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MSc Cognitive Neuroscience

Graduation Project

Investigating the relation between delayed recall and familiarity-based recognition using atlas-based LSM

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RECOGNITION USING ATLAS-BASED LSM

Abstract

Every year millions of people are affected with post-stroke deficits. These deficits comprise episodic verbal memory processing. Although, extensive research has been done to examine verbal long-term memory, the underlying mechanisms of recall and familiarity-based recognition are not well understood. Therefore, the present study examined the influence of ischemic stroke on recall and recognition memory performance in 115 stroke patients. Verbal long-term memory was examined using Dutch version of the Rey Auditory-Verbal Learning Test and atlas-based LSM analysis was performed to identify neural correlates in white and grey matter underlying recall and recognition memory performance. The current study demonstrated an association between delayed recall and familiarity-based recognition memory, which could suggest they depend on similar processes. Atlas-based LSM did not reveal brain regions that were related to both performances. These results suggest that recall and recognition memory may not depend on one specific neural locus but could be attributed to a complex neural network that could not be detected by LSM. Future studies could gain more insight in the underlying neural mechanisms of verbal episodic memory by investigating brain networks.

Keywords: verbal episodic memory, RAVLT, ischemic stroke, atlas-based lesion-symptom mapping

Introduction

Stroke is a neurological disease that affects approximately 13 million people across the world every year (World Stroke Organization [WSO], 2019). A large number of stroke patients experience post-stroke memory deficits (Al-Qazzaz et al., 2014; Tuladhar et al., 2013). In particular, episodic memory is frequently disrupted as a result of stroke (Brown & Zorilla, 2001; Schouten et al., 2009).

Episodic memory can be described as a memory system that enables you to consciously access information for unique events. These events represent past experiences

and can be retrieved in service of present and future objectives (Tulving, 1983). Remembering a past event can occur through recall or recognition. The former process is more demanding whilst recognition is less effortful since it does not require retrieving of specific details about the episode (Papagno, 2018). Recognition can be distinguished in two memory processes that are known as recollection and familiarity. Familiarity is often used as a reliable measure of prior exposure in recognition tasks during which subjects are asked to discriminate between studied and unstudied items (Heathcote et al., 2006; Manns et al., 2003). In contrast, recollection is defined as the retrieval of a more detailed memory in terms of when and where an episode occurred (Yonelinas, 2002).

Prior neuroimaging studies have identified several neural correlates that are involved in episodic memory. Typically, in these studies healthy participants were asked to remember events from their past, in order to respond to various experimental cues. Episodic memory retrieval has been attributed to activations in a large brain network encompassing the right prefrontal cortex, cortical midline structures (ventral and dorsal medial prefrontal cortex and posterior cingulate) and medial temporal regions (Bird, 2017; Cabeza, 2000; Cabeza, 2007; Maguire, 2001). Other studies showed activations in the hippocampal region, prefrontal, parietal, lateral entorhinal and perirhinal cortex when participants both correctly and incorrectly recognized previously learned items (Cabeza, 1997; Eichenbaum, 2007; Kapur et al., 1995; McDermott et al., 1999; Nyberg et al., 1996; Stark & Squire, 2000). These results suggest that although there is an overlap in certain brain structures, familiarity-based recognition and episodic retrieval also seem to depend on distinct brain regions.

Apart from functional neuroimaging studies, numerous lesion and neuropsychological studies have investigated recall and familiarity-based memory performance in various patient groups. An early neuropsychological study by Morris, Abrahams, Baddeley and Polkey

(1995) examined the role of the temporal lobe in 47 patients that underwent left or right temporal lobe resection. Patients performed The Doors and People Test that tests visual and verbal memory. It was found that impaired verbal retrieval and recognition memory was associated with left temporal lobe lesions and visual memory dysfunction was related to right temporal lobe lesions. Manns, Hopkins, Reed, Kitchener and Squire (2003) investigated recall and recognition performance in seven patients that had a bilateral lesion in the hippocampus, using the Rey Auditory Verbal Learning Test (RAVLT) and The Doors and People Test to examine verbal and visual memory. Results showed that these patients were impaired on recall and recognition memory on both tests compared to the control group. Similar to the research of Morris et al. (1995), MacPherson, Turner, Bozzali, Cipolotti, and Shallice (2016) examined retrieval and recognition memory in 47 patients with frontal lobe lesions using The Doors and People Test. Results showed that both visual and verbal recall and recognition memory performance was impaired in these patients compared to healthy controls. Moreover, these studies show evidence that the medial temporal and frontal lobe are involved in verbal and visual recall and recognition information processing. In addition to these studies, Schouten, Schiemanck, Brand and Post (2009) elucidated the influence of infarct characteristics such as volume, cortical or subcortical lesions and lesion side on visual and verbal memory one year after stroke onset. Verbal memory performance was accessed using the RAVLT. It was shown that left hemispheric stroke patients with subcortical and large lesions performed significantly worse on immediate and delayed recall compared to right hemispheric stroke patients. Verbal recognition memory impairment was not associated with lesion side. Andrews et al. (2014) examined long lasting effects of ischemic stroke on verbal recall and recognition performance in 20 left, 21 right hemispheric stroke patients and 41 healthy controls. The Hopkins Verbal Learning Test was used to access verbal memory.

Left hemispheric stroke patients showed impaired recall and recognition performance compared to healthy controls. Right hemispheric stroke patients, on the other hand, showed comparable performance to the control group. In addition, left hemispheric stroke patients performed worse on delayed recall compared to right hemispheric stroke patients, but showed similar results on the recognition test. These results suggest that the left hemisphere is predominantly involved in verbal retrieval performance, whereas verbal recognition memory is not related to a specific side. Finally, a recent study by Biesbroek et al. (2015) examined the neural correlates underlying two factors that recognition memory depends on, based on the signal detection theory. This theory states that the ability to detect whether something has previously been presented depends on two processes during which an individual obtains sufficient information about a certain object (discriminability) and then determines whether the object was old or new (criterion setting), based on the information. Voxel-based lesion symptom mapping (VLSM) analysis was performed in 83 first-ever stroke patients and the RAVLT was used to access verbal memory. Results showed that discriminability was related to left medial temporal lobe, left temporo-occipital regions, thalamus, and the right hippocampus. Criterion setting was associated with the right inferior frontal gyrus. These findings indicate that the processes underlying verbal recognition memory are related to left and right hemispheric brain structures.

In sum, although multiple studies have explored the neural underpinnings of memory dysfunction after stroke, most studies used different neuropsychological tests, small sample size or various neuroimaging techniques to investigate the neural correlates of verbal long-term memory. This led to divergent results. As a consequence, it remains unclear to what extent ischemic stroke affects retrieval and recognition memory and which specific brain regions are associated with retrieval and familiarity-based recognition memory impairment.

Therefore, the current study aimed to examine the influence of stroke location on recognition and delayed recall in 115 participants. The strengths of the study are the large sample size and the use of one neuropsychological test (RAVLT) to access both verbal recall and recognition. Apart from this, the study is generalizable since patients were not preselected on a lesion location. Finally, an atlas-based lesion symptom mapping (LSM) analysis was performed to identify which brain regions are significantly associated with verbal recall and recognition performance. LSM offers insight in brain-behaviour associations in patient populations (Bates et al., 2003). One its main advantages over techniques such as functional MRI (fMRI), is that with LSM the function of a particular brain area can strongly be inferred by examining the behavioural impairment in relation to a damaged region (Rorden & Karnath, 2004). With fMRI, activity in brain regions is correlated to a task, which does not necessarily mean that these areas are required for a task. It could be that areas that are not directly related also show activity since they are connected to regions that are necessary for a particular task (Rorden & Karnath, 2004). Thus, with fMRI the differential contribution of brain regions is difficult to infer. In addition, compared to VLSM, LSM has the advantage that thousands of voxels are grouped into anatomical regions, which in turn reduces the issue with multiple comparisons, whereas with VLSM multiple individual *t*-tests are conducted in each voxel, thereby increasing the probability of false-positives.

Based on previous studies described above, it is hypothesized that there is a partial association between recall and recognition memory. Additionally, is hypothesized that recall and recognition memory share partially similar and partially distinct brain regions. In the present study, regions that are considered to be similar in recall and recognition are prefrontal cortex and medial temporal regions, whereas regions that are considered to be distinct are regions surrounding the medial temporal cortex as well as parietal cortex.

Methods

Participants

A total of 251 sub-acute ischaemic stroke patients between the ages of 20 and 90 (*M* = 58,0; *SD* = 11,9 years) participated in this study, of whom 105 were excluded due to absence of MRI data (n = 56), incomplete behavioural data (n = 23), no evident lesion (n = 13), high levels of white matter hyper intensities (n = 11) and extensive atrophy (n = 2). Patients were recruited from the Amsterdam University Medical Center, Radboud University Medical Center, Groningen University Medical Center and Utrecht Medical Center between 3 and 16 weeks post stroke. They were recruited either during their hospitalization or after they were discharged from the hospital. The main selection criteria were: supratentorial ischemic stroke including the cerebellum, and good apprehension of the Dutch language. Exclusion criteria were: substance abuse (alcohol or drugs), psychiatric disorders that could influence cognitive functions such as schizophrenia and current major depression, pre-existing cognitive impairment as examined using the short Informant Questionnaire on cognitive decline in elderly (IQ-CODE, cut-off 3.6; De Jonghe et al., 1997) and neurological diseases that affect cognition. The medical ethics committee (METC Utrecht, The Netherlands) approved the study protocol. All patients gave their written informed consent to partake in this study and travel and lunch costs were reimbursed. Demographic and neuropsychological characteristics are presented in Table 1.

Episodic memory examination

The RAVLT is a neuropsychological test that is widely used to evaluate verbal episodic memory impairment (Crawford et al., 1998). This test examines a variety of functions such as individual memory strategies, differences between encoding and retrieval of information and

was used to access verbal episodic memory in the current study (Vakil and Blackstein, 1993; Saan and Deelman, 1986). Patients were instructed to listen to an audio fragment of 15 unrelated Dutch words with a rate of 1 second per word, over 5 consecutive trials. This was followed by an immediate recall during which patients were asked to remember as many words as possible in any order. After a 30- min. delay, the patients were asked to recall the words they could remember from the list of 15 words (total sum of correctly recalled words after a delay of after the 5th trial). Immediately after the delayed recall, a list of 30 words was read out loud that contained 15 distractors and 15 targets and patients were requested to indicate whether each word was from the list of 15 words that was repeated over five trials.

In the current study, delayed-recall (30 minutes) and delayed recognition were used as outcome measures to investigate the difference between both performances.

Procedure

All patients were briefed about the goal of the research prior to the neuropsychological examination and MRI procedure. Hereafter, the patients were placed in the MRI scanner and were requested to not move during the scan. A pillow was positioned between the head coil and the patient's head to help stabilize the patient during the MRI procedure and to reduce head movements. The MRI protocol was completed within 45 minutes. This was followed by an extensive neuropsychological assessment. Each patient was seated in a quiet room in order to prevent interference by sounds from the environment. The room was equipped with two computers, a keyboard, mouse, speakers, 3 chairs and a table. The cognitive assessment commenced with an anamnesis during which the patients were asked to answer questions about post-stroke deficits and medical background questions in order to gain more insight into the nature of the patient's symptoms. Then, the verbal episodic memory was examined

using the Dutch version of the RAVLT. Apart from this, various cognitive domains were assessed such as working memory, language, attention, executive functions and visuospatial functions. The educational level was classified according to the Dutch Verhage scale (Verhage, 1964). This classification system comprised 7 categories in ascending order from 1 (did not complete primary school) and 7 (obtained an university degree).

Magnetic Resonance Imaging

Images at Radboud University Medical Center and Groningen University Medical Center were acquired at the radiology department on a 3-T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany), with a 32-channel head coil. T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR) images were used for the purpose of this study. The MRI parameters were a T2 Flair scan with a repetition time of TR = 4800ms, time to echo TE = 484ms, voxel size 0.9 x 0.9 x 0.9 mm^3, field of view = 280mm. Images at Amsterdam University Medical Center and Utrecht University Medical Center and were acquired on a 3-T MRI scanner (Achieva, Philips Medical Systems, The Netherlands), with a 32-channel head coil. The MRI parameters were a T2 Flair scan with a repetition time of TR = 4800ms, time to echo TE = 253ms, voxel size 1.12 x 1.12 x 0.56 mm^3, field of view = 250mm. All patients were instructed to lie still during scanning.

Behavioural data analysis

The behavioural data was analysed using IBM SPSS Statistics 24.0. The data for delayed recall was normally distributed, as assessed by the Kolmogorov-Smirnov test ($p > 0.05$). The data for recognition memory was not normally distributed, ($p < 0.05$). Therefore, the non-parametric Spearman's rank correlation was carried out to examine the relationship between

delayed recall and recognition memory. In the present study three assumptions that must be met in order to conduct the Spearman's rank correlation were not violated. First, the variables that were examined were continuous. Second, the two variables reflect measurements from the same participant. Third, the association between the two variables was monotonic. A scatterplot was used to observe the relationship between both variables. There were no outliers as examined by boxplots. A *P* value of 0.05 was considered statistically significant.

Lesion delineation and spatial normalisation

MRI acquisition was followed by manual lesion delineation on all slices, in axial, coronal and sagittal plane of the structural FLAIR image using the ITK-SNAP software (www.itksnap.org; Yushkevich et al., 2006). FLAIR images suppress the cerebrospinal fluid (CSF), which makes the CSF appear dark, whilst the anomalies remain bright (Gauvrit et al., 2005). Thus, FLAIR images are useful in detecting infarction (Brant-Zawadzki *et* al., 1996). Subsequently, all patient's brains were spatially normalised to the MNI space using Clinical Toolbox (Rorden *et* al., 2012) for SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB (version 2014b; The MathWorks, Inc., Natick, Massachusetts, United States). This toolbox encompasses specialized templates that allow spatial normalization of brain images of elderly subjects in particular. Based on the type of lesion (unilateral or bilateral) two different corrections were applied during spatial normalization. These were enantiomorphic normalization (Nachev et al., 2008) and cost function masking (Brett et al., 2001). The latter method entails the exclusion of lesioned voxels using a binary lesion map. Contrarily, enantiomorphic normalization is applied to correct the damaged brain area by replacing it with the intact analogous area within the contralesional hemisphere. Hence, enantiomorphic normalization is

shown to perform better when damaged brain are extensive and unilateral as opposed to cost function masking (de Haan & Karnath, 2018). Cost-function masking works more effectively when the lesions are bilateral and influence identical regions in both hemispheres (Brett et al., 2001; Nachev et al., 2008).

Atlas-based LSM

Atlas-based LSM using NiiStat software (https://www.nitrc.org/projects/niistat/) was conducted in order to identify regions of voxels that were significantly associated with the behavioural data. Matlab version 2016 or later versions (https://nl.mathworks.com/products/new_products/release2016a.html) and SPM version 12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) are necessary to run the analysis. The analysis for delayed recall and recognition memory was performed separately. In atlas-based analysis voxels are distributed into brain regions provided by the atlases that are incorporated in the NiiStat software. For this study a combination of the white matter AAL atlas and grey matter CAT atlas (AALCAT) was used to investigate the neural correlates of recall and recognition memory (Tzourio-Mazoyer et al., 2002; Catani & Thiebaut de Schotten, 2008). A *t*-test was performed between ROI's in order to compare the behavioural data of patients with and without damage in those regions. In voxel-wise analysis, multiple individual *t*-tests are performed at each voxel, resulting in increased probability of false positives. In atlas-based analysis, this multiple comparisons issue is reduced as a smaller number of *t*-tests are performed. 3000 permutations were computed to account for family-wise error. The statistical threshold was set at p=0.05. Only regions that were damaged in at least 5% of the sample size of 115 patients (n = 5) were included in the analysis (Sperber & Karnath, 2017).

