

Cognitive and emotional effects of carotid stenosis

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Summary

PRINCIPLES: Patients with carotid artery stenosis (CAS) are at risk of ipsilateral stroke and chronic compromise of cerebral blood flow. It is under debate whether the hypoperfusion or embolism in CAS is directly related to cognitive impairment. Alternatively, CAS may be a marker for underlying risk factors, which themselves influence cognition. We aimed to determine cognitive performance level and the emotional state of patients with CAS. We hypothesised that patients with high grade stenosis, bilateral stenosis, symptomatic patients and/or those with relevant risk factors would suffer impairment of their cognitive performance and emotional state.

METHODS: A total of 68 patients with CAS of $\geq 70\%$ were included in a prospective exploratory study design. All patients underwent structured assessment of executive functions, language, verbal and visual memory, motor speed, anxiety and depression.

RESULTS: Significantly more patients with CAS showed cognitive impairments (executive functions, word production, verbal and visual memory, motor speed) and anxiety than expected in a normative sample. Bilateral and symptomatic stenosis was associated with slower processing speed. Cognitive performance and anxiety level were not influenced by the side and the degree of stenosis or the presence of collaterals. Factors associated with less cognitive impairment included higher education level, female gender, ambidexterity and treated hypercholesterolemia.

CONCLUSIONS: Cognitive impairment and increased level of anxiety are frequent in patients with carotid stenosis. The lack of a correlation between cognitive functioning and degree of stenosis or the presence of collaterals, challenges the view that CAS *per se* leads to cognitive impairment.

Key words: carotid artery stenosis; CAS; cognitive function; emotional state

Introduction

Patients with carotid artery stenosis (CAS) are at risk of chronically reduced cerebral blood flow and recurrent emboli to the brain. Reports on cognitive performance in patients with CAS vary widely: some studies report cognitive impairment [1–3] even in asymptomatic patients without history of stroke [4–6], whereas others suggest no cognitive deficits [7]. A systematic review addressing cognitive performance in patients with symptomatic and asymptomatic CAS reported cognitive deficits in 14 out of 18 studies [8]. Differences in study results are likely due to variations in patients' characteristics, sample size, study design, assessment methods, interpretation of results and also publication bias and hence, comparison of studies is difficult.

Two probable mechanisms relating to cognitive impairment in carotid artery disease are hypoperfusion and embolisation, both of which decrease the cerebral blood supply. According to the 'Spencer curve' [9], the brain blood perfusion remains stable in mild and moderate CAS, and decreases only when high-grade CAS occurs [10]. Cognitive performance is likely determined not only by the degree of stenosis but also by an interaction of various factors, including advanced age [5] and the location of stroke [6, 11]. Arguments against the hypothesis that embolisation causes cognitive impairment come from the Tromsø Study [4] and the Cardiovascular Healthy Study [5]. These studies suggested that cognitive performance in patients with CAS was independent of vascular lesions. The Tromsø Study found a graded relationship between the degree of CAS and cognitive performance, which points towards the crucial role of haemodynamic mechanisms. However, in most patients of the Tromsø Study, the degree of stenosis was low and hence unlikely to significantly influence haemodynamic mechanisms.

A further controversial issue is whether CAS directly causes cognitive impairment or whether it is a marker for underlying risk factors that predispose patients to cognitive

impairment. CAS is related to a number of risk factors such as hypertension, diabetes mellitus, smoking and dyslipidemia. Each of these risk factors may influence cognitive performance [12]. A direct intervention, such as endarterectomy or stenting, may only prevent cognitive decline if the carotid artery disease itself is the cause of cognitive impairment. If there is no direct association between stenosis and cognitive impairment, treatment of the risk factor itself will more efficiently influence cognitive impairment. A comparison study described no difference between endarterectomy or stenting in effect on cognition [13]. The aim of the present prospective study was to assess cognition and the emotional state of a large sample of patients with symptomatic and asymptomatic CAS. We hypothesised that patients with high grade stenosis, bilateral stenosis, symptomatic patients and/or those with relevant risk factors would suffer impairment of their cognitive performance and emotional state. Results of the present study should add a further aspect in therapeutic decision taking in patients with CAS and aid in the assessment of the benefits of available treatment modalities.

