

Cognitive Deficits After First-Ever Stroke: A Comparison Between Patients with Regard to Type of Stroke, Hemispheric Lateralization, Gender and Post-Stroke Duration

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Abstract

Objective: In this study we evaluated cognitive functioning of patients with a first-ever stroke.

Methods: A sample of 100 stroke patients was compared with a matched control group of 30 Healthy Controls (HC). They were examined with an extensive neuropsychological test battery assessing attention, memory, visuospatial functions, naming and executive functions.

Results: For the stroke group in global we detected a significant worse performance for (divided, focused and alternating) attention, visuospatial memory, (phonetic and semantic) verbal fluency and (verbal and non-verbal) abstract reasoning in comparison to the HC group. No significant differences could be found between both groups concerning audioverbal memory, visuospatial functions and naming. The left hemisphere stroke patients showed significant more problems with verbal cognitive functions (i.e., naming) compared to right hemisphere stroke patients and the right hemisphere stroke patients showed significant more problems with non-verbal cognitive functions (i.e., visuospatial judgement, visuospatial hemi-attention and spatial abstract reasoning) compared to left hemisphere stroke patients.

Conclusion: We can conclude that there is a hemispheric lateralization effect on cognitive functioning in our stroke patients. Furthermore, no significant differences in cognitive performance could be documented with regard to infarction versus hemorrhage, cortical infarction versus subcortical infarction, subarachnoid hemorrhage versus intracerebral hemorrhage, female gender versus male gender and post-acute phase versus chronic phase.

Keywords: Stroke; Infarction; Hemorrhage; Cognitive Functions

Introduction

There are two main categories of stroke, namely infarction (or ischemic stroke) and hemorrhage (or hemorrhagic stroke). An infarction means that the blood supply to a part of the brain is decreased. This will lead to lesions in the tissue of that brain area. An infarction can take place in a cortical region (cortical infarction) or a subcortical region (such as the internal capsule, the thalamus or the basal ganglia) (subcortical infarction) and is mostly the result of thrombosis (an obstruction of a blood vessel by a blood clot) or embolism (an obstruction of a blood vessel due to an embolus from elsewhere in the body (for example the

internal carotid arteries or the heart)). Some patients have a Transient Ischemic Attack (TIA). A TIA can be defined as a sudden interruption of the blood flow associated with focal neurological deficits (for example hemiparesis and/or hemianopia) and cognitive deficits (for example aphasia and/or visuospatial neglect) lasting less than 24 hours and not associated with a cortical or subcortical infarction seen on a CT scan and/or MRI. A hemorrhage results from a ruptured blood vessel in the brain. There are two main types of hemorrhage, namely intracerebral hemorrhage and subarachnoid hemorrhage. An intracerebral hemorrhage is a bleeding within the brain itself when an artery in the brain bursts. A subarachnoid hemorrhage is a bleeding that occurs outside the brain tissue but still within the skull, more precisely in the subarachnoid space between the arachnoid mater and the pia mater. It is mostly the result of a ruptured aneurysm [1,2].

Cognitive deficits are very common after first-ever stroke. In the etiology of these deficits, differences in type of ischemic stroke (cortical infarction versus subcortical infarction) or hemorrhagic stroke (intracerebral hemorrhage versus subarachnoid hemorrhage), hemispheric lateralization, gender and post-stroke duration might be of particular importance as previous research has tried to investigate the impact of these variables on cognition in stroke patients [3-7]. However, more insight in the role of these causal variables on cognitive functioning after stroke is necessary and can result in a more personalized approach to cognitive rehabilitation instead of the administration of a more commonly cognitive rehabilitation program.

Most of these patients demonstrate cognitive impairment on neuropsychological tests measuring attention, memory, visuospatial functions, language, calculation and executive functions [3-14]. Cognitive problems can occur along with emotional and/or behavioral changes and motor, sensory, visual and/or speech problems or as isolated problems. Most studies on cognitive consequences of stroke used only limited and global cognitive screening instruments like for example the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), the Neurobehavioral Cognitive Status Examination (NCSE), the Addenbrooke's Cognitive Examination-Revised (ACE-R), the Cambridge Cognitive Examination (CAMCOG) or the Oxford Cognitive Screen (OCS) [15-21]. These screening instruments, however, do not allow detailed and valid conclusions about most cognitive functions [4, 12]. Other studies have focused on isolated cognitive symptoms such as memory, aphasia, apraxia or visuospatial neglect [22-28]. However, the last three decennia some studies have tried to evaluate cognitive functioning in detail by means of an extensive neuropsychological test battery in a large group of patients with a first-ever stroke.

A first study about the relation between stroke and cognition was carried out by Tatemichi, et al., in a group of 227 patients with a first-ever infarction [3]. The cognitive functioning of these patients (who were 60 years of age or older) was examined 3 months after infarction with an extensive neuropsychological test battery. This battery included tests to evaluate attention, (audioverbal and visuospatial) memory, orientation, language, visuospatial abilities and executive abilities (verbal fluency and (verbal and non-verbal) abstract reasoning). They noticed that their patients as a group showed deficits on all neuropsychological test variables. Cognitive impairment (defined as a failure on four or more test variables) occurred in 35% of the patients. They showed a significant worse performance compared with a matched group of Healthy Controls (HCs) for the cognitive domains attention, memory, orientation and language. Among the patients, cognitive impairment was most frequently associated with left hemisphere infarction (46%) (compared with right hemisphere or bilateral infarction (30%)) and female gender (42%) (compared with male gender (27%)). When cognitive impairment was compared between patients with a cortical or subcortical infarction, no significant differences were found.

A large study was conducted by Hochstenbach, et al. [4]. They examined cognitive functioning in a group of 229 patients with a first-ever stroke and a mean age of 55.9 years. For this purpose, they also used an extensive neuropsychological test battery to assess attention, audioverbal memory, orientation, visuospatial functions, calculation and language. An important disadvantage of this study was that visuospatial memory and executive functioning were not evaluated. The global stroke group showed a significant poorer performance on almost all test variables in comparison to a matched HC group. In this study, patients with a score below the 15th percentile of the HC group for a specific test variable were considered to show a significant deficit. Taking this rule into account, more than 70% of their patients showed a reduced speed of information processing and attention deficits. Besides this, at least 40% of their patients showed problems with visuospatial abilities, language (especially verbal fluency) and calculation and at least 30% of their patients showed problems with audioverbal memory. Concerning audioverbal memory, long-term memory was more affected than short-term memory and (total immediate and delayed) recall was more affected than recognition of recently stored information. With regard to gender, women performed significant better on audioverbal memory tests and men performed significant better on tests assessing visuospatial abilities. The data also showed that aphasia has a

disruptive impact on test performances, even on tests where a verbal response was less important. Indeed, performance was significantly better after a right hemisphere stroke than after a left hemisphere stroke with an exception for visuospatial construction. Furthermore, no significant differences were found between ischemic stroke patients and hemorrhagic stroke patients and between patients with a cortical infarction and patients with a subcortical infarction. There was also no significant effect for the interval between stroke and neuropsychological assessment.

Rasquin, et al., evaluated overall cognitive functioning (with the CAMCOG), audioverbal memory, mental speed and cognitive flexibility in a group of 139 patients within 1 month after a first-ever infarction [12]. All patients were older than 40 years. Fifty-eight% of the ischemic stroke patients showed problems with mental speed, 45% showed problems with cognitive flexibility, 28% showed problems with overall cognitive functioning and 22% showed problems with audioverbal memory. Female patients showed a significant worse performance for audioverbal memory and mental speed than male patients. In a second study of this research group, a total of 176 patients with a first-ever infarction and again older than 40 years underwent a CT scan and the CAMCOG. Based on their study results the authors concluded that cortical infarction, older age and lower educational level were predictors of cognitive disorders after ischemic stroke.

Another study was carried out by Srikanth, et al. [11]. These authors examined cognitive functioning in a group of 99 patients 3 months after a first-ever infarction. The mean age (70.5 ± 14.0 years) of this group was rather high. For their purpose they used a comprehensive neuropsychological test battery to evaluate attention, memory, orientation, visuospatial abilities, language and executive abilities. In comparison to a matched HC group, the ischemic stroke patients showed a significant worse performance on tests measuring divided attention and visuospatial construction. No significant differences could be documented between both groups concerning verbal and non-verbal intellectual abilities, audioverbal and visuospatial memory, phonetic verbal fluency and verbal abstract reasoning. However, when cognitive domain-based performance was considered, the stroke patients showed a significantly greater risk of single-domain cognitive impairment but not of multiple-domain cognitive impairment. A cognitive domain was regarded as impaired only if more than one measure examining that domain was impaired according to the test norms. The stroke patients were most frequently impaired in the following cognitive domains: spatial ability (26%), memory (23%), attention and executive ability (both 15%), language (13%) and orientation (9%).

Sachdev, et al., tried to characterize the cognitive profile of a group of 163 patients with an ischemic stroke or TIA. These patients underwent a detailed neuropsychological test battery at 3 to 6 months after stroke [10]. The battery was used to measure attention, speed of information processing, (audioverbal and visuospatial) memory, audioverbal working memory, naming, visuospatial construction, praxis, gnosis and executive functions [(phonetic and semantic) verbal fluency, (verbal and non-verbal) abstract reasoning and cognitive flexibility]. The global group of stroke patients showed disturbances for all cognitive functions, with audioverbal memory (especially recall of recently learned information) being clearly less affected. In comparison with a matched HC group, the stroke patients showed a significantly poorer performance for divided attention, speed of information processing, working memory, visuospatial memory, visuospatial abilities and executive functions (semantic verbal fluency, cognitive flexibility and verbal abstract reasoning). No significant differences between both groups were noticed for audioverbal memory. Therefore, the authors conclude that the cognitive deficits seen in their stroke sample are mainly characterized by a disturbance of the prefrontal lobe.

In the study of Nys, et al., a group of 168 patients underwent a neuropsychological examination within 3 weeks after a first-ever (ischemic or hemorrhagic) stroke [6]. The raw test scores of the patients were transformed into z-scores based on the means and standard deviations of a matched group of 75 HCs. After this, the z-scores were averaged for tests belonging to the same cognitive domain according to the clinical experience of the authors. The cut-off score for each domain was a performance associated with the 5th percentile. For the global group, 39% of the patients showed deficits for the domain (verbal and non-verbal) executive functioning, 38% showed deficits for the domain visuospatial perception and construction, 31% showed deficits for the domain visuospatial neglect, 26% showed deficits for the domains (verbal and non-verbal) abstract reasoning, audioverbal memory and language and 22% showed deficits for the domain visuospatial memory. With regard to the subgroup of 151 patients with an infarction, problems with the domains executive functioning (39%) and visuospatial perception and construction (38%) were the most common. The prevalence and severity of problems concerning the domains audioverbal memory, language, (verbal and non-verbal) abstract reasoning and (verbal and non-verbal) executive functioning were significantly worse following left hemisphere stroke compared to right hemisphere stroke.

Lesniak, et al., carried out a study in 200 patients who were neuropsychologically examined in the second week after a first-ever (ischemic or hemorrhagic) stroke [9]. All patients underwent a neuropsychological test battery. The results of each patient on these tests were compared with cut-off scores. The most frequently affected cognitive functions in the acute phase after stroke were attention (48%), language (27%), short-term memory (24%), executive functions (18%) and long-term memory (13%). Constructional apraxia was found in 8.5% of the patients, disorientation in time was found in 7% of the patients and visuospatial neglect was found in 5.5% of the patients.

In the study of Brand, et al., cognitive functioning was examined at an average of 6 months post stroke in patients with a hemorrhage [7]. They noticed that 60 patients who have suffered a subarachnoid hemorrhage revealed significant more deficits with regard to divided attention, speed of information processing, word recognition, visuospatial construction and judgement and logical thinking in comparison to 25 patients with an intracerebral hemorrhage. In contrast, patients with an intracerebral hemorrhage displayed significant more problems with short-term and long-term memory compared to patients with a subarachnoid hemorrhage. In this study the results of both patient groups were not compared with a matched HC group.

In the study of Turunen, et al., 75 patients with an infarction were neuropsychologically evaluated within the first weeks post stroke [8]. As in the study of Nys, et al., the raw test scores of the patients were transformed into z-scores based on the means and standard deviations of a matched group of 50 HCs [6]. After this, the z-scores were averaged within several cognitive domains. Each domain consists of several neuropsychological tests. In this study the domain-specific performance of each patient was also considered as impaired when it was below the 5th percentile. Impairment in the domain psychomotor speed (34%) was the most common finding, followed by impairment in the domains executive functions (27%), visuospatial memory (21%), visuospatial abilities (20%), audioverbal memory (18%) and language (11%).

Studies in which a detailed neuropsychological assessment of cognitive performances after stroke in general and between different types of stroke is used, are very rare. Therefore, our study is one of the few studies in which a broad range of cognitive domains (attention, memory, visuospatial functions, naming and executive functions) was assessed by means of a comprehensive neuropsychological test battery in a large population and several subgroups of stroke patients. The aim of our study was to investigate differences in cognitive functioning between (1) stroke patients and a matched HC group, (2) patients with (cortical versus subcortical) infarction and patients with (subarachnoid versus intracerebral) hemorrhage, (3) male patients and female patients, (4) patients with a left hemisphere stroke and patients with a right hemisphere stroke and (5) patients in the post-acute phase (more than 1 month and less than 6 months post stroke) and patients in the chronic phase (more than 6 months post stroke).

Methodology

Patients

Our study included 100 consecutive patients with a diagnosis of a first-ever stroke and 30 HCs matched on age and years of education. All patients were admitted to the Center for Epilepsy and Acquired Brain Injury (CEPOS; Duffel, Belgium) from the department of neurology or neurosurgery of a general or university hospital with the purpose of starting a neuropsychological rehabilitation program and this in the period between 2020 and 2025. Of stroke patients, 67 had an infarction and 33 had a hemorrhage. The type and hemispheric lateralization of stroke was diagnosed by means of neuroimaging (Computed Tomography (CT) and/or magnetic resonance imaging (MRI)) in the acute phase (first month post stroke). HCs were recruited from the community.

For all stroke patients the exclusion criteria were as follows: 1) cognitive impairments prior to the first-ever stroke, 2) treatment with any psychotropic medication (which could have an influence on cognitive performances), 3) older than 70 years of age (to minimize the possible confounding effect of other medical factors on cognition), 4) substance use dependence (drugs and/or alcohol), 5) severe language deficits, 6) severe visual deficits (such as homonymous hemianopia), 7) severe visuospatial neglect, 8) psychiatric comorbidity, 9) a previous neurological disorder and 10) a 'transient ischemic attack' (TIA). For the HC group, participants were excluded when using psychotropic medication, when older than 70 years of age, when reporting cognitive complaints and when showing abuse of drugs or alcohol, a psychiatric illness or a neurological disorder in the personal history. All participants had Dutch as their native language and gave written informed consent for participation.

Neuropsychological Assessment

Patients were examined with an extensive neuropsychological test battery (see below) in the first week of hospitalization for neuropsychological rehabilitation at CEPOS. This battery covered a broad range of verified reliable and valid tests divided into five cognitive domains: attention, memory, visuospatial functions, language and executive functions. The neuropsychological examination lasted an average of 2 to 3 hours, with a short break, per participant. The tests were carried out by the same experienced neuropsychologist and also followed a standardized sequence. In addition to the neuropsychological assessment, a check list was filled out by a relative of each patient. This check list was used to detect possible cognitive problems and/or emotional and behavioral changes which were observed by relatives during daily life activities of the patients.

Attention

The Digit Symbol Coding Subtest from the Wechsler Adult Intelligence Scale (4th Edition) (WAIS-IV (DSC)) [29] was used to assess divided attention. The total correct symbols within the allowed time of 120s is used as outcome measure. The Dutch version of the Stroop (Color/word Interference) Test [30] was used to measure focused and alternating attention. The interference score (time for card III minus time for card II) (for the evaluation of focused attention) and the interference score (time for card IV minus time for card II) (for the evaluation of alternating attention) were used as outcome measures.

Memory

The Coetsier Story Recall Test (CSRT) was used to evaluate audioverbal memory. Visuospatial memory was assessed by means of the Rey Complex Figure Test (RCFT) [31-33]. We used two measures for both memory tests. These are immediate recall and long-term delayed recall (after a 20-min interval) of recently learned information.

Visuospatial Functions

The Judgement of Line Orientation Test (JLOT) was used to measure visuospatial judgement. The outcome measure is the total correct answers (the maximum score is 30) [30,34]. The copy of the Rey Complex Figure Test (RCFT) was administered to evaluate visuospatial construction [32,33]. The total score (with a maximum of 36) was recorded. The Bells Test (BT) was administered to assess visuospatial hemi-attention [30,35]. The outcome measures are the total amount of bells (total correct) which are crossed out (with a maximum of 35) and the total left and right neglects (or the number of bells missed at the left or right side of the page).

Language

In our study we administered the short form of the Boston Naming Test (BNT-SF) to measure naming of 29 objects. The outcome measure is the total correct answers [36].

Executive Functions

The Controlled Oral Word Association Test (COWAT) and the Word Fluency Test (WFT) were used to assess phonetic verbal fluency and semantic verbal fluency, respectively [37,38]. The total words generated was used as outcome measure for both tests. The Subtests Similarities and Matrix Reasoning from the Wechsler Adult Intelligence Scale (4th Edition) (WAIS-IV (S) and WAIS-IV (MR)) were selected to measure verbal abstract reasoning and spatial abstract reasoning, respectively. The total raw score was used as outcome measure for both subtests [29].

Cognitive Problems and Emotional and Behavioral Changes in Daily Life

The 'Checklist for Cognitive and Emotional Consequences following Stroke' (CLCE-24) was used to detect possible cognitive problems and/or emotional and behavioral changes which were noticed by relatives during daily life activities of the patients [39]. This checklist consists of 22 items with a rating of 0 (no problem), 1 (a problem but not annoying) or 2 (an annoying problem) for each item. Besides this, the checklist also consists of two scales. These scales are cognitive problems (13 items) and emotional/behavioral changes (9 items). The checklist was filled out by a relative of the patients. The total score was used as outcome measure for both scales.

Data Analysis

Statistical Package for the Social Sciences IBM SPSS Statistics 26 was used to analyze the data. Normality of the data was examined for each variable using the Kolmogorov-Smirnov test. Between-group analyses were performed with Mann-Whitney U test when data were not normally distributed. Independent samples t test was used to compare between-group characteristics of patients. Data are presented as means \pm standard deviation. A p-value of 0.05 was considered statistically significant. For the neuropsychological assessment, a Bonferroni correction was applied to correct for multiple comparisons (using a p value of 0.05 for 17 comparisons (stroke patients compared to HCs) or 19 comparisons (different subgroups of stroke patients compared with each other)). For this reason, the p-value of 0.05 was corrected to a p-value of 0.003.

Results

Demographics

A global stroke group of N = 100 patients participated to our study with a mean age of 55.3 years (range: 25-70 years) and a mean educational level of 13.2 years (range: 8-17 years). The other characteristics for the global stroke group were as follows: lateralization of stroke (right hemisphere N = 37; left hemisphere N = 53; bilateral N = 10), gender (males N= 68; females N= 32) and time between stroke and neuropsychological assessment (post-acute phase (more than 1 month and less than 6 months post stroke) N = 78 and chronic phase (more than 6 months post stroke) N = 22). This global stroke group was further divided into two subgroups. These are a group of N = 67 patients with an infarction (cortical infarction N = 45; subcortical infarction N = 22) and a group of N = 33 patients with a hemorrhage (intracerebral hemorrhage N = 17; subarachnoid hemorrhage N = 16). Besides this, a group of N = 30 HCs with a mean age of 53.0 ± 8.1 years (range: 26-70 years) and a mean educational level of 14.3 ± 2.0 years (range: 12-18 years) was also investigated.

Neuropsychological Assessment: Stroke Patients Compared to HCs

The two groups were similar in age (stroke 55.3 ± 7.4 years; HC 53.0 ± 8.1 years; ANOVA $p = 0.27$) and years of education (stroke 13.2 ± 2.4 years; HC 14.3 ± 2.0 years, ANOVA $p = 0.11$).

Attention

On the WAIS IV (DSC), total correct was significantly higher for HCs (71.6 ± 11.3) compared to stroke patients (51.3 ± 15.5 ; $p < 0.003$). Both interference scores (III-II and IV-II) on the Stroop Test were significantly lower for HCs (33.8 ± 15.8 and 48.8 ± 19.0 , respectively) compared to stroke patients (63.6 ± 40.4 and 98.4 ± 54.5 , respectively; both $p < 0.003$).

Memory

On the RCFT, HCs showed a significantly better outcome for immediate recall (24.1 ± 5.5) and long-term delayed recall (22.9 ± 5.6) compared to the stroke group (18.1 ± 7.8 and 17.6 ± 7.6 , respectively; $p < 0.003$ and $p = 0.003$, respectively). No significant differences were noted between the stroke group and the HC group for immediate recall and long-term delayed recall on the CSRT.

Visuospatial Functions

No significant differences were found between HCs and stroke patients for total score (copy) on the RCFT, total correct on the JLOT and total correct and total left and right neglects on the BT.

Language

On the BNT-SF, no significant difference was detected for total correct between the stroke group and the HC group.

Executive Functions

For total words generated on the COWAT and WFT, HCs (39.2 ± 9.0 and 43.8 ± 7.3 , respectively) showed a significantly better result in comparison to the stroke group (25.1 ± 10.2 and 27.0 ± 9.8 , respectively; both $p < 0.003$). Also for total raw score on the WAIS-IV (S) and WAIS-IV (MR), stroke patients (19.7 ± 4.9 and 14.7 ± 5.6 , respectively) performed significantly worse than HCs (25.3 ± 4.0 and 19.0 ± 4.3 , respectively; $p < 0.003$ and $p = 0.003$, respectively) (Table 1).

	Stroke (N= 100)	HC (N= 30)	P-value
WAIS IV subtest 'Digit Symbol Coding'			
Total correct	51.3 ± 15.5	71.6 ± 11.3	< 0.001*
Stroop Test			
Interference score (III-II) (s)	63.6 ± 40.4	33.8 ± 15.8	0.001*
Interference score (IV-II) (s)	98.4 ± 54.5	48.8 ± 19.0	< 0.001*
Coetsier Story Recall Test			
Immediate recall	57.2 ± 18.2	65.7 ± 12.1	0.053 (NS)
Long-term delayed recall	52.5 ± 17.9	62.8 ± 11.9	0.014 (NS)
Rey Complex Figure Test			
Immediate recall	18.1 ± 7.8	24.1 ± 5.5	0.001*
Long-term delayed recall	17.6 ± 7.6	22.9 ± 5.6	0.003*
Judgement of Line Orientation Test			
Total correct	24.4 ± 4.3	26.5 ± 2.6	0.078 (NS)
Rey Complex Figure Test			
Copy (total score)	33.2 ± 4.3	35.7 ± 0.7	0.010 (NS)
Bells Test			
Total correct	34.1 ± 1.5	34.3 ± 1.1	0.624 (NS)
Total left neglects	0.6 ± 1.3	0.3 ± 0.5	0.381 (NS)
Total right neglects	0.3 ± 0.7	0.3 ± 1.0	0.778 (NS)
Boston Naming Test (short form)			
Total correct	23.6 ± 5.6	26.2 ± 1.8	0.024 (NS)
Controlled Oral Word Association Test			
Total words generated	25.1 ± 10.2	39.2 ± 9.0	< 0.001*
Word Fluency Test			
Total words generated	27.0 ± 9.8	43.8 ± 7.3	< 0.001*
WAIS IV subtest 'Matrix Reasoning'			
Total raw score	14.7 ± 5.6	19.0 ± 4.3	0.003*
WAIS IV subtest 'Similarities'			
Total raw score	19.7 ± 4.9	25.3 ± 4.0	< 0.001*
Data are presented as mean ± standard deviation. A p-value of 0.003 Bonferroni corrected was considered statistically significant.			
Abbreviations: HC (healthy controls); NS (not significant); * (significant).			

Table 1: Overview of cognitive functioning in stroke patients compared to Healthy Controls (HC).

Neuropsychological Assessment: Patients With an Infarction Compared to Patients with a Hemorrhage

The two subgroups were similar in age (infarction 54.9 ± 10.1 years; hemorrhage 56.0 ± 9.9 years; ANOVA p = 0.628) and years of education (infarction 12.9 ± 2.5 years; hemorrhage 13.7 ± 2.2 years; ANOVA p = 0.142). No significant differences could be detected between both groups for all measures of the administered neuropsychological tests and the CLCE-24.

Neuropsychological Assessment: Patients with a Left Hemisphere Stroke Compared to Patients with a Right Hemisphere Stroke

Patients with a left hemisphere stroke compared to patients with a right hemisphere stroke.

Demographics

The two subgroups were similar in age (left hemisphere 55.4 ± 9.0 years; right hemisphere 55.9 ± 10.9 years; ANOVA $p = 0.363$) and years of education (left hemisphere 13.3 ± 2.3 years; right hemisphere 12.8 ± 2.5 years; ANOVA $p = 0.796$).

Attention

Total correct on the WAIS-IV (DSC) and both interference scores (III-II and IV-II) on the Stroop test did not differ significantly between both groups.

Memory

For immediate recall and long-term delayed recall on the RCFT and the CSRT, no significant differences could be found between both groups.

