

Distinct Anatomical Correlates of Discriminability and Criterion Setting in Verbal Recognition Memory Revealed by Lesion-Symptom Mapping

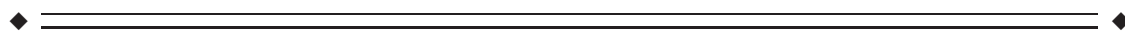
J. Matthijs Biesbroek,^{1*} Martine J.E. van Zandvoort,^{1,2} L. Jaap Kappelle,¹ Linda Schoo,² Hugo J. Kuijf,³ Birgitta K. Velthuis,⁴ Geert Jan Biessels,¹ and Albert Postma,^{1,2} On behalf of the Utrecht VCI study group

¹Department of Neurology, Utrecht Stroke Center, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands

²Experimental Psychology, Helmholtz Institute, Utrecht University, the Netherlands

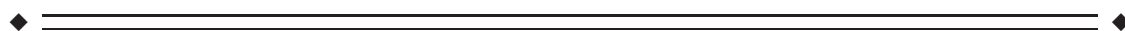
³Image Sciences Institute, University Medical Center Utrecht, Utrecht, the Netherlands

⁴Department of Radiology, University Medical Center Utrecht, Utrecht, the Netherlands



Abstract: Recognition memory, that is, the ability to judge whether an item has been previously encountered in a particular context, depends on two factors: discriminability and criterion setting. Discriminability draws on memory processes while criterion setting (i.e., the application of a threshold resulting in a yes/no response) is regarded as a process of cognitive control. Discriminability and criterion setting are assumed to draw on distinct anatomical structures, but definite evidence for this assumption is lacking. We applied voxel-based and region of interest-based lesion-symptom mapping to 83 patients in the acute phase of ischemic stroke to determine the anatomical correlates of discriminability and criterion setting in verbal recognition memory. Recognition memory was measured with the Rey Auditory Verbal Learning Test. Signal-detection theory was used to calculate measures for discriminability and criterion setting. Lesion-symptom mapping revealed that discriminability draws on left medial temporal and temporo-occipital structures, both thalami and the right hippocampus, while criterion setting draws on the right inferior frontal gyrus. Lesions in the right inferior frontal gyrus were associated with liberal response bias. These findings indicate that discriminability and criterion setting indeed depend on distinct anatomical structures and provide new insights in the anatomical correlates of these cognitive processes that underlie verbal recognition memory. *Hum Brain Mapp* 36:1292–1303, 2015. © 2014 Wiley Periodicals, Inc.

Key words: recognition memory; discriminability; criterion setting; response bias; lesion-symptom mapping



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*Correspondence to: J. Matthijs Biesbroek, Department of Neurology, Brain Center Rudolf Magnus, University Medical Center

Utrecht, PO box 85500, G.03.232, 3508 GA Utrecht, the Netherlands. E-mail: J.M.Biesbroek@umcutrecht.nl

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INTRODUCTION

Recognition memory can be defined as the ability to judge whether an item has been previously encountered in a particular context [Berry et al., 2008]. According to signal-detection theory, recognition depends on two factors: (1) discriminability and (2) a decision criterion, according to which the item is judged to be old or new [Berry et al., 2008; Wixted, 2007]. Discriminability reflects the process of gathering the “strength of evidence” of having previously encountered a specific item and depends on memory processes. Criterion setting (the actual decision whether an item is old or new based on the evidence, i.e., the application of a threshold) is regarded as a process of cognitive control [Jacoby et al., 2005]. Thus, an individual is assumed to decide whether an item is old or new by assessing the “strength of evidence” relative to a subjective decision criterion located at some point along this continuum. If the strength of evidence of having previously encountered the item exceeds the criterion then it will be judged to be old, otherwise it will be judged new [Berry et al., 2008].

Functional and lesion studies have provided insight in the anatomical correlates of several aspects of explicit memory, for example, working memory (dorsolateral parts of prefrontal cortices and lateral parietal cortices) and encoding for long term memory (medial temporal lobes, fornices, mammillary bodies, amygdala, thalamus) [Markowitsch, 2008; Rosen and Viskontas, 2008; van Strien et al., 2009; Vann et al., 2009]. Regarding recognition memory, there is substantial evidence for distinct anatomical correlates of the processes that underlie discriminability: recollection depends on a system centering on the hippocampus, whereas familiarity depends on a system centering on parahippocampal structures [Brown et al., 2010; Vann et al., 2009; Yonelinas et al., 2010]. Discriminability and criterion setting are also assumed to have distinct anatomical correlates, although there is no conclusive evidence from lesion studies that have attempted to compare the correlates of these two processes. There is some evidence for a role of the medial temporal lobes and thalamus in discriminability [Wixted and Squire, 2010; Yonelinas, 2002]. Functional studies have suggested that the parietal cortices might be involved in discriminability as well, although lesion studies have never been able to confirm these fMRI findings [Schoo et al., 2011; Vilberg and Rugg, 2008]. Lesion studies that have attempted to identify the anatomical correlates of criterion setting (also referred to as “response bias”) mainly focused on the frontal lobes. Two case studies have reported on patients with focal frontal lesions (one in the left, the other in the right prefrontal cortex), who showed remarkable high false alarm rates (i.e., false recognition); in both studies it was suggested that this may be due to extremely liberal response bias [Parkin et al., 1996; Schacter et al., 1996]. In a series of 14 patients with acquired brain damage, nonamnesic patients with isolated frontal lesions had a higher false

alarm rate in a verbal word recognition test than patients with medial temporal lobe lesions, but the false alarm rate was not increased compared with controls [Melo et al., 1999]. In a more recent series of 46 patients, no difference in discriminability was found between nonamnesic patients with frontal lesions and controls in a visual word recognition test, whereas several of these patients with frontal lesions did demonstrate pathologically elevated false alarm rates [Verfaellie et al., 2004]. A recent lesion-symptom mapping study, which applied voxel-wise analyses in 11 stroke patients, demonstrated an association between right fronto-temporal lesions and impaired discriminability for pictures and sounds and between right frontal lesions and liberal response bias (i.e., tendency toward high false alarm rate) for sounds and visually presented words [Haramati et al., 2008]. In summary, lesion studies on criterion setting in recognition memory have thus far been limited by low spatial resolution (grouping patients as either “frontal” or “medial temporal”), small sample size, and have yielded conflicting results. Moreover, in all but one of these studies the analyses were driven by the hypothesis that criterion setting takes place in either the frontal or temporal lobe, meaning potential involvement of other brain areas was not assessed. Thus, definite evidence regarding the anatomical correlates of criterion setting is lacking.

In this study, we therefore aimed to further clarify the anatomical correlates of recognition memory by applying lesion-symptom mapping in a cohort of 88 patients with first-ever ischemic stroke. We used the Rey Auditory Verbal Learning Test (RAVLT) to assess verbal memory [Rey, 1958]. Signal-detection theory was used to calculate measures for discriminability and response bias [Donaldson, 1992; Snodgrass et al., 1985]. We subsequently performed assumption-free voxel-based lesion-symptom mapping (VLSM) and region of interest-based analyses to determine the anatomical correlates of recognition memory and, more specifically, discriminability and criterion setting.

MATERIAL AND METHODS

Subjects

A flowchart of the inclusion of patients for this study is provided in Supporting Information Fig. 1. Neuropsychological examination was performed in ischemic stroke patients who are admitted to our service in the setting of standard clinical care, if their condition permitted testing and testing facilities were available. All 243 ischemic stroke patients who were admitted from November 2005 through December 2012 and underwent neuropsychological assessment during admission were eligible for the present study (see Supporting Information Fig. 1). We subsequently applied a stepwise exclusion procedure to select patients without interfering pre-existent neurological conditions or brain lesions, in whom the ischemic lesion

could be segmented on CT or MRI, and with available data on recognition memory. In the first step, we excluded 79 patients with pre-existent neurological conditions or imaging abnormalities: 26 patients with (probable) pre-existent cognitive impairment (history of cognitive impairment ($n = 7$), traumatic brain injury ($n = 5$), brain tumor ($n = 4$), epilepsy ($n = 1$), multiple sclerosis ($n = 1$), moyamoya disease ($n = 1$), or severe white matter hyperintensities, reflected in large confluent lesions on CT/MRI (i.e., Fazekas grade 3; see Fazekas et al., 1987; $n = 7$), 21 patients with prior stroke, 30 patients with old (silent) infarcts on brain imaging, and 2 patients with recurrent stroke between brain imaging and neuropsychological examination. In the second step, we excluded 43 patients for whom no brain imaging was available (no follow-up imaging in 24 patients, no ischemic lesion detected on follow-up imaging in 19 patients). In the final step, we excluded 20 patients who had no data on the RAVLT, 12 patients who were not right-handed, and one patient who performed far below chance on the recognition test (recognition score -11 [4/30 correct]). The application of these exclusion criteria resulted in the inclusion of 88 patients. This study was approved by the institutional review board of the University Medical Center Utrecht. Neuropsychological examinations and brain imaging were performed in the setting of standard clinical care.

Neuropsychological Assessment

Neuropsychological assessment was performed within 1 month after ischemic stroke (mean 7.6 days, range 1–30 days). We have previously demonstrated that the applied cognitive assessment battery is feasible and reliable in the acute stage (first days to weeks) of ischemic stroke [Nys et al., 2005]. Verbal memory was assessed with the Dutch version of the RAVLT, the Groningen Vijftienwoorden Test (Groningen Fifteen Words Test) [Brand and Jolles, 1985; Rey, 1958; Van der Elst et al., 2005]. Participants were presented with 15 common, monosyllabic words in auditory format. Directly after the presentation, they were asked to recall as many of the presented words as possible. The trial was repeated four more times, in which the same words were presented in identical order. Following the five consecutive trials, a battery of unrelated tests was conducted for approximately 20 min. After the delay, participants had again to recall the words of the initial test. This was immediately followed by a delayed recognition test: the 15 words of the initial test (target words) were mixed with 15 new words (distracter words) and the participants were asked to indicate for each word whether it was a target or not (yes/no). Educational level was divided into seven categories (scored according to [Verhage, 1964]) with scores ranging from unfinished primary school education (Category 1) to an academic degree (Category 7) according to the Dutch educational system).

Generation of Lesion Maps

Infarcts were manually delineated on transversal slices of either follow-up CT ($n = 59$), or MRI scans ($n = 29$) by two trained raters. Slice thickness (i.e., voxel-size along the z-axis) ranged from 4–6 mm; the in-plane voxel-size (i.e., along x- and y-axis) of the original CT and MRI scans was less than 1 mm in all cases. The infarct maps were registered to the T1 MNI-152 (Montreal Neurological Institute) template utilizing a lesion-masking approach [Brett et al., 2001; Fonov et al., 2009]. Registration of MRI images was performed using elastix; CT images were registered using an in-house developed algorithm which is described elsewhere [Klein et al., 2010; Kuijf et al., 2013]. A detailed description of the generation, registration, and quality checks of the lesion maps is provided in the online supplementary methods.

Statistics

Performance on the recognition test of the RAVLT was used to calculate the following measure for recognition: number of correct hits minus the number of false positives, with a score of 0 indicating chance performance. This recognition measure was norm-corrected for age, sex, and level of education, and transformed into z-scores using norms that were obtained in a large cohort of healthy Dutch individuals [Van der Elst et al., 2005]. Performance below the fifth percentile was considered abnormal. As the focus of this study was on the mechanisms involved in recognition memory, we did not consider the preceding recall scores of the RAVLT.

To study recognition memory in more detail, we used a previously described nonparametric model that estimates discriminability and response bias based on the hit rate ($H = \text{number of correct hits}/\text{number of old items}$) and the false alarm rate ($FA = \text{number of false alarms}/\text{number of new items}$) [Donaldson, 1992; Snodgrass et al., 1985]. Discriminability (A' ; varies from 0 to 1 with 0.5 indicating chance performance, and 1 indicating flawless performance) was calculated using the following formula: $A' = 1/2 + [(H - FA) (1 + H - FA)]/[4H (1 - FA)]$. Response bias (B''_D ; values >0 indicate conservative bias, values <0 indicate liberal bias) was calculated using the following formula: $B''_D = [(1 - H) (1 - FA) - HFA]/[(1 - H) (1 - FA) + HFA]$. For a detailed description of the theory behind these formulas, see Donaldson, 1992. This nonparametric model can reliably estimate discriminability and response bias when an individual has a hit rate of 1 or a false alarm rate of 0, whereas the parametric alternative to calculating discriminability (d') and bias (C) cannot be used when a subject has a hit rate of 1 or a false alarm rate of 0. Several methods have been proposed to correct the parametric model for such floor and ceiling effects, although these do not resolve the issue entirely [Stanislaw and Todorov, 1999]. Because a significant proportion of patients had a hit rate of 1 or a false alarm rate of 0, we

TABLE I. Characteristics of the study cohort

Characteristics	Study cohort ($n = 88$)
Demographic characteristics	
Age, mean (SD)	61.1 (13.5)
Male, n (%)	55 (63)
Education, mean (SD) ^a	5.0 (1.4)
Time interval between stroke and NPE in days, mean (SD; range)	7.6 (5.2; 1–30)
RAVLT results (raw scores)	
Recognition, mean (SD; range)	11.2 (3.8; –2 to 15)
Discriminability (A'), mean (SD; range) ^b	0.92 (0.11; 0.38–1.00)
Bias (B_D), median (range) ^b	0.19 (–1.00 to 1.00)

NPE: neuropsychological examination. RAVLT: Rey Auditory Verbal Learning Test.

^aEducation scored according to Verhage scoring system (1: Did not finish primary school, 2: finished primary school, 3: did not finish secondary school, 4: finished secondary school, low level, 5: finished secondary school, medium level, 6: finished secondary school, highest level, and/or college degree, 7: university degree).

^bBased on 83 patients with data on the number of false and true positive and negative responses in the recognition test.

chose to use the nonparametric model in the current study. Discriminability and response bias were calculated for 83 out of 88 patients, because data on the hits and false alarms had not been registered for the remaining five patients. Discriminability and response bias were corrected for age, sex, and level of education using linear regression because no norms are available for these measures. Mean corrected z -scores for discriminability and response bias were related to the location of ischemic lesions using a Student's t -test.

Voxel-based lesion-symptom mapping (VLSM) was used to determine the relationship between verbal memory measures and the location of brain injury [Kimberg et al., 2007; Rorden and Karnath, 2004; Rorden et al., 2007]. One major advantage of this method over traditional approaches to lesion-symptom mapping is that instead of grouping of patients with or without lesions in one or more pre-defined areas of interest, it allows for assumption-free calculation of association at each voxel. VLSM analyses were done on z -scores for performance on the RAVLT using Non-Parametric Mapping (most recent version, December 2012) [Rorden et al., 2007]. The Non-Parametric Mapping software provides two tests for VLSM: the parametric t -test and the nonparametric Brunner–Munzel (BM) statistic. Because the t -test has higher power than the BM statistic in small sample sizes, and because the t -test is particularly robust as it becomes conservative rather than liberal (i.e., reporting false alarms) when the underlying assumptions are violated, we chose to use the t -test in our main analyses [Rorden et al., 2007]. We additionally performed a supplementary analysis using the BM statistic.

Voxels affected by ischemic lesions in less than 3 patients were not considered for analysis (the threshold for the minimum number of patients with a lesion per voxel is arbitrary, but generally in the range of 3–5) [Biesbroek et al., 2013; Haramati et al., 2008; Knutson et al., 2014; Molenberghs and Sale, 2011; Schwartz et al., 2009; Thothathiri et al., 2012]. Correction for multiple testing was achieved using a false discovery rate (FDR) threshold with $q < 0.05$.

In the next step, we complemented the VLSM analysis with a region of interest-based approach because these techniques have complementary strengths and weaknesses. Region of interest-based analyses have limited power for detecting patterns that are only present in a subset of voxels in the region; VLSM is more sensitive for detecting such patterns due to its high spatial resolution. Conversely, VLSM requires a far greater number of statistical tests and should, therefore, be followed by correction for multiple testing, which reduces statistical power [Kimberg et al., 2007; Thothathiri et al., 2012]. Ideally, the discordance in anatomical correlates of discriminability and criterion setting should, therefore, be confirmed in the region of interest-based analysis to rule out method-dependent type 2 errors.

For this purpose, regions of interest for 90 cerebral cortical regions were extracted from the automatic anatomical labeling (AAL) atlas [Tzourio-Mazoyer et al., 2002]. These 90 regions were projected on the VLSM results and the amount of voxels with a statistically significant correlation within each region was quantitatively assessed. Regions that appeared to be involved in discriminability or criterion setting (operationally defined as at least 5% of tested voxels having a statistically significant association between the presence of a lesion and performance, with a total of no less than 100 significant voxels) were selected and used to calculate regional infarct volume within these regions for every patient. These regional infarct volumes were entered as independent variables in a linear regression model with either discriminability or response bias as dependent variables, before and after adding total infarct volume to the model. The rationale behind adding infarct volume as a covariate was that brain regions that are crucial when performing a certain task should predict performance, independent of total infarct volume [Karnath et al., 2004].

RESULTS

Clinical characteristics of the study cohort are provided in Table I. Twenty-two out of 88 patients had impaired recognition. Impaired recognition was more common in patients with isolated left hemispheric lesions (11/30; 37%) than with isolated right hemispheric lesions (7/38; 18%; Table II). Out of the 83 patients with complete data on the number of hits and false alarms, 24 patients had a hit rate of 1 (15/15 old items correctly identified), and 44 patients

TABLE II. Location of ischemic lesion in relation to the presence of impaired verbal recognition memory

	Lesion location			
	Left (<i>n</i> = 30)	Right (<i>n</i> = 38)	Infratentorial (<i>n</i> = 12)	Multiple (<i>n</i> = 8)
Impaired recognition				
Yes (<i>n</i> = 22)	11/30 (37%)	7/38 (18%)	1/12 (8%)	3/8 (38%)
No (<i>n</i> = 66)	19/30 (63%)	31/38 (82%)	11/12 (92%)	5/8 (63%)

Left: left cerebral hemisphere. Right: right cerebral hemisphere. Infratentorial: cerebellum and/or brainstem. Multiple: lesion located at multiple sites.

had a false alarm rate of 0 (no false alarms). Seventeen patients had perfect recognition performance (hit rate of 1 and a false alarm rate of 0). Mean corrected discriminability scores (*A'*) were lower in patients with isolated left hemispheric lesions (mean *z*-score -0.29 (SD1.25)) than in patients with isolated right hemispheric lesions (mean *z*-score 0.22 (SD 0.62); $P = 0.05$). In contrast, mean corrected response bias scores (B''_D , low score indicates liberal bias) were lower in patients with right hemispheric lesions (mean *z*-score -0.19 (SD 1.04)) than in patients with left hemispheric lesions (mean *z*-score 0.31 (SD 0.75); $P = 0.04$).

Voxel-Based Lesion-Symptom Mapping

The spatial distribution of infarcts is illustrated by the lesion prevalence map of the 88 included patients (Fig. 1). The lesion prevalence was highest for voxels in the right cerebral hemisphere in the vascular territory of the middle cerebral artery. Lesion frequency was relatively low for left hemispheric voxels. As a consequence, some left temporal, occipital, insular, inferior frontal, and thalamic regions could be included in the analyses while the remaining left hemispheric regions were lesioned in less than three patients and could not be included in the VLSM analyses (Fig. 1). VLSM identified clusters of voxels with a statistically significant association between the presence of a lesion

and poor recognition and discriminability (entered as continuous variables; corrected for age, sex, and level of education). Poor recognition and discriminability were associated with lesions in the left medial temporal lobe and left temporo-occipital structures (hippocampus, parahippocampal, inferior temporal, fusiform, lingual, inferior and medial occipital gyrus, and calcarine gyri), the left and right thalamus, and the right hippocampus. Liberal response bias (i.e., low B''_D) was associated with lesions in the opercular part of the right inferior frontal gyrus. The VLSM results for recognition, discriminability, and response bias are provided in Figure 2. The number of significant voxels for each region is provided in Table III.

Region of Interest-Based Analyses

Next, we analyzed the impact of lesion volumes in specific cortical regions of interest (Table IV). These regions were selected based on the VLSM results to reproduce their involvement and quantify the impact of regional lesion volumes on discriminability and criterion setting. Age, sex, and level of education explained 9% of variance in discriminability and only 3% of variance in response bias. Infarct volume within the left hippocampus, parahippocampal, inferior temporal, fusiform, lingual, inferior and medial occipital, and calcarine gyri, and the left thalamus inversely correlated with discriminability. The increase in explained variance in discriminability was highest for lesion volume within the left inferior occipital gyrus (additional explained variance of 37%; Table IV). Infarct volume within the opercular part of the right inferior frontal gyrus inversely correlated with response bias and explained an additional 11% of variance. The results of the linear regression analyses remained essentially the same after additional adjustment for total infarct volume (Supporting Information Table 1).

Nonparametric Analyses

It should be noted that the distribution of *z*-scores for recognition, discriminability, and response bias were skewed, as is often the case when using cognitive performance of stroke patients as the dependent variable (e.g.,

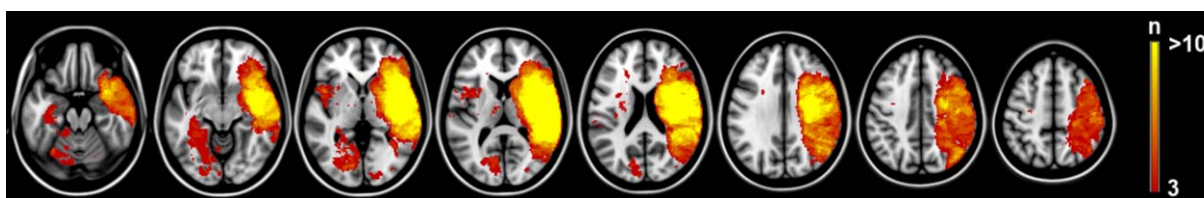


Figure 1.

Distribution of ischemic lesions. Voxels that are damaged in at least three patients are projected on the 1 mm MNI-152 template (*Z* coordinates: $-20, -10, 0, 10, 20, 30, 40, 50$). Bar indicates the number of patients with a lesion for each voxel. The right hemisphere is depicted on the right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

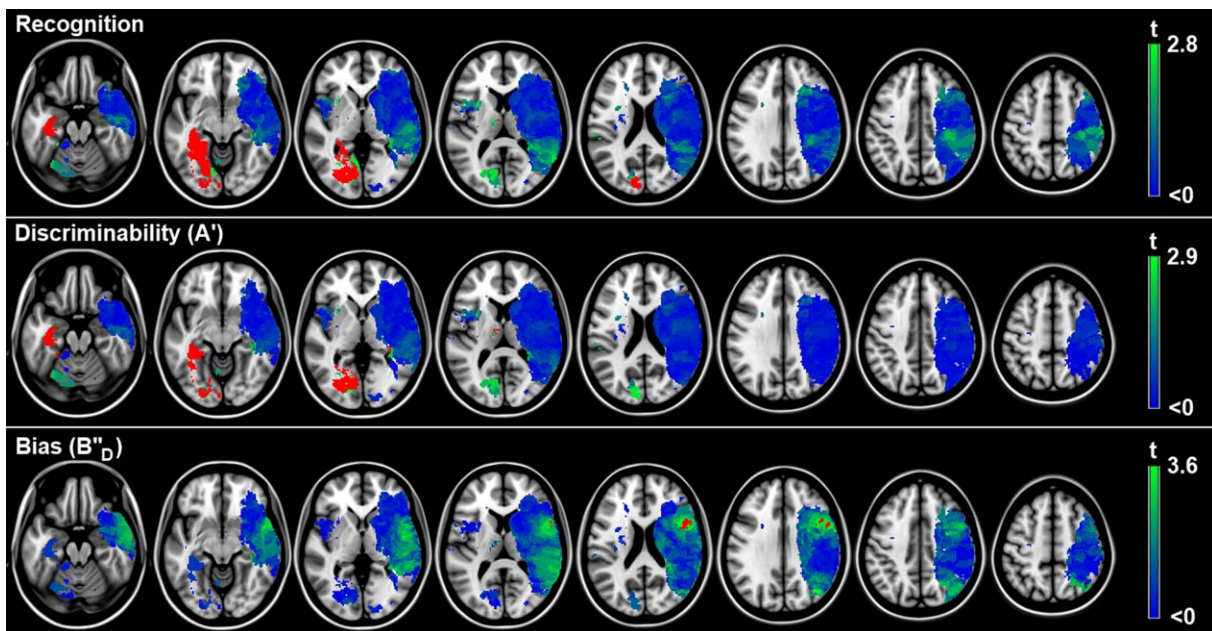


Figure 2.

Voxel-based lesion-symptom mapping results. Map of the voxel-wise association (t -statistic) between the presence of a lesion and cognitive performance. Voxels exceeding the FDR threshold ($q = 0.05$) are rendered in red. Nonsignificant voxels are rendered on a scale from blue ($t < 0$) to bright green (t -value just below threshold). Recognition was norm-corrected for age, sex, and level of education; discriminability and bias were corrected for age, sex, and level of education using linear regression. Neg-

ative t -values (meaning the presence of a lesion was associated with better cognitive performance or with a conservative bias) were not statistically significant. The results are projected on the MNI 1-mm template (Z coordinates: $-20, -10, 0, 10, 20, 30, 40, 50$). The right hemisphere is depicted on the right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

skewness for the residuals of the multivariate model in which we corrected raw scores for age, sex and level of education was -2.6 (SE 0.26) for discriminability and -0.41 (SE 0.26) for response bias). To assess the robustness of our findings, we therefore also performed two nonparametric analyses: a lesion-subtraction analysis and a voxel-wise BM statistic. The qualitative lesion-subtraction analysis using dichotomized measures of discriminability (z -score below or above group mean) and response bias (liberal versus neutral or conservative) reproduced our main finding of distinct anatomical correlates for discriminability (left temporo-occipital regions and left thalamus) and criterion setting (right frontal regions; Fig. 3). The results of the nonparametric BM statistic (Supporting Information Fig. 2) also essentially showed the same pattern as the t -test results (Fig. 2), although in this less sensitive BM analysis the association remained statistically significant in only a few voxels after correction for multiple testing.

DISCUSSION

In this study, we determined the anatomical correlates of cognitive processes underlying verbal recognition mem-

ory by performing lesion-symptom mapping in patients with first-ever ischemic stroke. Our findings indicate that the left medial temporal lobe, left temporo-occipital structures, both thalami, and the right hippocampus are crucial structures underlying discriminability, while the right inferior frontal gyrus plays a crucial role in criterion setting. More specifically, lesions in the right inferior frontal gyrus are associated with liberal response bias but not with impaired discriminability.

The main strengths of this study are the substantial sample size, the assumption-free nature of the analyses (as opposed to hypothesis-driven analyses, in which the analyses are focused on predefined regions of interest), and the application of quantitative voxel-wise analyses that provide high spatial resolution.

Our findings regarding involvement of the left medial temporal lobe, right hippocampus, and both thalami in verbal recognition memory corroborate and extend previous findings [Wixted and Squire, 2010; Yonelinas, 2002]. Functional studies have suggested that the parietal cortices might be involved in recognition memory, although lesion studies have never been able to confirm these fMRI findings [Schoo et al., 2011; Vilberg and Rugg, 2008]. We

TABLE III. Voxel-based lesion-symptom mapping results for discriminability and criterion setting: tested and significant voxels for each AAL region

Anatomical regions (AAL atlas)	Patients with lesion (<i>n</i>) ^a	Region size in voxels (<i>n</i>)	Tested voxels (<i>n</i>)	Significant voxels criterion setting (<i>n</i> [%])	Significant voxels discriminability (<i>n</i> [%])
Inferior frontal opercular R	25	11174	9385	868 (9.25)	0
Precentral R	24	27058	14536	185 (1.27)	0
Rolandic operculum R	26	10733	10025	30 (0.30)	0
Inferior frontal triangular R	20	17132	8863	17 (0.19)	0
Superior temporal pole R	20	10654	6266	6 (0.10)	0
Middle temporal R	18	35484	28161	16 (0.06)	0
Superior temporal R	25	25258	22465	7 (0.03)	0
Insula R	31	14128	14091	2 (0.01)	0
Hippocampus L	7	7469	850	0	850 (100)
Parahippocampal L	4	7891	843	0	843 (100)
Fusiform L	9	18333	3875	0	3875 (100)
Inferior temporal L	5	25647	514	0	514 (100)
Inferior occipital L	5	7536	1207	0	1174 (97.27)
Lingual L	12	16932	4542	0	4185 (92.14)
Medial occipital L	8	25989	455	0	392 (86.15)
Thalamus L	9	8700	324	0	100 (30.86)
Calcarine L	10	18157	3029	0	655 (21.62)
Hippocampus R	17	7606	1934	0	106 (5.48)
Thalamus R	13	8399	1587	0	40 (2.52)
Parahippocampal R	7	9028	289	0	4 (1.38)

R: right. L: left. AAL regions in which no significant voxels were observed for either discriminability or criterion setting are not shown. ^aIndicates how many of the 83 patients had a lesion (≥ 1 voxel) within the specified region of interest.

TABLE IV. Results of linear regression models with z-scores of cognitive performance as outcome

Model	Independent variables	Discriminability (A')			Response bias (B'_D)		
		R^2	$P \Delta R^2$	B (95% CI)	R^2	$P \Delta R^2$	B (95% CI)
1	Age, sex, level of education	0.09	0.053	—	0.03	0.516	—
2	Model 1 + total IV	0.11	0.169	-0.00 (-0.01 to 0.00)	0.06	0.110	-0.00 (-0.01 to 0.00)
3a	Model 1 + IV R inferior frontal opercular part	0.09	0.826	0.01 (-0.09 to 0.11)	0.14	0.002	-0.15 (-0.24 to -0.06)
3b	Model 1 + IV L hippocampus	0.45	<0.001	-0.85 (-1.09 to -0.61)	0.03	0.848	-0.03 (-0.35 to 0.29)
3c	Model 1 + IV L parahippocampal gyrus	0.45	<0.001	-0.86 (-1.11 to -0.62)	0.03	0.884	-0.02 (-0.35 to 0.30)
3d	Model 1 + IV L fusiform gyrus	0.43	<0.001	-0.29 (-0.38 to -0.21)	0.03	0.900	-0.01 (-0.12 to 0.11)
3e	Model 1 + IV L lingual gyrus	0.42	<0.001	-0.33 (-0.42 to -0.23)	0.03	0.854	0.01 (-0.12 to 0.14)
3f	Model 1 + IV L inferior temporal gyrus	0.42	<0.001	-0.30 (-0.39 to -0.21)	0.03	0.989	0.00 (-0.12 to 0.12)
3g	Model 1 + IV L inferior occipital gyrus	0.46	<0.001	-1.19 (-1.52 to -0.86)	0.03	0.897	-0.03 (-0.47 to 0.41)
3h	Model 1 + IV L medial occipital gyrus	0.19	0.003	-0.69 (-1.13 to -0.24)	0.03	0.779	-0.07 (-0.56 to 0.42)
3i	Model 1 + IV L Calcarine gyrus	0.22	0.001	-0.35 (-0.55 to -0.16)	0.03	0.650	-0.05 (-0.27 to 0.17)
3j	Model 1 + IV L thalamus	0.17	0.009	-0.62 (-1.08 to -0.16)	0.05	0.229	-0.30 (-0.79 to 0.19)
3k	Model 1 + IV R hippocampus	0.12	0.100	-0.40 (-0.88 to 0.08)	0.06	0.128	-0.39 (-0.88 to 0.11)

The explained variance (R^2) in discriminability and response bias is given for each model with the corresponding P -value for the difference in explained variance ($P \Delta R^2$) between the model and the previous model. Unstandardized coefficients (B) with corresponding 95% CIs are provided. The unstandardized coefficient applies to the change in z-score for every 1 ml increase in infarct volume. IV: infarct volume. R: right. L: left. Low response bias corresponds with liberal bias.