In addition, age, gender, education level and lesion volume were used as covariates in order to account for possible effects of those variables. These covariates were controlled for using a regression analysis that is implemented in the LSM analysis software (Karnath et al., 2019). A lesion overlay map was created that represents the regions that were analysed in the LSM analysis. These are regions that were lesioned in at least five patients and are illustrated in fig 1.

Results

Thirty-one participants have been excluded from the data analysis. These participants had an error in the MRI file. The atlas-based analysis and statistical analyses were performed with the remaining 115 participants.

Table 1. Demographic and neuropsychological characteristics of stroke patients

Characteristics	Stroke patients (n = 115)		
Lesion side No. (Left, right, bilateral)	43	52	20
Gender (m, f)	88		27
Education level (Mdn, range)	6		3-7
Age (M, SD)	58.0		11.9
NLV (M, SD)	100.9		15.1
RAVLT-Delayed recall (M, SD)	7.9		3.5
RAVLT-Recognition (M, SD)	28.2		2.2

M: mean, *SD*: standard deviation, M: median; m: males; f: females; NLV: the Dutch version of the National Adult Reading Test: Nederlandse leestest voor volwassenen; RAVLT = Rey Auditory Verbal Learning Test.

Education level was classified according to seven categories of the Dutch Verhage scale (Verhage, 1964) (1 = did not complete primary school and 7 = obtained an university degree).