Visuospatial Functions

Patients with a right hemisphere stroke showed a significant worse performance for total correct (22.5 ± 4.8) on the JLOT and for total correct (33.5 ± 1.8) and left neglects (1.2 ± 1.7) on the BT in comparison to patients with a left hemisphere stroke (25.8 ± 3.6 , 34.4 ± 1.2 and 0.1 ± 0.8 , respectively; $p < 0.003$, $p = 0.003$ and $p < 0.003$, respectively). For total score (copy) on the RCFT, no significant difference was found between both groups.

Language

Patients with a right hemisphere stroke performed significantly better for total score (25.5 ± 2.4) on the BNT-SF compared with patients with a left hemisphere stroke (21.8 ± 6.9 ; $p < 0.003$).

Executive Functions

For total raw score on the WAIS-IV(MR), patients with a left hemisphere stroke showed a significantly better result (16.8 ± 5.1) than patients with a right hemisphere stroke (12.1 ± 5.3 ; $p < 0.003$). With regard to the COWAT, the WFT and the WAIS-IV(S), no significant differences were documented between both groups for all test variables.

Emotional and Behavioral Changes

No significant differences between both groups were found for the scales cognitive problems and emotional/behavioral changes on the CLCE-24 (Table 2).

	LH stroke (N= 53)	RH stroke (N= 37)	P-value
WAIS IV subtest 'Digit Symbol Coding'			
Total correct	51.0 ± 16.3	50.8 ± 15.0	0.863 (NS)
Stroop Test			
Interference score (III-II) (s)	61.4 ± 39.5	64.0 ± 42.9	0.974 (NS)
Interference score (IV-II) (s)	96.0 ± 55.3	100.5 ± 56.1	0.784 (NS)
Coetsier Story Recall Test			
Immediate recall	53.8 ± 20.7	61.5 ± 13.3	0.071 (NS)
Long-term delayed recall	48.6 ± 20.0	57.5 ± 13.1	0.016 (NS)
Rey Complex Figure Test			
Immediate recall	20.3 ± 7.3	16.1 ± 8.0	0.013 (NS)
Long-term delayed recall	19.8 ± 7.1	15.6 ± 7.9	0.011 (NS)
Judgement of Line Orientation Test			
Total correct	25.8 ± 3.6	22.5 ± 4.8	$< 0.001^*$
Rey Complex Figure Test			
Copy (total score)	34.3 ± 1.8	31.4 ± 6.4	0.027 (NS)

Bells Test	34.4 ± 1.2	33.5 ± 1.8	
Total correct	0.1 ± 0.8	1.2 ± 1.7	0.001*
Total left neglects	0.4 ± 0.8	0.1 ± 0.5	
Total right neglects			
Boston Naming Test (short form)	21.8 ± 6.9	25.5 ± 2.4	0.001*
Total correct			
Controlled Oral Word Association Test			
Total words generated	22.9 ± 10.1	27.1 ± 9.5	0.076 (NS)
Word Fluency Test			
Total words generated	25.8 ± 10.0	27.0 ± 7.6	0.278 (NS)
WAIS IV subtest 'Matrix Reasoning'			
Total raw score	16.8 ± 5.1	12.1 ± 5.3	< 0.001*
WAIS IV subtest 'Similarities'			
Total raw score	19.2 ± 5.3	20.0 ± 4.5	0.705 (NS)
CLCE-24			
Cognitive problems	8.6 ± 4.3	8.0 ± 3.9	0.518 (NS)
Emotional/behavioral changes	4.9 ± 2.9	6.1 ± 3.6	0.112 (NS)
Data are presented as mean ± standard deviation. A p-value of 0.003 Bonferroni corrected was considered statistically significant.			
Abbreviations: LH (left hemisphere); RH (right hemisphere); NS (not significant); * (significant); CLCE-24 (Checklist for Cognitive and Emotional Consequences following stroke).			

Table 2: Overview of cognitive functioning in patients with a left hemisphere stroke compared to patients with a right hemisphere stroke.

Neuropsychological Assessment: Male Stroke Patients Compared to Female Stroke Patients

The two subgroups were similar in age (males 56.9 ± 8.6 years; females 52.0 ± 12.1 years; ANOVA p = 0.363) but not similar in years of education (males 12.9 ± 2.5 years; females 13.7 ± 2.2 years; ANOVA p = 0.046). The male stroke patients showed a significant lower education in comparison to the female stroke patients. No significant differences could be detected between both groups for all measures of the neuropsychological tests and the checklist. However, the significant difference between both groups with regard to education may have influenced the results.

Neuropsychological Assessment: Patients with a cortical infarction Compared to Patients with a Subcortical Infarction

The two subgroups were similar in age (cortical infarction 54.3 ± 9.8 years; subcortical infarction 56.2 ± 11.0 years; ANOVA p = 0.489) and years of education (cortical infarction 13.0 ± 2.6 years; subcortical infarction 12.7 ± 2.4 years; ANOVA p = 0.660). No significant differences could be detected between both groups for all neuropsychological measures.

Neuropsychological Assessment: Patients with a Subarachnoid Hemorrhage Compared to Patients with an Intracerebral Hemorrhage

The two subgroups were not similar in age (subarachnoid hemorrhage 49.7 ± 8.3 years; intracerebral hemorrhage 61.9 ± 7.3 years; ANOVA p < 0.001) and years of education (subarachnoid hemorrhage 14.6 ± 1.8 years; intracerebral hemorrhage 12.8 ± 2.2 years; ANOVA p = 0.018). Patients with an intracerebral bleeding showed a significant lower educational level and a significant older age compared to patients with a subarachnoid hemorrhage. No significant differences could be detected between both groups for all neuropsychological measures. However, the significant differences between both groups concerning age and educational level may have influenced these results.