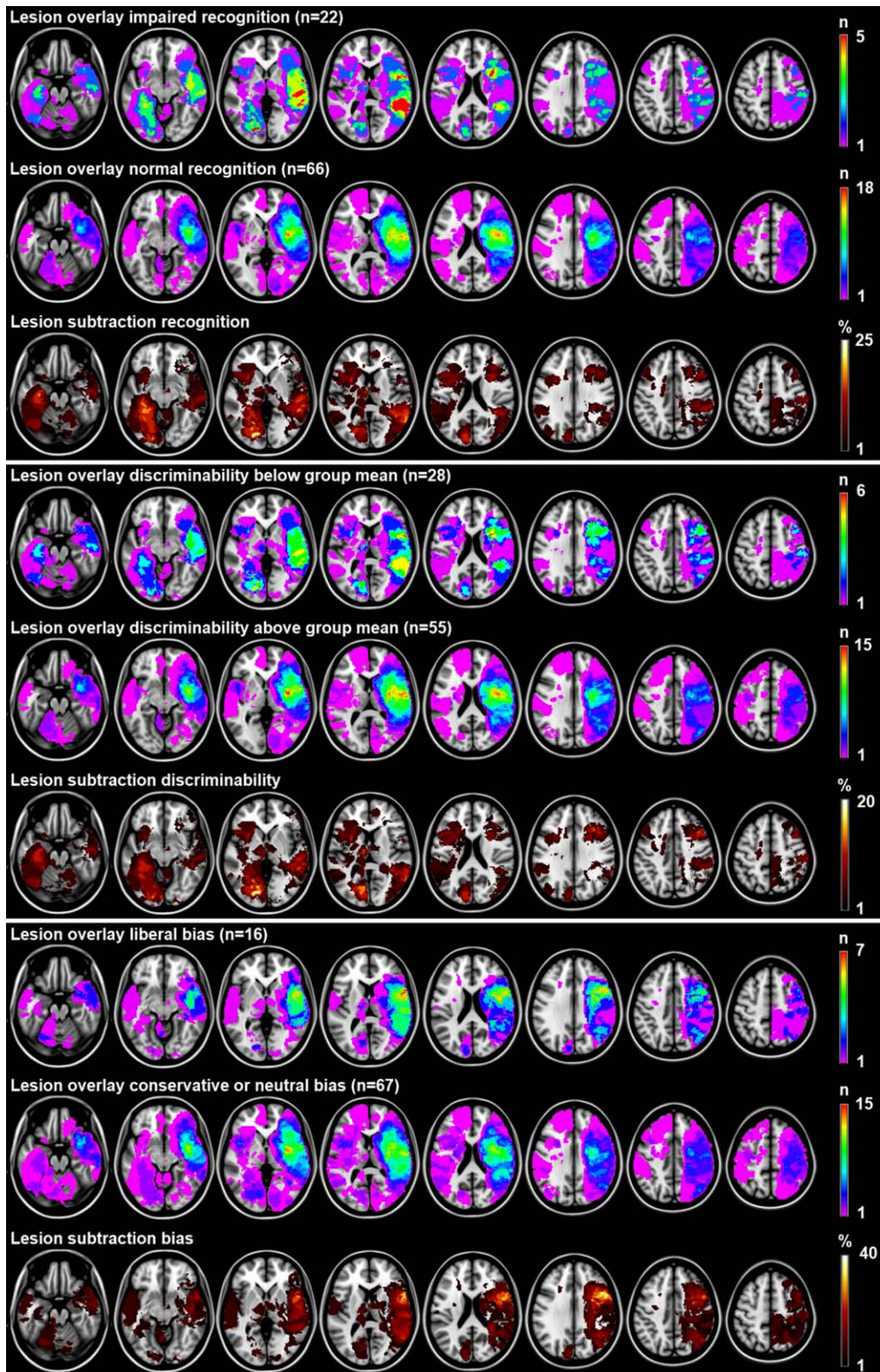


Figure 3.
(See legend on the following page.)

found no associations between right parietal lesions and poor recognition, which is in line with these previous findings. Regarding the previously assumed role of the frontal lobe in recognition, we have demonstrated that the inferior frontal gyrus is involved in criterion setting while frontal structures do not appear to be involved in discriminability.

Based on several case reports and lesion studies with relatively small sample size, it has previously been suggested that the frontal lobes play an important role in criterion setting [Haramati et al., 2008; Melo et al., 1999; Parkin et al., 1996; Schacter et al., 1996; Verfaellie et al., 2004]. Our results provide statistical evidence for the previously assumed crucial role of the right frontal lobe in criterion setting, and further localize this function in the inferior frontal gyrus. To our knowledge, this study is the first to demonstrate a crucial role of the right inferior frontal gyrus in criterion setting in verbal recognition memory. Criterion setting depends on context (instructional motivation, proportion of old test items) and is to some extent subject to trait-like variability, as introvert persons tend to use more conservative recognition criteria than extroverts as they exercise greater “response cautiousness” [Kantner and Lindsay, 2012; McNally et al., 2009]. Pathological processes that are known to influence response bias typically lead to extremely liberal bias (resulting in false recognition); to our knowledge there have been no reports of patients with extremely conservative bias following brain damage. It has been hypothesized that false recognition may be induced by several conditions: (1) partial memory for the study lists, (2) the inability to extract the semantic gist of the list, and (3) defective strategic monitoring of cognitive processes, which is assumed to depend on frontal structures in particular and may result in a false sensation of familiarity [Melo et al., 1999]. Our findings indicate that discriminability and criterion setting have separate anatomical correlates. Thus, our results suggest that patients with medial temporal, temporo-occipital, or tha-

lamic lesions may show false recognition due to impaired discriminability (reflecting condition 1 and 2), whereas patients with isolated frontal lesions might show false recognition due to liberal bias (reflecting condition 3).

Despite the fact that we have used well accepted lesion-symptom mapping techniques that are commonly used, some challenges and limitations that are inherent to these techniques should be taken into account. These include how deal with low lesion frequencies in certain anatomical regions, skewed data, and the problem of identical origins. We will discuss these limitations in the following section. First, a potential limitation of this study is the relatively low lesion frequency in the left cerebral hemisphere (despite the substantial number of patients with left hemispheric lesions). This is explained by the fact that neuropsychological examination is not always feasible in patients with severe global aphasia, especially when applying tests that require processing of verbal information. Most voxels in the left cerebral hemisphere were therefore not included in the VLSM analysis. Due to this limitation, we cannot draw any conclusions regarding the involvement of the left frontal lobe in criterion setting in verbal recognition memory. Similarly, we cannot draw any strong conclusions regarding the role of left parietal and frontal structures in discriminability. Second, there was some skewing of measures for discriminability and response bias (see results section). Our main findings (Fig. 2) were supported by the results of the qualitative lesion-subtraction analysis (Fig. 3). Moreover, the results of the supplementary analysis using the nonparametric BM statistic showed essentially the same pattern as the *t*-test results (Supporting Information Fig. 2). However, in this analysis most of the voxels lost statistical significance after correction for multiple testing which is explained by the fact that the BM statistic has lower power than the *t*-test when applied to voxels with less than 10 patients with a lesion [Rorden et al., 2007]. Finally, the region of interest-

Figure 3.