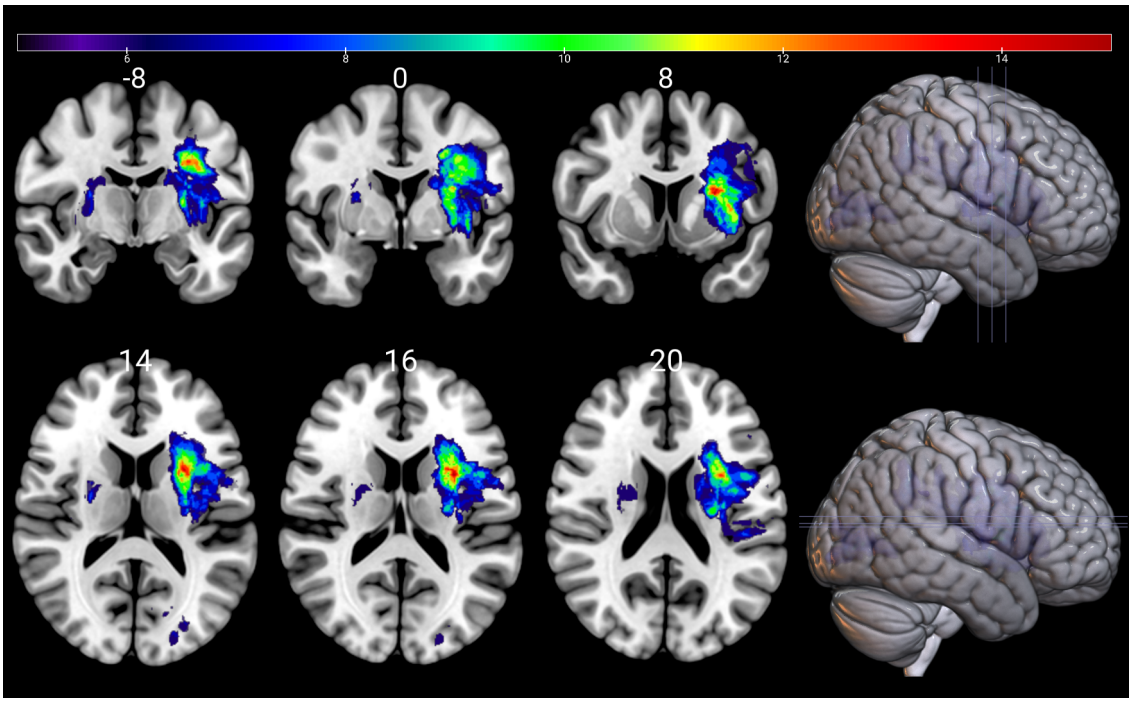

Fig.1 Lesion overlay map for 115 stroke patients is portrayed, using MRIcroGL (Rorden, 2012). The bar illustrates the number of patients with a lesion in an area. Only regions that are damaged in at least five patients are displayed. These are the regions that have been included in the VLSM analysis. Numbers above the slices depict the *x and z* coordinates in the MNI space. MNI = Montreal Neurological Institute.

Results behavioral data

Patients showed a mean score for delayed retrieval of 7.9 (*SD* = 3.5) and a mean score for recognition memory of 28.2 (*SD* = 2.2), as depicted in table 1. These results demonstrate that these stroke patients recalled 8 words from a total of 15 words on the delayed recall test. On the recognition test patients correctly classified 28 words from a total of 30 words.

The Spearman's rank correlation revealed that there was a statistically positive association between delayed recall and recognition memory $r_s(115) = .75$, $p < .001$.

Atlas-based LSM results

Atlas-based analysis was applied on 115 patients. The AALCAT atlas was used to group voxels in predefined anatomical regions, consisting of 116 grey matter and 34 white matter regions and to identify neural correlates. The LSM analysis was conducted separately for delayed recall and recognition memory. 98 regions from 150 regions were included in both analyses. Results from the LSM analysis did not reveal any regions of voxels that were associated with recall and recognition memory before and after correcting for education level, age, gender and lesion volume. The range of the *z* scores for recognition memory and delayed recall was -3.08 and 1.54 and for -2.15 and 2.55, respectively. *Z* scores represent the number of standard deviations that a participants' performance varies from a mean. The threshold in the current study was one-tailed since it is expected that damaged tissue will result in impaired performance and not improved performance. Thus, a *z* value of >2.87 and >2.06 would lead to a significant result for delayed recall and recognition memory performance, respectively.

Discussion

The present study aimed to investigate the influence of lesion location on verbal delayed recall and familiarity-based recognition memory performance in ischemic stroke patients. Apart from this, the relation between delayed recall and familiarity-based recognition was examined.

Findings from the behavioural data show that ischemic stroke patients correctly recalled 8 words on average from a total of 15 words after a delay of 30 minutes on the RAVLT. In contrast to delayed recall, patients correctly classified 28 words on average from a total of 30 words on the recognition test. These findings demonstrate that stroke patients

seem to have difficulties to recall words compared to recognize words. However, recognition memory performance could be the result of a ceiling effect. Although, there was sufficient variability in the data, a large number of patients performed closely to the maximum score. As a consequence, the distribution of the recognition memory performance was skewed. These findings are supported by early studies in which recognition memory has been shown to be less demanding as external cues are presented to examine this type of memory processing, whereas retrieval requires the ability to remember previously encoded information, which makes this more difficult (Manns et al., 2003; Papagno, 2018).

Spearman's rank correlation revealed a statistically positive association between delayed recall and recognition memory, as hypothesized. This result suggests that recall and recognition memory may depend on similar underlying processes.

Atlas-based LSM analyses did not show any regions of lesioned voxels that were associated with delayed recall and recognition memory performance. These findings are in contrast with a recent study in which machine-based multivariate lesion-symptom mapping (MLSM) was performed to investigate lesion-behavior relationships. Contrary to VLSM, MSLM takes the entire brain into account instead of single voxels and multiple variables can be examined simultaneously. This allows for a better understanding of how multiple brain areas could contribute to behavioral performance. MLSM results showed that structural damage explained a smaller proportion of variance for verbal memory deficits (17%) as opposed to other behavioral domains such as motor deficits. Regions that were shown to be associated with verbal memory dysfunction were confined to the left hemisphere and comprised the frontal white matter, basal ganglia and caudate and thalamus. These findings suggest that verbal memory processes may depend on a distributed network and therefore could not be attributed to a specific neural locus (Corbetta et al., 2015; Karnath et al., 2019).