Neuropsychological Assessment: Stroke Patients in the Post-Acute phase Compared to Stroke Patients in the Chronic Phase

The two subgroups were similar in age (post-acute phase 55.9 ± 10.3 years; chronic phase 53.0 ± 8.5 years; ANOVA $p = 0.220$) and years of education (post-acute phase 12.9 ± 2.4 years; chronic phase 13.9 ± 2.2 years; ANOVA $p = 0.116$). No significant differences could be detected between both groups for the measures of the neuropsychological tests to evaluate attention, memory, visuospatial functions, naming and executive functions. In contrast to this finding, significant differences could be documented between both groups concerning the CLCE-24. Based on this checklist, relatives of stroke patients in the chronic phase (more than 6 months post stroke) observed significant more cognitive problems (11.0 ± 4.6) and emotional/behavioural changes (8.0 ± 3.1) in comparison to relatives of patients in the post-acute phase (more than 1 month and less than 6 months post stroke) (7.5 ± 3.5 and 4.5 ± 2.8 , respectively; both $p < 0.003$).

Discussion

For our global stroke group we detected a significant worse performance for (divided, focused and alternating) attention, visuospatial memory, (phonetic and semantic) verbal fluency and (verbal and non-verbal) abstract reasoning in comparison to a matched HC group. However, no significant differences could be found between both groups concerning audioverbal memory, visuospatial functions and naming. Our study results are for the most part in line with the findings of other studies [3-12]. Concerning memory, our findings agree with the results of the study of Sachdev, et al. [10]. As in our study, these authors also found a significant poorer performance of stroke patients (as compared to a HC group) for visuospatial memory but not for audioverbal memory. Nevertheless, it may be argued that our patient sample is biased because we included stroke patients with cognitive deficits of lesser severity. Indeed, we did not include stroke patients with for example severe language deficits. It is known from the literature that this may have led to an underestimation of cognitive deficits because severe aphasia can interfere with the performance on several neuropsychological tests [6,11]. However, we do agree with other authors that it is important to mention that even nonaphasic patients or patients with a mild to moderate aphasia can demonstrate manifest cognitive deficits after stroke and that severe aphasia can clearly prevent a reliable assessment of cognitive functions [3,4,10]. Another bias is that our global stroke sample was mixed with patients in the post-acute phase (more than 1 month and less than 6 months post stroke) or the chronic phase (more than 6 months post stroke). So, it can be assumed that the post-stroke duration may also have influenced the cognitive performances of our stroke patients.

Our study results could not confirm the assumption made by some authors that there is a close relation between language and complex cognitive processes after stroke because of the confounding effect of language problems on cognitive performances. According to these authors, this may explain why cognitive deficits are more pronounced following left hemisphere stroke compared to right hemisphere stroke. In the studies of Tatemichi, et al., Hochstenbach, et al. and Nys, et al., it was found that cognitive functioning was significant worse following left hemisphere stroke compared to right hemisphere stroke [3,4,6]. However, our study results are not consistent with their findings. Our patients with a left hemisphere stroke showed in general no more cognitive problems in comparison with patients with a right hemisphere stroke. In contrast, our left hemisphere stroke patients showed significant more problems with verbal cognitive functions (i.e., naming) compared to right hemisphere stroke patients and our right hemisphere stroke patients showed significant more problems with non-verbal cognitive functions (i.e., visuospatial judgement, visuospatial hemi-attention and spatial abstract reasoning) compared to left hemisphere stroke patients. Based on our study results, we can therefore conclude that there is rather a certain hemispheric lateralization effect on cognitive functioning after stroke but not a predominant effect of left hemisphere lesions on cognitive performances after stroke. However, as one might not have expected, we could not detect significant differences between both groups concerning audioverbal and visuospatial memory. This finding is similar with the study outcome of Tatemichi, et al. [3]. A comparison between our study and the study of Nys, et al., and Hochstenbach, et al., is not possible because visuospatial memory was not investigated by these authors [7,8].

When we compared several subgroups of stroke patients with each other, we noticed that no significant differences in cognitive performances could be documented between patients with an infarction versus a hemorrhage, patients with a cortical infarction versus a subcortical infarction, patients with a subarachnoid hemorrhage versus an intracerebral hemorrhage and patients with female gender versus male gender. Also, in other studies no significant effect on cognition was found for infarction versus hemorrhage and for cortical infarction versus subcortical infarction [3,4]. However, in other studies significant differences between stroke subgroups could be found. First, with regard to cortical infarction versus subcortical infarction, Rasquin, et al., noticed that cortical infarction (and not subcortical infarction) was a predictor of cognitive deficits after ischemic stroke. Second,