Methods

Patients: Between 2009 and 2012, 94 patients with CAS were recruited from the stroke units, outpatient stroke clinic, and the neuroradiology departments at two university hospitals. In this prospective exploratory study, consenting patients with enough time for a neuropsychological assessment before intervention were consecutively included in the trial. Patients with extracranial CAS of $\geq 70\%$, were included (see details below). They were considered symptomatic if a minor stroke (modified Rankin Scale ≤ 2 at time of inclusion) or transient ischemic attack (TIA) with either motor, sensory, speech or visual impairment had occurred within three months prior to inclusion. Exclusion criteria were major stroke, progressive cerebral pathology (such as tumour, multiple sclerosis, Alzheimer's disease), and

Table 2: Risk factors.

	yes (n)	%
Arterial hypertension	46	67.6
Diabetes mellitus	17	25.0
Hypercholesterolemia	48	70.6
Smoking		
current	11	16.7
non smoker for last 5 years	7	10.3
Atrial fibrillation	5	7.4

Table 1: Neuropsychological assessments.

Function	Test	Reference
<i>Executive Functions</i>		
Processing speed	Stroop naming Stroop reading	Delis-Kaplan Executive Function System (D-KEFS; [34])
	Symbols	Wechsler Intelligenztest für Erwachsene (WIE; [35])
	TMT A time*	Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus; [36])
Interference control	Stroop interference	Delis-Kaplan Executive Function System (D-KEFS; [34])
Shifting	TMT B time*	Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus; [36])
<i>Language</i>		
Word production	Boston naming	Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus; [36])
Verbal fluency	Animal naming	Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus). Norms see [37]
<i>Verbal Memory</i>		
Episodic memory	Word rey Learning (Σ trial 1 to 5) Recognition (immediately) Late recall (after 40 min)	Verbaler Lern- & Merkfähigkeitstest (VLMT; [38])
Short term memory	Digit span	Wechsler Intelligenztest für Erwachsene (WIE; [35])
<i>Visual Memory</i>		
Episodic memory	Signs Learning (Σ trial 1 to 5) Recognition (immediately) Late recall (after 40 min)	Rey Visual Design Learning Test (RVDLT; [39])
	Rey Osterrieth Complex Figure Copy Immediate recall Late recall (after 45 min)	Rey Osterrieth Figure [40, 41]
<i>Emotional State</i>		
Anxiety Depression	HADS	Hospital Anxiety and Depression Scale [42] Norms see [43]
Motor Speed	PPD Dominant hand Non-dominant hand	Purdue Pegboard Norms [44]

Note: *TMT A, Trail making test Part A; *TMT B, Trail making test Part B; HADS: Hospital Anxiety and Depression Scale; PPD: Purdue Pegboard

standard exclusion criteria for magnetic resonance (MR) imaging. We determined the required sample size according to the power analysis by Cohen [14]. With an alpha-level <0.05 , a large effect size = .50 and power = .80 we aimed to recruit a minimum of 26 patients. The study protocol was approved by the corresponding local ethics committees and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients prior to study inclusion.

Degree of stenosis and collaterals: The degree of CAS was determined based on Duplex ultrasound. Peak systolic velocities of >215 were graded as stenosis of $\geq 70\%$. Near occlusion was defined as visible plaque that led to marked narrowing of the lumen, and occlusion was defined as no detectable patent lumen seen on colour Doppler ultrasound. If Duplex data were unavailable, data from digital subtraction angiography, CT- or MR- angiography were used instead. The degree of stenosis was defined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [15]. Collateralisation was assessed by categorising the completeness of the circle of Willis as determined on time-of-flight MR angiography images. The completeness of the circle of Willis was categorised into three groups according to Ryan and colleagues [16]: classical complete circle of Willis (entirely normal circle of Willis), hypoplastic group (hypoplasia but no absent vessels) and incomplete circle of Willis (absent vessels).

Neuropsychological assessment: Eleven well-known standardised neuropsychological tests were selected covering a wide range of cognitive functions (table 1). Patients' scores were compared to age-, sex- and education adjusted normative scores of the tests indicated in the respective test manuals. Risk factors were assessed in an interview (see table 2). Handedness was measured using the Laterality Index of Oldfield [17] modified after Salmasso & Longoni [18]. Trained psychologists carried out the neuropsychological assessment in the same order and in a standardised fashion, with a break after 90 minutes. The total assessment lasted 3 hours (table 1).

Analysis: All statistical analyses were conducted using IBM SPSS Statistics 20.0 for Windows. As we used explorative analyses, statistical tests were two-sided with a 5% significance level. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. The majority of the variables were not normally distributed. