandel* [f], *Leo Bonati* [a,g] *and Wiebke Trost* [a]

[a] *Research Department, Reha Rheinfelden, Rheinfelden, Switzerland*
[b] *Department of Psychology, University of Zurich, Zurich, Switzerland*
[c] *Department of Neurology, Zurich University Hospital, Zurich, Switzerland*
[d] *Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*
[e] *Neurozentrum Bern, Switzerland*
[f] *Institute for Optimisation and Data Analysis, Bern University of Applied Sciences, Switzerland*
[g] *Department of Neurology, Department of Clinical Research, Basel University Hospital, Switzerland*

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ABSTRACT

The detection of right temporal lobe dysfunction with nonverbal memory tests has remained difficult in the past. Reasons for this might be the potential influence of other biasing cognitive functions such as executive functions or the verbalisability of nonverbal material. The aim of this study was to investigate three classic nonverbal memory tests by identifying their neuroanatomical correlates with lesion-symptom mapping (LSM) and by probing their independence from verbal encoding abilities and executive functions.

In a cohort of 119 patients with first-time cerebrovascular accident, memory performance was assessed in the Nonverbal Learning and Memory Test for Routes (NLMTR), the Rey Complex Figure Test (RCFT), and the Visual Design Learning Test (VDLT). Calculating multivariate LSM, we identified crucial brain structures for these three nonverbal memory tests. Behavioural analyses were performed to assess the impact of executive functions and verbal encoding abilities with regression analyses and likelihood-ratio tests.

LSM revealed for the RCFT mainly right-hemispheric frontal, insular, subcortical, and white matter structures and for the NLMTR right-hemispheric temporal (hippocampus), insular, subcortical, and white matter structures. The VDLT did not reach significance in LSM analyses. Behavioural results showed that amongst the three nonverbal memory tests the impact of executive functions was most pronounced for RCFT, and the impact of verbal encoding abilities was most important in VDLT. Likelihood-ratio tests confirmed that only for NLMTR did the goodness of fit *not* significantly improve by adding executive functions or verbal encoding abilities.

These results suggest that amongst the three nonverbal memory tests the NLMTR, as a spatial navigation test, could serve as the most suitable marker of right-hemispheric temporal lobe functioning, with the right hippocampus being involved only in this test.

* *Corresponding author*. Frauenklinikstrasse 26, CH-8091, Zurich, Switzerland.
E-mail address: nadia.mock@usz.ch (N. Mock).
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In addition, the behavioural results propose that only NLMTR seems mostly unaffected by executive functions and verbal encoding abilities.

1. Introduction

Since the pioneering neuropsychological observations in patients with unilateral temporal lobe surgery (Milner, 1966), a view of material-specific lateralisation of memory function in the brain has been established. Whereas a robust relationship between left-temporal functioning and verbal memory has been demonstrated in the past, finding a convincing association between right-temporal functioning and nonverbal memory has remained difficult (Dalton et al., 2016; Kneebone et al., 2007; Lee et al., 2002; Saling, 2009). Even though ample evidence can be found in the literature suggesting that nonverbal memory deficits are associated with right temporal lobe dysfunction (Abrahams et al., 1997; Baxendale et al., 1998; Gillespie et al., 2006; Mock et al., 2022), it seems difficult to capture truly nonverbal aspects with commonly used nonverbal memory tests. Several reasons for the ostensibly low sensitivity of these tests have been discussed. It has been proposed that many nonverbal memory tests rely on other cognitive functions such as drawing abilities, attention and executive functions (Busch et al., 2005; Chun & Turk-Browne, 2007; Duff et al., 2005; Helmstaedter et al., 1991) and a poor performance in nonverbal memory tests might not only be due to a pure visual memory deficit. Furthermore, some nonverbal memory tests seem to share variance with verbal measures (Moye, 1997) and verbal encoding strategies such as verbalizing visual stimuli seem to improve nonverbal memory performance in these tests (Glockner-Rist et al., 1987; Gutbrod et al., 1987; Silverberg & Buchanan, 2005; Zannino et al., 2020).

In clinical practice, several neuropsychological tests are commonly used to assess nonverbal memory with the aim of mapping right temporal lobe functioning that can be impaired after a cerebro-vascular accident (CVA). These tests include learning, recall and recognition of abstract figures and designs, but also of spatially represented information (e.g. Baxendale et al., 1998; Brown et al., 2007; Rey, 1941). In this study we keep the focus on three nonverbal memory tests that represent different approaches of assessing nonverbal memory, namely the Rey Complex Figure Test (RCFT), the Visual Design Learning Test (VDLT) and the Nonverbal Learning and Memory Test for Routes (NLMTR). The goal was to compare these three tests in a cohort of patients with CVA, because to our knowledge there is little agreement on how to assess nonverbal memory in the best way in this patient group. Furthermore, the vast majority of studies regarding lateralization of memory have been performed with patients with intractable temporal lobe epilepsy (TLE) and results from these studies cannot simply be generalized to CVA patients.

The RCFT is an adaption of the Rey–Osterrieth Complex Figure Test (ROCFT) (Rey, 1941) using the same stimulus material but different coding. In this test, a previously copied complex figure has to be drawn from memory after a short distraction. Although the ROCFT is considered one of the most widely used nonverbal memory tests (Barr et al., 1997), the ability of this test to measure right temporal impairment has been discussed controversially. While some studies report poorer performances in patients with right compared to patients with left temporal lobe damage (Fedio & Mirsky, 1969; Taylor, 1969), several authors could not replicate these findings (Lee et al., 1989; McConley et al., 2008; Powell et al., 1985). Many studies have outlined the importance of organizational strategies and more generally of executive functions on ROCFT recall (Kixmiller et al., 2000; Savage et al., 1999a, 1999b; Westervelt et al., 2000).

The VDLT was adapted from the Rey Visual Design Learning Test (RVDLT) (Rey, 1964; Spreen & Strauss, 1991). In this test a set of fifteen figures is presented serially and has to be learnt in five learning trials. After 15 interference figures and a short delay recall, there is a long delay recall after 30 min followed by a recognition trial. For the RVDLT, which has unlike the VDLT no interference list, it was found in previous literature that bilateral brain structures seem to contribute to the performance (Begré et al., 2007, 2009). Moreover, left and right TLE patients did not differ in RVDLT performances (Castro et al., 2013; Fuentes et al., 2014) and there was no postoperative change in RVDLT performance of right TLE patients (Janszky et al., 2005; Jokeit et al., 2005). Previous research has discussed the spontaneous use of verbal strategies in design learning tests (Lezak, 1995; Wilhelm et al., 2011) which might be a reason for the contribution of left-hemispheric structures (Golby et al., 2001; Kelley et al., 1998) in this type of test.

The NLMTR is a modification of the Ruff-Light Trail Learning Test (RULIT) by Balzer and co-workers (Balzer et al., 2011) in which a route on a schematic map has to be learnt and remembered. The NLMTR contains five learning trials, in which a visually presented route should be learned without feedback. The route is presented on a complex configuration of circles that are interconnected by lines. The examiner presents the route by pointing with an index finger to sixteen circles from the START to the END circle. Subsequently, the respondent is asked to repeat the route. After an interference route and the following short delay recall, there is a long delay recall trial after 30 min. Thus, unlike for the RULIT and for other maze learning and spatial navigation tasks (Milner, 1965; Walsh, 1991), the correct learning of the visual route does not have to be guaranteed. The neuroanatomical correlates of NLMTR have not yet been studied. For other spatial navigation tests, it was found that patients with right-hemispheric lesions performed significantly worse than patients with left-hemispheric lesions (Abrahams et al., 1999; Allen & Ruff, 2007; Brown et al., 2010; Corkin, 1965; Corsi, 1972;

Milner, 1965). A specialised role has thus been assumed for the right hippocampus in the processing and manipulation of spatial information (Abrahams et al., 1997).

To investigate the neuronal correlates of the aforementioned nonverbal memory tests in patients with CVA, we used the methodology of lesion-symptom mapping (LSM). This technique has the advantage of being able to statistically link behavioural data with lesion data. LSM has been refined in recent years such that LSM can also be performed as a multivariate approach (DeMarco & Turkeltaub, 2018; Karnath et al., 2020; Pustina et al., 2018; Zhang et al., 2014). The technique of LSM has already been applied for different cognitive functions, also including memory processes (Bowren et al., 2020; Mock et al., 2022; Paulraj et al., 2018), but not yet on the level of different nonverbal memory tests.

The goal of our study was to identify crucial brain structures for three nonverbal memory tests, namely NLMTR, RCFT, and VDLT with the aim of finding a neuropsychological marker for right temporal lobe functioning. For this purpose, we used multivariate LSM in a relatively large cohort of neurological patients ($n = 119$) with single first-time CVA. To disentangle, on a behavioural level, the differential influence of executive functions and verbal encoding abilities on nonverbal memory performance we used likelihood-ratio tests to investigate the biasing impact of these cognitive functions. In addition, we calculated sensitivity and specificity to detect right hemispheric and right hippocampal dysfunction for each of the three tests.

2. Materials and methods

2.1. Subjects

Patients were recruited as inpatients at the Reha Rheinfelden rehabilitation clinic in Switzerland between December 2013 and December 2019. As recommended for LSM studies the maximum number of suitable patients during the recruitment time period was included (Karnath et al., 2020). Written informed consent was obtained from each participant in accordance with the guidelines of the local ethics committee (Ethikkommission Nordwest-und Zentralschweiz EKNZ). Patients ($n = 145$) were recruited if they had suffered a single first-time ischaemic or haemorrhagic CVA and had undergone standard neuropsychological testing during clinical care. Patients with severe acute CVA symptoms such as global aphasia or severe neglect symptoms were not considered. All patients were fluent German speakers and right-handed. No other previous cerebral damage, including neurodegenerative processes, no obstructive sleep apnoea syndrome, nor any psychiatric illnesses were reported in their medical histories. Patients had no prior history of drug or alcohol abuse. Patients ($n = 26$) that had at least one value missing from one of the three nonverbal memory tests were excluded. The final sample comprised 119 patients (42 female). Their age ranged from 20 years to 69 years (mean 54.52 years, SD 10.67 years) with an average of 13.70 years of education (SD 3.30). The mean time between neuropsychological testing and CVA onset was 33.54 days (SD 27.98 days). Cognitive deficits were thus assessed in the acute and subacute stages when they are most pronounced. Brain imaging was performed in the acute stage, with a mean time of 3.87 days (SD 10.61 days) after CVA onset. The ratio of patients with left-hemispheric CVA and right-hemispheric CVA was almost balanced: patients with right-hemispheric CVA accounted for 42% of the sample, compared to 43% of patients with left-hemispheric CVA and 15% with bilateral CVA. In the patient sample, 30 patients had right hippocampal lesions and 16 patients had left hippocampal lesions (Table 1).

2.2. Neuropsychological assessment

Neuropsychological testing was performed as standard during each patient's clinical stay for rehabilitation. For this purpose, the "Materialien und Normwerte für die neuropsychologische Diagnostik (MNND)" neuropsychological test set (http://www.normdaten.ch; Balzer et al., 2011) was used. The test set includes standardized and frequently used classic neuropsychological tests that assess memory, executive functions, attention, and visuospatial functions orally or in paper-and-pencil versions. To assess the nonverbal memory, we used three tests out of the MNND: (i) Visual Design Learning Test (VDLT), (ii) Nonverbal Learning and Memory Test for Routes (NLMTR), (iii) Rey Complex Figure Test (RCFT). Furthermore, we assessed verbal encoding performance with (iv) Auditory-Verbal Learning Test (AVLT) and with (v) Logical Memory (LM) and executive functions with (vi) word fluency test (WF), (vii) design fluency test (DF), (viii) Kramer categorization test (KC), and (ix) Stroop test (ST) (Table 2). All additional behavioural scores were only present in a subsample of 108 patients.

2.3. Behavioural analysis

The patients' behavioural performance in the neuropsychological tests was transformed to z scores according to the normative data provided by the MNND, stratified by age, sex, and education (Supplement Table S1). To be able to compare the three nonverbal memory tests as validly as possible, we used the long delay recall which is the only memory process that is assessed by all three nonverbal memory tests. The long delay recall refers to the number of correctly remembered items after a time delay. Regression analyses and model comparison were computed with R (4.2.2) and RStudio (2022.07.2).

Table 1 – Lesion characteristics specified by hemisphere and hippocampal involvement.

Characteristics	Study cohort *n* (%)
Lesion location	
Right	50 (42)
Left	51 (43)
Bilateral	18 (15)
Total	119
Hippocampal involvement	
Right	30 (25)
Left	16 (13)

Table 2 – Test procedures for nonverbal episodic memory, verbal encoding measures and executive functions, which are included in the neuropsychological test battery MNND.

Subtest	Adapted from	Description	Test parameter
Memory tests			
Visual Design Learning Test (VDLT)	RVDLT (Rey, 1964; Spreen & Strauss, 1991)	Figure list learning	✓Long delay
Nonverbal Learning and Memory Test for Routes (NLMTR)	RULIT (Ruff & Allen, 1999; Ruff, Light, & Parker, 1996)	Route learning	✓Long delay
Rey Complex Figure Test (RCFT)	RCFT (Rey, 1941; Taylor, 1969)	Figural memory	✓Long delay
Verbal encoding measures			
Auditory-Verbal Learning Test (AVLT)	RAVLT (Rey, 1958, 1964)	Word list learning	✓Sum of learned words over five learning trials ✓Immediate recall
Logical Memory (LM)	WMS-R/WMS-III (Wechsler, 1987, 1997)	Text recall	
Executive function tests			
Word fluency test (WF)	Word fluency/COWA (Benton, Hamsher, & Sivan, 1994; Thurstone, 1938)	Letter fluency (letter S)	✓Correct words
Design fluency test (DF)	Five-point test (Regard, Strauss, & Knapp, 1982)	Figural fluency	✓Correct patterns
Kramer categorization test (KC)	Kramer intelligence test (German; Kramer, 1972)	Categorization task	✓Correct categories
Stroop test (ST)	Victoria stroop test (Regard, 1981)	Interference control	✓Stroop time (C-A) ✓Stroop errors

2.3.1. *Multiple linear regression*

Multiple linear regression models were calculated to determine the variance explained by executive functions in each nonverbal memory test (see supplement material for analysis script). As explanatory variables we used the number of correct answers for KC, DF and WF, while for ST the time difference between the interference and no-interference condition (STCAdiff), as well as the number of errors in the interference condition (STCerror) were chosen. For the three nonverbal memory tests, the following identical linear regression models were performed:

$$NLMTR_i = b_0 + b_1 KC_i + b_2 DF_i + b_3 WF_i + b_4 STCAdiff_i + b_5 STCerror_i + \varepsilon_i,$$

while bk denote the six regression coefficients and ε_i denotes the error term for each patient i. It is assumed that $\varepsilon_i \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \sigma^2)$ for a given σ^2, depending on the memory test performed. For RCFT and VDLT the linear regression models were analogously calculated.

To determine the variance explained by verbal encoding abilities in each nonverbal memory test, we performed multiple linear regression models accordingly. To assess verbal encoding abilities, we used the learning variable in AVLT and the immediate recall in LM as explanatory variables:

$$NLMTR_i = b_0 + b_1 AVLTenc_i + b_2 LMenc_i + \varepsilon_i$$

For RCFT and VDLT the linear regression models were analogously calculated.

2.3.2. *Model comparison*

To evaluate the influence of executive functions on nonverbal memory we compared two regression models for each nonverbal memory test: the full model with several nonverbal mnemonic and executive predictors was compared to a reduced nested model with only nonverbal mnemonic predictors (see supplement material for analysis script). The two models were then compared using a likelihood-ratio test. The rationale behind this analysis was that the three nonverbal memory tests are supposed to measure nonverbal memory performance. Therefore, it can be assumed that the performances in two nonverbal memory tests can serve as suitable predictors of the performance in the third nonverbal memory test. If the nonverbal memory performance does not depend on additional non mnemonic variables, adding these variables as predictors should not improve the goodness of fit of the regression model.

Full model:

$$NLMTR_i = b_0 + b_{1\,RCF} T_i + b_2 VDLT_i + b_3 KC_i + b_4 DF_i + b_5 WF_i + b_6 STCAdiff_i + b_7 STCerror_i + \varepsilon_i$$

Reduced model:

$$NLMTR_i = b_0 + b_{1\,RCF} T_i + b_2 VDLT_i + \varepsilon_i$$

For RCFT and VDLT the full and reduced model were analogously calculated.

To assess the influence of verbal encoding abilities on nonverbal memory we used the same rationale as mentioned above. We compared, for each nonverbal memory test, the full

model with several nonverbal and verbal encoding predictors to a reduced nested model with only nonverbal mnemonic predictors.

Full model:

$$NLMTR_i = b_0 + b_{1\ RCF}T_i + b_2VDLT_i + b_3AVLTenc_i + b_4LMenc_i + \varepsilon_i$$

Reduced model:

$$NLMTR_i = b_0 + b_{1\ RCF}T_i + b_2VDLT_i + \varepsilon_i$$

For RCFT and VDLT the full and reduced model were analogously calculated.

For the full and the reduced models, the R^2 (percentage of variation explained by the model) were assessed to compare quantitatively the amount of variance explained by the predictors.

2.4. Lesion maps

Each patient underwent a standard radiological examination in the acute CVA stage, from which MR ($n = 108$) and CT images ($n = 37$) were obtained. Because the brain images were acquired in different primary care hospitals, the scanning procedure for image acquisition was not uniform. Images were acquired on 1.5 T or 3 T scanners. The lesions were drawn directly onto the MR or CT image with MRIcron software (Rorden & Brett, 2000; https://www.nitrc.org/projects/mricron) by a trained clinical neuropsychologist blind to the patient's diagnosis. All lesion maps were double-checked by a neuroradiologist. Brain images and lesions were then reoriented to the anterior commissure using Statistical Parametric Mapping SPM8 (http://www.fil.ion.ucl.ac.uk/spm) running in Matlab (http://www.mathworks.com) and were then mapped into $1 \times 1 \times 1$ mm stereotaxic space with the spatial normalization algorithms provided by the Clinical Toolbox (Rorden et al., 2012). Because no high-resolution T1 brain images were available, no segmentation-based normalization procedure could be applied. The quality of normalization was evaluated through visual inspection and was judged satisfactory for all patients. The normalized lesion images were then used for further statistical analysis.

2.5. Brain imaging and LSM

A multivariate LSM approach (Pustina et al., 2018) was employed in this study to investigate the relationship between performance in standard nonverbal memory tests and the localization of brain lesions (Rorden & Karnath, 2004). This multivariate approach examines the joint contribution of multiple voxels, representing brain networks, to account for a given behaviour (Karnath et al., 2020).

We used the Lesymap package (version 0.0.0.9221), which runs in R (version 4.0.2) and is based on the ANTsR packages (version 0.5.6.2) to apply the sparse canonical correlation analysis for neuroimaging (SCCAN) technique (Pustina et al., 2018). SCCAN is a technique that gradually selects a multivariate model of voxels that correlate optimally with behaviour by identifying optimal sparseness through cross-validations. This procedure proposes a group of voxels as a multivariate solution that provides the best explanation of the behavioural data with one global p-value for the entire solution. Therefore, the significance threshold does not have to be corrected for multiple comparisons. Only voxels affected by lesions in at least 10% of the patients were considered for the analyses, and a significance level of .05 was adopted (see supplement material for analysis script).

2.6. Analyses of pre-classified lesions and behaviour

To complement the LSM analyses, we calculated further analyses with pre-classified lesions and behaviour. For this purpose, lesion sites were classified according to their hemispheric lateralisation, with a functional reclassification for cerebellar lesions due to crossed cerebello-cerebral connections. Left cerebellar lesions were classified to the right functional group, whereas right cerebellar lesions were classified to the left functional group (Supplement Table S2).

Means of performances in all cognitive parameters were compared between right and left functional lesions using independent t-tests. For each of the three nonverbal memory tests, numbers of patients with below average performances ($z < -1$) were compared with χ^2-tests, to probe for significant relationships between functional lesion lateralisation and a below average performance. In addition, we compared means of performances in the three nonverbal memory tests in patients with right functional lesions with or without right hippocampal involvement using independent t-tests. Moreover, χ^2-tests were calculated to test significant relationships between right hippocampal involvement and a below average performance in patients with right functional lesions. Furthermore, Cohen's Kappa was calculated to assess the proportion of agreement between the three nonverbal memory tests to detect a deficit. Analyses of pre-classified lesions and behaviour were computed with SPSS (28.0.0.0).

2.7. Preregistration, reporting, and availability

No part of the study procedure or analyses were preregistered prior to the research being conducted. We report how we determined our sample size, all data exclusions, all inclusion and exclusion criteria, whether inclusion and exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. The conditions of our ethics approval do not permit public archiving of the data. The datasets generated and analysed during the current study are available from the corresponding author on request and on prior consultation with the ethics committee. Legal copyright restrictions prevent public archiving of the neuropsychological tests described in section 2.2. These can be obtained from the copyright holders in the cited references.

3. Results

3.1. Behavioural results

3.1.1. Multiple linear regression

Multiple linear regression analyses showed relevant differences regarding the amount of variance explained.

Considerably more variance was explained by executive functions in RCFT ($R^2 = .23$) than in NLMTR ($R^2 = .12$) and VDLT ($R^2 = .14$). Furthermore, more variance was explained by verbal encoding abilities in VDLT ($R^2 = .29$) than in RCFT ($R^2 = .14$) and NLMTR ($R^2 = .03$).

3.1.2. *Model comparison*

The results of the likelihood ratio tests are shown in Table 3. The comparison of a full model with several nonverbal mnemonic and executive predictors to a reduced model with only nonverbal mnemonic predictors as described in section 2.3.2 revealed a significant difference only in RCFT. For RCFT, the full model showed that significantly more variance ($p < .05$) could be explained ($R^2 = .33$) compared to the restricted model ($R^2 = .23$). The comparison of the full model with several nonverbal and verbal encoding predictors to a reduced model with only nonverbal mnemonic predictors revealed a significant difference only in the VDLT ($p < .001$). For the VDLT, the full model showed that more variance could be explained ($R^2 = .39$) compared to the restricted model ($R^2 = .22$).

3.2. *LSM results*

The overlap of cerebral lesions in all 119 patients is shown in Fig. 1. The highest prevalence of lesions was found in the right-sided vascular territory of the middle cerebral artery and with substantially less coverage in left-hemispheric regions (Fig. 1).

Multivariate LSM analyses identified several clusters of voxels where damage significantly predicted poorer performance in two of the three nonverbal memory tests. For the VDLT, the LSM analysis could not identify any significant solution.

For NLMTR LSM analyses revealed significant involvement only of right-hemispheric brain regions in temporal (hippocampus), insular, and subcortical structures (caudate nucleus, pallidum, thalamus). Furthermore, right-sided white matter involvement was found in the fornix, superior longitudinal fasciculus, internal capsule (posterior limb and retrolenticular part), corona radiata (anterior and superior), sagittal stratum, and external capsule (Table 4, Figs. 2 and 3).

For the RCFT, significant involvement of right-hemispheric brain areas was evident in insular, frontal (rolandic operculum), subcortical (caudate nucleus, putamen, pallidum, thalamus), and white matter structures (internal capsule anterior and posterior limb, corona radiata anterior and superior limb, external capsule, superior longitudinal fasciculus and superior fronto-occipital fasciculus). Significant involvement of left-hemispheric brain areas was evident in the putamen and the posterior limb of the internal capsule (Table 4, Figs. 2 and 3).

3.3. *Results of pre-classified lesions and behaviour analyses*

In the comparison of means, significant differences between right and left functional lesions were found for NLMTR and tests based on verbal material, namely AVLT, LM and WF (Supplement Table S3). For NLMTR, the mean was significantly lower in the right compared to the left functional group. The means of tests based on verbal material were significantly lower in the left compared to the right functional group. Comparing the number of patients with below average performance with right and left functional lesions, showed only for NLMTR a trend towards a relation between behavioural deficit and functional lesion lateralisation (Supplement Table S4).