Biesbroek et al. (2015) investigated the brain areas of two components that recognition memory depends on, based on the signal detection theory. This theory states that the ability to detect whether something has previously been presented depends on two processes during which an individual obtains sufficient information about a certain object (discriminability) and then determines whether the object was old or new (criterion setting), based on the information. VLSM results demonstrated that impaired recognition memory was related to left medial temporal and temporo-occipital structures, both thalami and the right hippocampus. In addition to these studies, a recent study by Zhao et al. (2018) examined the impact of strategic lesion locations on cognitive dysfunction in stroke patients. MLSM was conducted in a large sample of 410 patients. Strategic lesion locations can be described as brain regions that cause significant impairments, whereas other regions may affect cognitive functions to a lesser extent. Results showed that verbal memory impairment was associated with lesions in brain areas within the left hemisphere and consisted of left basal ganglia, left frontal, temporal, parietal and occipital, cortical and white matter areas.

In sum, as described above, several studies have examined the influence of infarcts on memory dysfunction in stroke patients. Contrary to the present findings, these studies found a distributed network encompassing different brain regions within the left hemisphere as well as some regions within the right hemisphere, in relation to verbal memory. A possible explanation for the discrepancy between the results of previous research and the present study could be the use of MLSM to examine the relation between lesion location and memory processing. With MSLM the whole brain is analyzed instead of single voxels and allows for a better understanding of how several brain regions could contribute to behavioral performance. Moreover, these results suggest that LSM might not be a suitable method to

detect the neural substrates underlying recall and recognition memory performance as they may depend on a widely distributed network.

Although the current study used a large sample size and a well-accepted lesion-symptom mapping analysis was applied to examine lesion-behavior relation, some limitations should be mentioned. First, a possible limitation could be that lesion coverage of the left hemisphere was not sufficient compared the right hemisphere. This is due to the fact that this study excluded patients who had larger lesions in the left hemisphere as this results in aphasia. As a consequence, patients with smaller infarcts were included. This may explain why no brain regions were detected since most previous studies found regions confined to the left hemisphere. Second, our sample consisted of some patients that have had multiple infarcts as well as recurrent infarcts. Previous studies have shown that recurrent infarcts within a patient substantially impair cognition (Renjen, Gauba & Chaudhari, 2015). Thus, these recurrent strokes could have already influenced the memory performance. This in turn, makes it difficult to examine to what extent the recent lesion affects recall and recognition. To overcome this, first-ever stroke patients could be examined in future studies. Third, although univariate LSM offers great understanding in the localization of behavioral deficits through lesion analysis, as previous studies have shown (Biesbroek et al., 2015; Pisoni et al., 2019), it is inherent to some limitations. One of its disadvantages is the limited capability to detect complex neural networks. This again, could explain why the current study was unable to find brain regions related to recall and recognition memory as they could be related to a larger network.

In conclusion, the present study demonstrated a strong relation between delayed recall and recognition memory, which could imply that they depend on similar processes. Atlas-based LSM did not reveal neural correlates that were related to both

performances. These results suggest that recall and recognition memory may not depend on one specific neural locus but could be attributed to a large neural network that could not be detected by LSM.

Future research could shed more light on the underlying mechanisms of these brains networks in relation to verbal episodic memory processes (immediate recall, delayed recall and familiarity-based recognition memory) using MLSM in a larger sample of first-ever stroke patients. The latter could be achieved by collaborating with multiple research centers. MSLM could give more insight in how several brain regions could contribute to behavioral performance in comparison to univariate LSM analysis.

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