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Association of the alterations in the components of working memory (WM) with the brain hemisphere affected after an ischemic stroke

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Abstract
 OBJECTIVE: Determine the alterations in the components of the WM and its relationship with the hemisphere of location of the lesion in patients with ischemic stroke.
 METHODS: This is an observational, analytical, correlational and cross-sectional study. The participants of this study were 49 patients between 50 and 75 years of age in the city of Medellín, Colombia, who had suffered an ischemic stroke with a period of evolution of the event equal to or greater than one year. We evaluated WM with the WAIS IV Working Memory Index and a WM self-report questionnaire. To exclude patients with major cognitive impairment and depressive symptoms, the Montreal Cognitive Assessment (MoCA) and the Geriatric Depression Scale (GDS) were used.
 RESULTS: There are no differences in the WM components' performance between the groups with right and left hemisphere lesions. It has been observed that patients with an

groups with right and left hemisphere lesions. It has been observed that patients with an ischemic stroke presented a performance in WM tests below average. The effect size was small.

CONCLUSIONS: There are no differences in the components of working memory performance according to the hemisphere injured by ischemic stroke. Some results seem to indicate that working memory affects metacognition and introspection.

Abbreviations:

WAIS IV: Adult Wechsler Intelligence Scale IV:
Comprehensive test measuring adult intelligence across four major cognitive domains
MoCA: Montreal Cognitive Assessment:
a 30-point test designed to assess different cognitive domains to detect mild cognitive impairment
GDS: Geriatric Depression Scale:
a screening tool consisting of 30 yes/no questions used to identify depression in older adults

RH:Right hemisphere:associated with spatial abilities and facial recognition,LH:Left hemisphere:associated with language and analytical tasksWM:Working memory: is a cognitive system associatedwith temporarily holding and processing information

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INTRODUCTION

Stroke is a chronic condition that leads to lesions in one or several brain areas due to ischemic attack, intracerebral hemorrhagic attack and subarachnoid hemorrhage (The National Institute of Neurological Disorders and Stroke 1990). Ischemic stroke is a generic term that refers to a clinical syndrome that affects blood vessels in the brain due to a pathological process of occlusion or rupture. In regard to ischemic stroke, there is a sudden event of neurological alteration caused by a focal infarction of the brain, spinal cord, or retina with evidence based on imaging or clinical data. Symptoms last 24 hours or more; they generally leave neurological sequelae or can cause death (Sacco et al. 2013). This event is caused by neuronal death in the nucleus of the infarction, ischemic penumbra zone and the edges of the affected area, whose functionalities can eventually be recovered. The risk of having a stroke doubles with each decade after the age of 55 (The National Institute of Neurological Disorders and Stroke 1990). Approximately 33% to 42% of survivors need help performing in the Instrumental Activities of Daily Living. Five years after the event, 36% continue with this disability (Feigin et al. 2008). A stroke can cause different cognitive deficits when they affect the neuronal circuits associated with specific cognitive functions (Amin & Schindler 2020). Infarcts that affect the white matter in the superior and inferior longitudinal fascicles, associated with neuronal connections of fronto-parietal areas, can compromise the performance of executive functions, especially in working memory (Lugtmeijer et al. 2020; Parto-Dezfouli et al. 2021; Peers et al. 2018; Peers et al. 2021; Llorens et al. 2020). WM is characterized by temporarily storing and manipulating information and exerting executive control over its processing (Baddeley 2007). Baddeley and Hitch proposed a WM model in the 1970s that has a good level of evidence and acceptance (Gontier 2004). This model consists of different hierarchical components: the central executive, the visuospatial agenda, and the phonological loop (Gontier 2004). At the beginning of this century, Baddeley included an additional component: episodic buffer (Baddeley 2012; Kumral et al. 2019). However, these components will not be delved into here, given their wide and frequent description in the psychological literature.

It has been reported associations between the central executive and the anterior cingulate lesions (Kumral *et al.* 2019; Roussel *et al.* 2012), whereas deficits in the visuospatial agenda have been associated with lesions in the right fronto-temporo-parietal attention network, the basal ganglia (Lugtmeijer *et al.* 2021), the inferior fronto-occipital fasciculus, the anterior cingulate (Toba *et al.* 2020) and in the arcuate fasciculus of the right hemisphere (Ferber *et al.* 2020). The phonological loop is affected due to damage to the left fronto-parietal areas, the basal ganglia (Geva *et al.* 2021) and the

anterior part of the left arcuate fasciculus (Lugtmeijer *et al.* 2021). The episodic buffer is affected when there are lesions in the right frontal operculum (Lugtmeijer *et al.* 2021; Martin 2019; Meier *et al.* 2011). In addition, in one study the central executive was associated with anterior areas of the brain, while the visuospatial sketchpad and the phonological loop were associated with posterior areas (Lugtmeijer *et al.* 2021).