When restricting the analyses to patients with right functional lesions, patients with right hippocampal involvement showed a significant lower performance than patients without right hippocampal involvement, again only for NLMTR among the three nonverbal memory tests

Table 3 – Model comparison with likelihood-ratio tests.

		Tests	df	Pr (>Chi^2)	R^2
Likelihood-ratio test model comparison – Influence of executive functions on nonverbal memory					
NLMTR	Full model	RCFT, VDLT, KC, DF, WF, STCAdiff, STCerror	9	.53	.25
	Reduced model	RCFT, VDLT	4		.22
RCFT	Full model	NLMTR, VDLT, KC, DF, WF, STCAdiff, STCerror	9	.01*	.33
	Reduced model	NLMTR, VDLT	4		.23
VDLT	Full model	NLMTR, RCFT, KC, DF, WF, STCAdiff, STCerror	9	.36	.26
	Reduced model	NLMTR, RCFT	4		.22
Likelihood-ratio test model comparison – Influence of verbal encoding on nonverbal memory					
NLMTR	Full model	RCFT, VDLT, AVLTenc, LMenc	6	.57	.23
	Reduced model	RCFT, VDLT	4		.22
RCFT	Full model	NLMTR, VDLT, AVLTenc, LMenc	6	.05	.27
	Reduced model	NLMTR, VDLT	4		.23
VDLT	Full model	NLMTR, RCFT, AVLTenc, LMenc	6	<.001***	.39
	Reduced model	NLMTR, RCFT	4		.22

Model comparison with likelihood-ratio tests with reduced models (nonverbal memory tests as predictors only) and full models (with either additional verbal encoding tests or executive function tests as additional predictors).Abbreviations: NLMTR = Nonverbal Learning and Memory Test for Routes; RCFT = Rey Complex Figure Test, VDLT = Visual Design Learning Test (for the three nonverbal memory tests long delay was used, i.e. correctly remembered items after time delay), AVLTenc = Auditory-Verbal Learning Test encoding (sum of learned words over five learning trials), LMenc = Logical Memory encoding (immediate recall), KC = Kramer categorization test (correct categories), DF = Design fluency test (correct patterns), WF = Word fluency test (correct words), STCAdiff = Stroop test (Stroop time C-A), STCerror = Stroop test (Stroop errors).
***$p < .001$.
*$p < .05$.

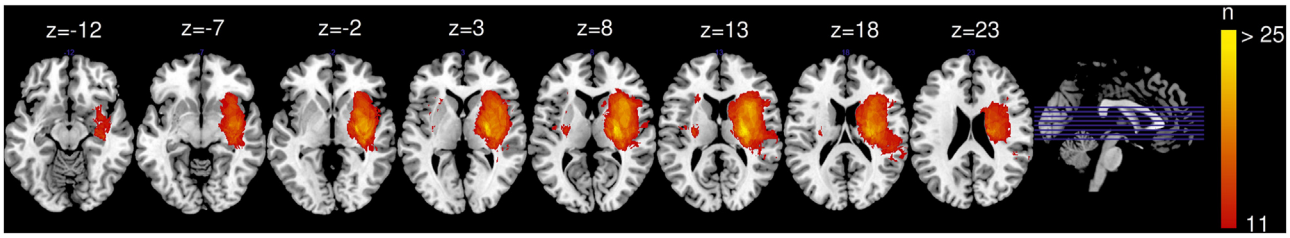

Fig. 1 – Lesion overlap for $n = 119$ patients. Voxels that are damaged in at least 11 patients are projected on a T1 template in MRIcron. Images shown in neurological orientation (right = right).

Table 4 – Multivariate LSM results for NLMTR and RCFT ($n = 119$). Regions with a cluster threshold of at least 50 significant voxels are listed.

Anatomical regions (AAL & JHU Atlas)	Region size in voxels (*n*)	Lesymap	
		Significant voxels (*n*)	Significant voxels (%)
NLMTR			
Grey matter			
Hippocampus_R	7606	647	8.5
Insula_R	14,128	321	2.3
Caudate_R	7941	70	.9
Pallidum_R	2188	320	14.6
Thalamus_R	8399	1015	12.1
White matter			
Posterior_limb_of_internal_capsule_R	3752	1790	47.7
Retrolenticular_part_of_internal_capsule_R	2469	904	36.6
Anterior_corona_radiata_R	6852	75	1.1
Superior_corona_radiata_R	7508	912	12.1
Sagittal_stratum_R	2231	302	13.5
External_capsule_R	5587	200	3.6
Fornix_(cres)_/_Stria_terminalis_R	1125	131	11.6
Superior_longitudinal_fasciculus_R	6605	173	2.6
RCFT			
Grey matter			
Rolandic_Oper_R 2332	10,733	51	.005
Insula_R 3002	14,128	434	.031
Caudate_R 7002	7941	1812	.228
Putamen_L 7011	7942	181	.023
Putamen_R 7012	8510	860	.101
Pallidum_R 7022	2188	789	.361
Thalamus_R 7102	8399	593	.071
White matter			
Anterior_limb_of_internal_capsule_R	3018	814	2.7
Posterior_limb_of_internal_capsule_L	3754	122	3.2
Posterior_limb_of_internal_capsule_R	3752	1024	27.3
Anterior_corona_radiata_R	6852	566	8.3
Superior_corona_radiata_R	7508	1905	25.4
External_capsule_R	5587	471	8.4
Superior_longitudinal_fasciculus_R	6605	1077	16.3
Superior_fronto-occipital_fasciculus_R	507	430	84.8

Abbreviations: NLMTR = Nonverbal Learning and Memory Test for Routes; RCFT = Rey Complex Figure Test.

(Supplement Table S5). Furthermore, within this subgroup, comparisons of numbers of patients with below average performance revealed a significant relation between involvement of right hippocampus and below average performance for NLMTR alone (Supplement Table S6).

In terms of sensitivity and specificity, NLMTR had the highest sensitivity among the three nonverbal memory tests regarding right functional lesions (.44) and right hippocampal involvement (.53), whereas RCFT had the highest specificity among the three nonverbal memory tests regarding right functional lesions (.80) and right hippocampal involvement (.95) (Supplement Tables S4 and S6).

The three nonverbal memory tests showed only a fair proportion of agreement ($\kappa = .21–.25$; Supplement Table S7).

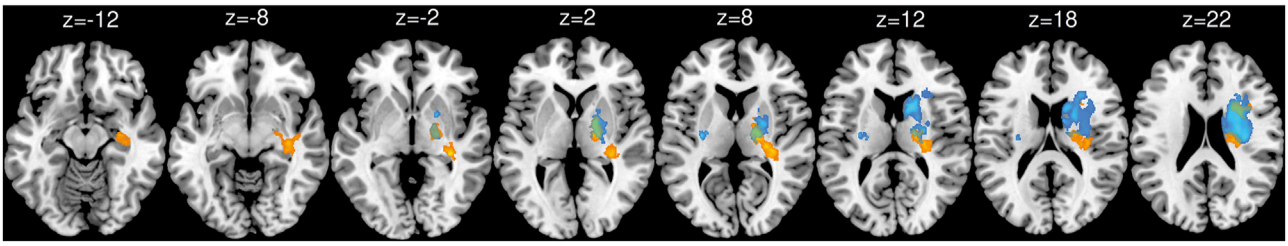

Fig. 2 – Multivariate LSM results for NLMTR and RCFT. Anatomical correlates for NLMTR are shown in orange and for RCFT in blue. The overlap of significant voxels for both tests is depicted in green. Only statistically significant voxels ($p \leq .05$) are shown. Slices correspond with MNI-152 z coordinates. Images shown in neurological orientation. Abbreviations: NLMTR = Nonverbal Learning and Memory Test for Routes; RCFT = Rey Complex Figure Test.

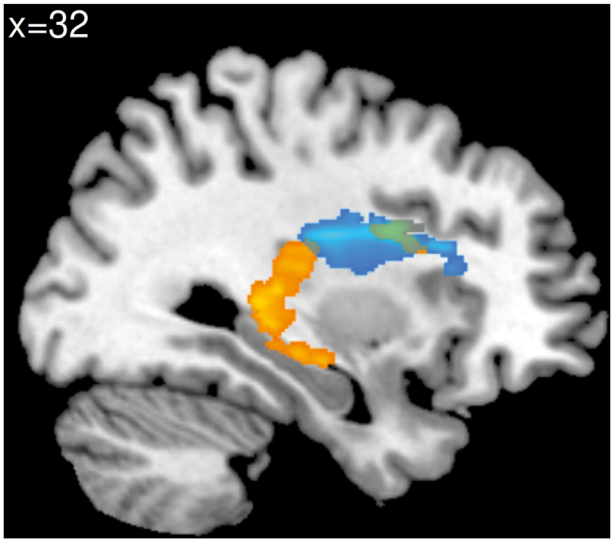

Fig. 3 – Sagittal view of multivariate LSM results for NLMTR and RCFT. Anatomical correlates for NLMTR are shown in orange and for RCFT in blue. The overlap of significant voxels for both tests is depicted in green. Only statistically significant voxels ($p \leq .05$) are shown. Slices correspond with MNI-152 z coordinates. Images shown in neurological orientation. Abbreviations: NLMTR = Nonverbal Learning and Memory Test for Routes; RCFT = Rey Complex Figure Test.

4. Discussion

The purpose of the present study was to identify anatomical correlates of three nonverbal memory tests – namely NLMTR, RCFT and VDLT – with the aim of identifying a neuropsychological marker for right-temporal lobe functioning. LSM analyses revealed, in a relatively large cohort of neurological patients ($n = 119$) with single first-time CVA, two clusters of crucial brain regions, with the NLMTR involving right-hemispheric temporal (hippocampus), insular, subcortical (caudate nucleus, pallidum, thalamus) and adjacent white matter structures and the RCFT involving mostly right-hemispheric frontal, insular, subcortical (caudate nucleus, putamen, pallidum, thalamus) and adjacent white matter structures. The VDLT did not reach significance in LSM analyses. However, due to the small lesion overlap on the left hemisphere, these correlates cannot be regarded as exclusive, as we cannot rule out the possibility of additional left hemispheric involvement. To disentangle the differential influence of executive functions and verbal encoding abilities on nonverbal memory we calculated multiple linear regressions, whereby the most variance was explained by executive functions for RCFT ($R^2 = .23$) and most variance was explained by verbal encoding abilities for VDLT ($R^2 = .29$) when comparing the three tests. Further model comparisons with likelihood-ratio tests revealed the full model with several executive predictors to be the significantly better model for RCFT and the full model with several verbal encoding predictors to be the significantly better model for VDLT than the restricted model with only nonverbal mnemonic predictors. Only for NLMTR could the amount of explained variance *not* be increased by adding executive or verbal encoding predictors. These results indicate that nonverbal memory tests have different anatomical correlates and are differently influenced by executive functions and verbal encoding abilities. In addition, the three tests differ in sensitivity and specificity to detect right temporal lobe lesions. The NLMTR with an anatomical correlate including the right hippocampus, relative robustness to biasing impact of other cognitive aspects and the highest sensitivity to detect right hippocampal lesions can be regarded as a suitable neuropsychological marker for right temporal lobe functioning in CVA patients.

Neuroanatomical correlates of the three nonverbal memory tests

Multivariate LSM could identify only significant solutions for NLMTR and RCFT, but not for VDLT. The identified clusters show partly overlapping but mostly distinct neuronal correlates. Notably, for the RCFT LSM analyses do not reveal any involvement of right-hemispheric temporal structures while for the NLMTR right medio temporal structures including hippocampus and fornix, as part of the Papez circuit, are crucial. Furthermore, the white matter results reveal a rather anterior involvement of projection and association fibres for RCFT and more posterior involvement for NLMTR (Fig. 3). These results point to a differential connectivity for these tests with either reaching posteriorly or connecting with frontal regions such as via fronto-striatal loops that are also known to play a role in executive functions (e.g. Chudasama & Robbins, 2006). If the

maximum number of patients available in the dataset of recruited participants ($n = 145$) for each nonverbal memory test is used to increase the power, an even more differentiated picture emerges. LSM analysis for VDLT ($n = 125$) remain not significant, but for RCFT and NLMTR the neuroanatomical correlates seem more specific with less overlap between the two tests (Supplement Table S8 and Supplement Fig. S1). For RCFT ($n = 142$), significant involvement of right-hemispheric brain areas was evident in caudate nucleus and thalamus and for NLMTR ($n = 135$), significant involvement of right-hemispheric brain regions was evident in temporal, insular and thalamic regions. Thus, there seems to be a shared but rather unspecific neuronal basis for the two tests including thalamic regions and white matter fibres such as parts of the internal capsule and the corona radiata. However, what becomes even more evident with higher power is that for RCFT, the caudate nucleus becomes specific, whereas for NLMTR, the involvement of right temporal lobe including hippocampus remains.