regarding subarachnoid hemorrhage versus intracerebral hemorrhage, Brand, et al., found that patients who have suffered a subarachnoid hemorrhage revealed significant more deficits with regard to divided attention, speed of information processing, word recognition, visuospatial construction and judgement and logical thinking in comparison to patients with an intracerebral hemorrhage [7]. In contrast, patients with an intracerebral hemorrhage displayed significant more problems with short-term and long-term memory compared to patients with a subarachnoid hemorrhage. Third, concerning male patients versus female patients with a stroke, Hochstenbach, et al., discovered that females performed significant better on audioverbal memory tests and that males performed significant better on tests measuring visuospatial abilities [41]. In the study of Rasquin, et al., female patients with an infarction showed also a significant worse performance for audioverbal memory and a significant reduced mental speed in comparison to male patients with an infarction. Finally, in the study of Tatemichi, et al., [3,12] female patients with an infarction performed significant better than male patients with an infarction concerning general cognitive functioning. The different findings between our study and the above mentioned studies are probably due to differences in patient selection (such as a mixed stroke sample versus a selected stroke sample and variations in the age and the post-stroke duration of the included stroke patients) and methodology (such as the use of different neuropsychological tests and different cognitive concepts and the application of a short versus extensive neuropsychological test battery). We also could not detect significant differences between patients in the post-acute phase and patients in the chronic phase with regard to their results on tests measuring attention, memory, visuospatial functions, naming and executive functions. This finding is in line with the outcome of the study of Hochstenbach, et al. [4]. In contrast, significant differences could be documented in our study between both groups concerning the CLCE-24. Based on this checklist, relatives of stroke patients in the chronic phase observed significant more cognitive problems and emotional/behavioral changes in comparison to relatives of patients in the post-acute phase. A possible explanation of this finding is that relatives become mostly aware of such problems only after the patient has left the hospital (and mostly after the patient has completed an extensive multidisciplinary rehabilitation program) and has returned to his or her familiar environment. Our study results are consistent with the outcome of other studies in which the CLCE-24 was used to evaluate cognitive problems and/or emotional/behavioral changes in daily life of patients in the post-acute or chronic phase after first-ever stroke.

Our study has several advantages. First, we included only patients with a first-ever stroke and we examined a relatively large sample of stroke patients who performed all the administered tests (to evaluate a broad range of cognitive (sub)functions) of an extensive neuropsychological test battery. Second, within our global stroke group we examined cognitive functioning between several subgroups (for example infarction versus hemorrhage, cortical infarction versus subcortical infarction, subarachnoid hemorrhage versus intracerebral hemorrhage, left hemisphere stroke versus right hemisphere stroke, male stroke patients versus female stroke patients and stroke patients in a post-acute phase versus stroke patients in a chronic phase). So, we had a more homogeneous group of stroke patients which makes it possible to extrapolate our results to a general population of patients with a first ever-stroke.

Besides this, our study has also some disadvantages. First, we performed a cross-sectional and not a follow-up study. It is known from the literature that many aspects of cognitive functioning in stroke patients are best studied longitudinally. Therefore, we would like to stress the importance of more longitudinal follow-up studies to better understand the progression or stabilization of several cognitive functions in a large group of stroke patients who were first neuropsychologically assessed in the acute or post-acute phase. Second, a large proportion of stroke patients was not included in our study because of severe aphasia, severe visuospatial neglect and/or severe visual deficits (such as homonymous hemianopia). Nevertheless, we do not consider these exclusion criteria to have introduced an important bias in our sample because the above mentioned severe symptoms can clearly prevent a reliable assessment of cognitive functions. Third, our stroke sample was mixed with patients in the post-acute or chronic phase. So, the post-stroke duration may also have influenced the results of our patients on the administered neuropsychological tests. Therefore, it is better that future studies focus on baseline assessment of cognitive functioning in stroke patients in the acute or post-acute phase and subsequently follow-up assessments at fixed intervals of time (i.e., several months or years after stroke) to evaluate the evolution and progression of cognitive performances.

Conclusion

To end with, we can make two remarks. First, the results of our study showed that stroke has a massive effect on many cognitive functions. So, the implication of these results for cognitive rehabilitation are clear. Indeed, it is really important that neuropsychologists, occupational therapists and speech therapists work interdisciplinary and focus their attention on the

treatment (i.e., restoration of cognitive deficits and compensation of cognitive disabilities) of a combination of several cognitive problems in stead of a monodisciplinary treatment of isolated and specific cognitive problems such as attention problems, amnesia or aphasia. The first approach will clearly increase the effect of such an optimal cognitive rehabilitation program. The latter approach will lead to an underestimation of the general effect of stroke on cognition. Second, it is rather difficult to compare the results of the few studies that have yet examined the relation between stroke and cognition. This statement is due to differences in patient selection (for example studies with a small sample of stroke patients, studies with no comparison between stroke patients and a matched HC group, studies with only the inclusion of patients with an infarction or a hemorrhage and not both subgroups) and methodological limitations (for example the use of different neuropsychological tests, the use of different cognitive concepts for the same neuropsychological test variables and the use of a short cognitive screening instrument or a comprehensive neuropsychological test battery). So, more consensus is needed among future studies.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Data Availability Statement

Yes, but only on a genuine request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Written informed consent was obtained from all individual participants included in the study.

Authors' Contributions

Responsibility for the integrity of the data and the accuracy of the data analysis: All authors. Acquisition or interpretation of data: All authors. Drafting of the manuscript: KB, ED. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: ED, LE, KL. Final approval of the submission: All authors.

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