Even all of these studies associated different WM components with specific brain areas in healthy people, such as the phonological loop with the left temporal lobe and the right temporal lobe with the visuospatial sketchpad (Baddeley 2007), there are other studies that suggest that WM is related to the simultaneous activity of multiple brain areas, since it encompasses several cognitive processes (Baddeley 2007; Eriksson *et al.* 2015).

In some antecedents of the previous section, patients with depression — a disorder that is frequent in patients with ischemic stroke (The National Institute of Neurological Disorders and Stroke 1990) and that influences WM performance (Amin & Schindler 2020). Neither were patients excluded with hemorrhagic stroke — events less focal and specific than the ischemic ones (Rodríguez & Rodríguez 2015). Likewise, it is evident that in some prior studies an adequate control of variables was not carried out, small samples were extracted, and not all the components of the WM were evaluated. That is why it is necessary to correct the methodological aspects indicated above in order to obtain true results and, consequently, to improve the neuropsychological characterization of patients with this pathology in the department of Antioquia, Colombia, which would allow for a more pertinent care for the deficit due to vascular damage in a brain area.

Based on what has been said so far, the aim of this study is to determine the association of the alterations in the components of the WM with the brain hemisphere affected after an event due to ischemic stroke.

MATERIAL AND METHODS

Type of study

This is an observational, analytical, correlational and cross-sectional study. The objective of this study was to determine the alterations in the components of the WM and its relationship with the hemisphere of location of the lesion in patients with ischemic stroke. WM components were taken as dependent variables and ischemic stroke as independent variables.

<u>Subjects</u>

In this study, a sample of 49 participants was conveniently obtained from a database of 1,522 patients from the Instituto Neurologico de Colombia (INDECO) with a history of stroke. The inclusion and exclusion criteria were as follows.

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Inclusion criteria

Stroke is more prevalent between 50 and 75 years (Petty et al. 1999), which is why outpatients were chosen in this age range, with 5 or more years of schooling, without involvement in rehabilitation programs after stroke, with period of evolution of the event equal to or greater than one year, with a diagnosis of ischemic stroke according to the criteria for this pathology (The National Institute of Neurological Disorders and Stroke 1990), and corroborated by neuroimaging, without dementia determined by the Montreal cognitive assessment (MoCA) test equal to or greater than 21 points for subjects with 10 or more years of schooling, and equal to or greater than 23 points for subjects with 11 or more years of schooling. In addition, they had to have a main caregiver and a computer or smartphone with Internet access in the case of virtual evaluation.

Exclusion criteria

Present aphasia and/or major neurocognitive disorder compatible with dementia, inability to manipulate the computer mouse, diagnosed psychiatric disorder or depressive disorder with a score greater than 10 points on the Geriatric Depression Scale (GDS), given that depression is a common disorder in this type of patients (The National Institute of Neurological Disorders and Stroke 1990).

Instruments

To assess cognitive ability, the Montreal cognitive assessment (MoCA) (Nasreddine *et al.* 2005) test was used, which has an internal consistency of 0.891 according to Cronbach's Alpha Index (Aguilar-Navarro *et al.* 2018). To examine WM and its components, except for the visuospatial sketchpad, the Working Memory Index of the Adult Wechsler Intelligence Scale IV (WAIS IV) test (Wechsler 2014) was used, which has a reliability of 0.94 (Rosas *et al.* 2014). The phonological loop was evaluated with the Direct Digits sub-test as proposed by Baddeley and Szmalec (Baddeley 1994; Marton & Schwartz 2003), which presents an internal consistency of 0.93 (Gignac *et al.* 2017). The central executive was evaluated with the reverse digits sub-test, a test suggested for this purpose (Swanson *et al.* 1999), which

Tab. 1. Sociodemographic, clinical and cognitive functioning characteristics

	Total (n = 49)	Lesion RH (n = 25)	Lesion LH (n = 24)	
Male gender, n (%)	25 (50)	12 (48)	13 (54)	
Age, Median [IR]	61.08 (7.80)	61.08 (7.8)	61.58 (6.31)	
Schooling, Median [RI]	11.40 (4.31)	12.52 (4)	10.50 (4.33)	
Economic income				
Low-low, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Low, n (%)	16 (32.0)	6 (24.0)	9 (37.5)	
Medium low, n (%)	20 (40.0)	14 (56.0)	6 (25.0)	
Medium, n (%)	5 (10.0)	1 (4.0)	4 (16.7)	
Medium high, n (%)	7 (14.0)	3 (12.0)	4 (16.7)	
High, n (%)	2 (4.0)	1 (4.0)	1 (4.2)	
Right-handed Laterality (%)	48 (96)	23 (92)	24 (100)	
Health background				
Months since stroke, n (%)	55.48 (34)	62.52 (39)	49.00 (28)	
Arterial hypertension, n (%)	21 (42)	14 (56)	6 (25)	
Diabetes, no. (%)	10 (20)	5 (20) 5 (20		
Smoking, n (%)	6 (12)	3 (12)	3 (12.5)	
Alcoholism, n (%)	5 (10)	3 (12)	2 (8.3)	
Arteriovenous malformation, n (%)	1 (2)	1 (4)	0 (0)	
Aortic aneurysm, n (%)	1 (2)	0 (0)	1 (4)	
Acute myocardial infarction, n (%)	3 (6)	0 (0)	3 (12.5)	
Heart failure, n (%)	3 (6)	2 (8)	1 (4)	
Arrhythmia, n (%)	1 (2)	0 (0)	1 (4)	
Geriatric Depression Scale, Median [IR]	2 [1, 3]	1 [0, 3]	2 [1, 3]	

Note: RH: Right hemisphere. LH: Left hemisphere. RI: Interquartile range. MoCA: Montreal cognitive assessment. ** Correlation is significant at the 0.01 level, * Correlation is significant at the 0.05 level

presents a reliability index of 0.93 (Gignac *et al.* 2017). The episodic buffer was evaluated with the Arithmetic sub-test (Tudesco *et al.* 2010). All of these tests were chosen because of their high reliability and internal consistency.

To assess the visuospatial agenda, the Corsi Block-Tapping Task test was used according to Kessels (Kessels *et al.* 2000). This test has been validated in Spanish (Ritter *et al.* 2011) and has an internal consistency of 0.90 even in its digital version (Siddi *et al.* 2020). To control for depression, the Geriatric Depression Scale (Yesavage *et al.* 1982) instrument was used, which has an internal consistency of 0.78 (Gómez & Campo 2010). The WM Questionnaire (Vallat-Azouvi *et al.* 2012) was also used, which has an internal consistency in patients with brain injury of 0.94.

Process

The sample of this study was shared with another ongoing investigation. Patients were selected through a database of the INDECO. Then, they were contacted by phone, the objective of the project was explained to them, and they were asked if they had a main caregiver and a computer or a cell phone with internet access. If they agreed to participate, the informed consent form was sent to them by mail for their review and subsequent signature. Subsequently, through Google Meet, the MoCA and the GDS were applied. After obtaining the signature of the informed consent, the candidates suitable for participating in this research were selected.

Working memory evaluation

Through Google Meet, the working memory questionnaire was applied, then the main caregiver was asked to share the screen from where the subjects were connected for the application of the Corsi Block-Tapping Task test, the working memory index and the sociodemographic interview (Ramírez *et al.* 2018).

Taking into account that in the present study there was no control group to compare the obtained data and that the WAIS IV does not propose scales for the specific evaluation of the direct digits, inverse digits or arithmetic sub-test, as a reference for the interpretation of the data, this study utilized the scores from the control group evaluated for the standardization of those sub-tests (Wechsler 2014). Regarding the Corsi Block-Tapping Task test, normative data was taken from the population of the Antioquia region (Ramírez *et al.* 2018).

Statistical analysis

For the socio-demographic and clinical characteristics, the analysis was carried out by means of the percentage and the calculation of the absolute frequency for the qualitative variables. For quantitative variables, measures of central tendency were performed; median and interquartile range were used.

The performance of working memory according to the affected hemisphere was described through measures of central tendency; median and interquartile range. The difference between groups was compared using the Mann Whitney U test. Nonparametric effect size was calculated using the r statistic software (Marton & Schwartz 2003; Ramírez *et al.* 2018). Therefore, measures equal to or greater than 0.5 are considered high, from 0.3 to 0.5 are considered moderate or medium, low are considered measures between 0.1 to 0.3, and zero those below 0.1 in absolute values.

Comparisons of the data obtained by the sample of the current study were also made with a control group of the standardization of the WAIS IV for the subtests of the said instrument (Wechsler 2014), while the results of the Corsi Block-Tapping Task test were compared with the control group of a study with a Colombian population (Antioquian people) (Romero *et al.* 2018), considering 3 hypothetical samples: of 30, 50 and 100 subjects. The Hedges g test was applied to know the performance effect size in stroke patients compared with the normative data (WAIS IV and Corsi Block-Tapping Task control group of the standardization) from a hypothetical sample (Table 3).

Ethical considerations

This study provided and socialized an informed consent, which was based on article 6 of the Nuremberg code of Resolution 008430 of October 4, 1993 AMM (Greek *et al.* 2012) and on the Declaration of Helsinki of the World Medical Association (Manzini 2000). Support

Tab. 2. Performance of working	a memory in stroke	patients, differentiated b	v affected hemisphere
	g memory in scione	putients, anterentiated b	y unceted nemisphere

	Lesion RH (n=25)	Lesion LH (n=24)	Effect size.	р	
Working memory components					
Visuospatial agenda	7.00 [6.00, 8.00]	7.00 [6.00, 8.00]	0.06206691	0.3304	
Phonological loop	7.00 [6.00, 8.00]	7.00 [6.00, 8.00]	0.1025697	0.2341	
Central Executive	6.00 [6.00, 7.00]	6.00 [5.00, 7.00]	0.1734147	0.1101	
Episodic buffer	8.00 [7.00, 9.00]	8.00 [7.00, 9.00]	0.06493638	0.3231	
Working memory index	37.00 [21.00, 45.00]	23.00 [19.75, 37.00]	0.1652119	0.1214	
Working memory self-report	37.00 [27.00, 46.00]	30.50 [26.75, 47.75]	0.01132527	0.4681	

P corresponds to nonparametric P with the Mann-Whitney U

Variable	Patients wi	Patients with stroke		Normative data from a hypothetical sample		Hedges ´g		
	Median	SD	Median	SD	n=30	n=50	n=100	
Visuospatial agenda	7.04	1.9	13.9	3.8	-2.775	2.4545	2.1639	
Phonological loop	6.54	1.51	10.3	2.9	-1.7592	1.6253	-1.488	
central executive	6.2	1.44	10.9	3	-1.8542	1.6993	1.5442	
episodic buffer	8.12	1.77	10.8	2.6	-1.2664	1.2053	1.1368	
General working memory	90.72	8.59	104.7	12.8	-1.3501	1.2827	1.2077	

Hedges' g corresponds to the measure used to determine effect size

was obtained from the INDEC ethics committee with the code RDGCOINVF05.

RESULTS

According to Table 1, the median age of the sample is 61 years. In addition, the majority of participants are men, right-handed, with completed secondary education, middle social class, 21 of the 49 suffer from high blood pressure.

In Table 2, it is evident that there are no differences (p: 0.1214) in the groups with left and right hemisphere lesions, with a small effect size in the central executive, WM Index and phonological loop, while in the visuo-spatial agenda, the episodic buffer and the self-reported WM, the effect size is zero. The participants do not show alterations in self-reported WM.

In Table 3, we show that there are differences (G: 1.2077) in all WM components in the group of stroke patients, compared to a reference sample of the general population, which indicates that stroke patients have clinical alterations in all components of the WM.

Discussion

This study aimed to determine the alterations in the components of the WM and its relationship with the hemisphere of location of the lesion in patients with ischemic stroke. We did not find differences in the performance of the WM components according to the hemisphere affected by ischemic stroke, although some studies report the association of the visuospatial agenda with the right hemisphere and the phonological loop and the episodic buffer with the left hemisphere (Berlingeri et al. 2008; Ocklenburg et al. 2018). Therefore, the results seem to be consistent with some experimental studies in which the association of these components with the two cerebral hemispheres is unclear and even contradictory (Baddeley 2007). Our results also seem to agree with research that concludes that WM is related to cognitive activity that occurs simultaneously in multiple areas of the brain (even subcortical areas) (Eriksson 2015; Lugtmeijer 2021). Compensation processes could enable circuits in both

hemispheres after damage (Ward 2005), which would make it difficult — at least until now — to make any kind of connections between components and the affected hemisphere.

Ischemic strokes could, however, be associated with a lower WM performance when compared with the control group of the WAIS IV validation (Wechsler 2014) and with normative data of the Corsi Block-Tapping Task test for the population from Antioquia region (Restrepo *et al.* 2018), a result consistent with another study associating stroke with WM impairment (Lugtmeijer 2021). It was also found that the patients presented average scores in the self-reported WM, which is inconsistent with the performance in the WM Index, where WM involvement is evident. This result is consistent with what some studies indicate that WM is related to self-monitoring, metacognition, and introspection (Komori 2016; Mondragón *et al.* 2019), so patients may not be aware of a deficit.

According to the results of this study, it is important to prioritize the neuropsychological evaluation and rehabilitation of WM in patients with ischemic stroke regardless of the affected brain region, in which it is imperative to consider the information provided by the caregivers or companions of these patients, given the influence in the metacognitive, self-monitoring and introspection processes.

Limitations

It is recommendable for future research to compare the stroke patients' WM performances with a control group, taking into consideration the evidenced difficulties, such as the inaccurate information provided by imaging, the poor ability of patients and their caregivers to manipulate technological devices, and connectivity problems in the case of telemetry assessment.

Relevance for practice

These results, in addition to contributing to the investigation of cognitive impairment after a stroke, could improve the accuracy of neuropsychological care protocols with the aim of optimizing time in the evaluation and rehabilitation in this type of pathology.

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