Comparing three nonverbal memory tests

In the following sections, we compare the three nonverbal memory tests VDLT, RCFT and NLMTR with regard to their neuroanatomical correlates and behavioural characteristics.

VDLT

For VDLT, behavioural analyses suggested a substantial amount of variance to be explained by verbal encoding abilities ($R^2 = .29$) and less by executive functions ($R^2 = .14$). Moreover, likelihood-ratio tests confirmed that performance in VDLT was significantly better explained by a model which included verbal encoding abilities than a model without. These results complement our recent finding that the VDLT loads largely on a verbal factor (Mock et al., 2022) and indicate that verbal skills influence performance in VDLT. This is in line with the frequently discussed verbalisability of nonverbal material which proposes that the pure measurement of visual memory is difficult, and that verbal mediation contributes to the encoding of nonverbal material (Helmstaedter et al., 1995; Silverberg & Buchanan, 2005; Zannino et al., 2020).

According to the longstanding hypothesis of material-specific lateralization in memory, nonverbal memory is thought to be controlled by the right hemisphere, whereas verbal memory is related to the left hemisphere (Milner, 1966). However, previous research has proposed that the lateralization effect of nonverbal memory is dependent on the degree of verbalisability of nonverbal stimuli: the more amenable the stimuli are to verbal encoding, the greater the left-hemispheric involvement and the smaller the material-dependent lateralization effect (Golby et al., 2001; Kelley et al., 1998). Confirmatively, findings point to a bilateral involvement regarding the performance in the RVDLT (Begré et al., 2007, 2009), another design learning task in which verbal encoding strategies have been discussed (Wilhelm et al., 2011). Furthermore, the fact that several studies with TLE patients using figures as nonverbal material do not find a group difference between right and left sided TLE patients (Barr et al., 2004; Castro et al., 2013; Fuentes et al., 2014) might be related to preserved verbal encoding strategies in right sided TLE patients. In our results we did not find any neuroanatomical correlates for VDLT. Given that VDLT has a clear verbal component it is likely to be determined by left-hemispheric correlates. However, due to poor left-hemispheric lesion coverage we may not have been able to find significant LSM results.

RCFT

LSM analyses for RCFT revealed a specific fronto-subcortical involvement including basal ganglia structures such as nucleus caudatus and anterior projection and association fibres. On a behavioural level, results showed that a considerable amount of variance for RCFT was explained by executive functions ($R^2 = .23$) and less by verbal encoding abilities ($R^2 = .14$). Moreover, model comparisons suggested that performance in RCFT was significantly better explained by a model including executive functions than a model without. Thus, performance in RCFT seems to be influenced by executive functions, requiring the integrity of fronto-striatal regions for a successful RCFT performance. Confirmatively, patients with obsessive-compulsive disorder, which is associated with a dysfunction of fronto-striatal circuits (Baxter, 1992, 1994; Kwon et al., 2003), do often show deficits in RCFT and executive functions. In this context, it is a well-known fact that memory problems in RCFT seem to be mediated by strategic processing difficulties due to a primary executive dysfunction (Savage et al., 1995, 1999a, 1999b), which in turn is related to a fronto-striatal deficiency (Penadés et al., 2005; Savage et al., 2000).

The missing involvement of right medio temporal structures in our results indicates that the right temporal lobe functioning is not related to performance in RCFT. This might serve as an explanation for why several studies do not find a difference in RCFT performance between patients with right and left TLE (Barr, 1997; Kilpatrick et al., 1997; Lee et al., 1989; Loring et al., 1988). Also, with other figural reproduction tests such as the widely used visual reproduction subtest form Wechsler Memory Scale (WMS-VR) (WMS: Wechsler & Stone, 1945; and WMS-R: Wechsler, 1987), group differences between patients with right and left temporal lobe dysfunction have often been lacking (Bornstein et al., 1988; Chelune et al., 1991; Ivnik et al., 1987; Moore & Baker, 1996) and the use of figural reproduction tests in detecting right temporal lobe dysfunction has been questioned (Barr et al., 1997).

In our study, LSM analyses for RCFT showed a small involvement of left putamen and of left capsula interna. Similar to VDLT, it has been argued that verbal strategies are helpful in encoding this complex figure and that left-hemispheric areas are accordingly required for successful RCFT performance (Hermann et al., 1992; Kilpatrick et al., 1997). However, it should be noted that these left-hemispheric areas are no longer part of the LSM solution when the number of included patients is increased (Supplement Table S8; Supplement Fig. S1). This suggests that the identified brain structures in the left hemisphere seem to play a rather marginal role for the performance in RCFT.

NLMTR

In the present study, the NLMTR was identified as the only test for which LSM analyses revealed an involvement of right-hemispheric temporal structures, namely the hippocampus. Also, with pre-classified lesions and behaviour analyses a significant relationship between below average performance in NLMTR and right hippocampal involvement, as well as a trend towards a relationship between a deficit in NLMTR and right functional lesions in general was confirmed. Behavioural results showed that only little variance in NLMTR was explained by executive functions ($R^2 = .12$) and verbal encoding abilities ($R^2 = .03$). In addition, it could be confirmed with likelihood-ratio tests that the model to predict NLMTR performance did not improve significantly when adding executive functions or verbal encoding abilities. This indicates that NLMTR seems to measure nonverbal memory performance in a more unbiased way than RCFT and VDLT.