Lesion subtraction analyses. Lesion overlay and subtraction plots of dichotomized measures of recognition (impaired yes/no based on previously described norms), discriminability (impaired defined as performance below group mean because norms are not available), and response bias (liberal versus neutral or conservative). The overlay plots show the number of patients with a lesion for a given voxel separately for patients with impaired and normal performance. The lesion subtraction plots show which voxels are more frequently affected in patients with impaired performance compared to patients with normal performance. For example, the recognition overlay plots show that 4 out of 22 (18%) patients with impaired recognition have a lesion in the left hippocampus, whereas none of the 66 (0%) patients with normal recognition have a lesion in the left hippocampus. The lesion subtraction plot shows the resulting 18% difference in lesion prevalence. This finding suggests a crucial role of the left hippocampus in recognition.

Because dichotomization of performance results in a decrease in statistical power and does not account for severity of the deficit, we chose to use the continuous outcome (analyzed with *t*-test) in our main analyses. These qualitative lesion subtraction analyses (lesion subtraction does not provide measures of statistical significance) are presented here to assess the robustness of our results. The results are essentially the same: left medial temporal and temporo-occipital structures were most consistently damaged in patients with impaired recognition and discriminability and spared in patients with normal recognition and discriminability (maximum difference in lesion density of 23% and 21%, respectively). The right inferior frontal gyrus was most consistently damaged in patients with liberal bias (maximum difference in lesion density of 36%). The right hemisphere is depicted on the right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

based analyses indicated that infarct volume within the regions that were identified by the *t*-test inversely correlated with discriminability and response bias, independent of total infarct size. The converging findings of these different analytical approaches indicate that our findings are robust, although the point estimates and *P*-values of the regression coefficients that are provided by the linear regression model should be interpreted with some caution. Third, we cannot rule out that the observed correlates of discriminability in left occipital structures might in fact be driven by hippocampal damage, because both regions are vascularized by the posterior cerebral artery and were, therefore, frequently lesioned together (i.e., were intercorrelated), as is shown in Supporting Information Figure 3. This limitation, which is referred to as the problem of identical origins, is inherent to VLSM studies, especially when lesion frequency is low. However, it should be noted that the differences in anatomical correlates of discriminability and criterion setting as observed in the current study cannot be attributed to this problem of identical origins. New methods for lesion-symptom mapping are currently emerging [Mah et al., 2014]. These new methods seek to resolve the above raised issues regarding the problem of identical origins by constructing “models using high-dimensional interference that captures the multivariate lesion distribution, explicitly modeling the voxel-voxel associations that are the source of the error” [Mah et al., 2014]. However, such models require hundreds to thousands of cases. As such, these new and more sophisticated methods could unfortunately not be applied in this study. Fourth, we used both CT and MRI scans for lesion segmentation, which is not uncommon in lesion-symptom mapping studies [Karnath et al., 2004; Robinson et al., 2012; Schwartz et al., 2009; Thothathiri et al., 2012; Theys et al., 2013]. Both modalities allow for accurate detection of the location on the ischemic lesion. However, the boundary of the lesion might be drawn differently between modalities. In addition, this boundary is also influenced by the elapsed time between stroke onset and CT/MRI scan acquisition. The variability in lesion segmentation could be minimized by applying a single scan modality in a certain time window (e.g., MRI acquired 48–72 h after stroke onset). However, we chose for a robust design including as many patients as possible (with either CT or MRI scans) to optimize statistical power while accepting some heterogeneity in scan acquisition. It should be noted that the marked differences in anatomical correlates of discriminability and criterion setting cannot be attributed to slight variability in the segmentation of lesion boundaries. Finally, it should be noted that the precision of the VLSM results is determined by the resolution of the original CT and MRI scans. The in-plane voxel-size (i.e., along *x*- and *y*-axis) of the original CT and MRI scans was less than 1 mm in all cases, but slice thickness (i.e., voxel-size along the *z*-axis) ranged from 4–6 mm, resulting in lower precision in that direction.

There are some considerations that should be taken into account when interpreting the findings of the current study. First, it should be noted that due to the applied inclusion criteria, the prevalence of cognitive impairment in the study group might not reflect the prevalence in the overall stroke population. However, our aim was not to assess the prevalence of disturbances in recognition memory following acute ischemic stroke but to determine the anatomical correlates of recognition memory by relating lesion location to variance in performance on recognition tasks within the study group. Importantly, the variance in discriminability and response bias in the patient group was high, which increases the power for correlational analysis (Table I). Second, a further distinction in processes that underlie discriminability has been proposed based on the introspective awareness state of the memory holder, contrasting conscious recollection with familiarity [Berry et al., 2008]. Since we have no data on whether our recognition responses were based on recollection or familiarity, we could not address this distinction here. Finally, when comparing the findings of our study with prior work, it should be kept in mind that we studied patients in the acute phase of ischemic stroke. Neuropsychological examination was performed within 30 days after ischemic stroke and the majority of scans were acquired in the acute phase as well. Therefore, the observed relations between lesion location and measures of recognition memory apply to the acute phase. In some cases, the extent of ischemic lesions on diffusion weighted imaging might be overestimated in the acute phase compared to imaging in the chronic phase [Jauch et al., 2013]. Furthermore, a prior study in which the prevalence of post-stroke cognitive impairment was assessed has shown that more than half of the patients with verbal memory impairments in the acute phase after stroke (within 3 weeks) will have recovered in the chronic phase (after 6–10 months) [Nys et al., 2005]. As such, it is possible that the anatomical correlates of discriminability and criterion setting might change in more chronic stages.

In conclusion, this study demonstrated a crucial role of left hemispheric medial temporal and temporo-occipital regions, both thalamic, and the right hippocampus in discriminability in verbal recognition memory while criterion setting depends on the inferior frontal gyrus. Lesions in the right inferior frontal gyrus are associated with liberal response bias but not with impaired discriminability. These findings indicate that discriminability and criterion setting depend on distinct anatomical structures and provide new insights in the anatomical correlates of these cognitive processes that underlie verbal recognition memory.

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