In fact, among nonverbal memory tests the most consistent results have been found in spatial memory tests to demonstrate a robust impairment of patients with right temporal lobe lesions (Abrahams et al., 1997, 1999). In particular, the involvement of the right hippocampus in allocentric spatial memory has been proposed (Abrahams et al., 1997; Kessels et al., 2001). This is in line with studies suggesting that the hippocampus contains 'place cells' that fire when an individual is in a particular location in an environment and provide a certain 'sense of location' (Bird & Burgess, 2008; O'Keefe et al., 1998). It has been suggested that this 'sense of location' is built up from the information that the hippocampus receives, via the ventral 'what' as well as the dorsal 'where' processing pathways of sensory information (Barr, 1997; Martins et al., 2014). A disruption of these pathways, notably in the hippocampus, seems thus to have the consequence of compromised topographical orientation (Maguire et al., 1996). The fact that NLMTR is sensitive to right hippocampal functionality suggests this test as a potential tool for assessing topographical disorientation. However, the sensitivity of NLMTR to capture the ability of topographical orientation has yet to be tested explicitly.

Furthermore, although the applicability of NLMTR in presurgical right-hemispheric TLE patients has not yet been investigated, it seems reasonable that this spatial navigation test can also be a useful instrument for the assessment of right-hemispheric temporal lobe functioning in TLE patients. However, adaption and reorganization processes in the brain related to a common early onset of seizures, make the patient group of TLE patients a special case (Bell et al., 2011; Binder et al., 2008; Hermann et al., 1997; Marques et al., 2007). Furthermore, given that the CVA population also has its own particular characteristics (e.g. higher age, cardiovascular risk factors) our study results cannot be transferred to TLE patients and other clinical populations without further investigations.

Looking for a neuropsychological marker for right temporal lobe functioning

In general, the three tests seem to capture different aspects of nonverbal memory, given that they only show a fair proportion of agreement in detecting a deficit. Moreover, the three tests differ in sensitivity and specificity to detect right temporal lesions. It should be noted that in particular the sensitivity was surprisingly low, although the values were comparable to other studies in this research field (Loring et al., 2008).

The aim of our study was to find a neuropsychological marker for right temporal lobe functioning. The criteria for such a marker include firstly that an appropriate neuroanatomical correlate can be identified as provided by the LSM method. Secondly, a neuropsychological marker should prove independent of other cognitive variables. Thirdly, test quality criteria such as sensitivity to correctly detect a lesion and specificity to correctly reject the presence of a lesion should be fulfilled. According to our comparisons of three nonverbal memory tests, NLMTR best meets these criteria as a neuropsychological marker to map right temporal lobe functioning. The NLMTR is the only test that includes right temporal brain structures as neuroanatomical correlates, it shows clear independence of verbal encoding and executive functions and has the highest sensitivity and acceptable specificity to detect a deficit in relation to the presence of a right hippocampal lesion. The RCFT also shows high specificity, which indicates that this test can very accurately reject the presence of a right hippocampal lesion. However, RCFT shows, at the same time, very low sensitivity to detect a right hippocampal lesion, the test performance does not seem to be independent of executive functions and the neuroanatomical correlates consist of a fronto-subcortical network without the involvement of right temporal structures. Therefore, we suggest that the designation as a neuropsychological marker for right temporal lobe functionality applies best to the NLMTR in our test selection.

5. Limitations

There are several limitations in our study. Although we were able to recruit an almost equal number of patients with left- and right-hemispheric lesions, the lesion coverage of the left hemisphere was lower than that of the right (Fig. 1). One reason for this might be that patients with global aphasia were not assigned to neuropsychological testing at this early stage of rehabilitation due to impaired language skills. Therefore, the patients included, suffering from relatively mild aphasia if any, might have had smaller lesion sizes in the left hemisphere. The probability of detecting anatomical correlates in the left hemisphere was therefore clearly diminished and we might have missed relevant structures for nonverbal memory in the left hemisphere.

Another limitation is that we only used recall performance to measure memory function. In our study we were restricted to the recall format, because only this format was available in all three nonverbal memory tests and the goal was to compare the three tests. Nonetheless, other memory processes such as encoding or recognition that are known to rely on the medio temporal lobe, could have been investigated as well (Eichenbaum et al., 2007; Rutishauser et al., 2006; Squire et al., 2007). However, the fact that anatomical correlates of the NLMTR include the right hippocampus confirms the sensitivity of this test for right temporal lobe functioning also in the recall format.

Finally, the selection of our tests is based on the use of MNND and can by far not be regarded as an exhaustive

examination of all nonverbal memory tests. Other nonverbal memory tests such as the "Diagnosticum für Cerebralschädigung DCS/DCS-R" (Weidlich, 1969; Weidlich et al., 2011) have not been considered and further research is needed to evaluate their sensitivity for right temporal lobe functioning. For example, several authors state an even better sensitivity for right temporal lobe functioning for tests relying on faces compared to tests using designs or scenes (Bentvelzen et al., 2021; Sherman et al., 2011; Vaz, 2004). However, some studies only find a modest group effect following right temporal lobe surgery in facial recognition paradigms (Hermann et al., 1995; Naugle et al., 1994) and the usefulness of such tests needs to be further reviewed.

7. Conclusion

Our findings suggest that out of three nonverbal memory tests only the NLMTR, as a spatial location learning and recall test, could serve as a neuropsychological marker for right temporal lobe functioning. Moreover, multivariate LSM results point to a dissociation between the anatomical correlates of the RCFT and the NLMTR, with the right temporal lobe and more specifically the hippocampus being involved only in the NLMTR. Furthermore, only the NLMTR seems to be mainly unaffected by other biasing cognitive functions such as executive functions and verbal encoding abilities.

CRediT author statement

Nadia Mock: Conceptualization, Methodology, Investigation, Data Curation, Writing-Original Draft, Project administration.

Christian Balzer: Conceptualization, Writing-Review & Editing.

Klemens Gutbrod: Conceptualization, Methodology, Writing-Review & Editing.

Lutz Jäncke: Methodology, Writing-Review & Editing, Supervision.

Jasmin Wandel: Methodology, Writing-Review & Editing.

Leo Bonati: Resources, Supervision.

Wiebke Trost: Conceptualization, Methodology, Investigation, Data Curation, Writing-Original Draft.

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Declaration of competing interest

None.

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Supplementary data

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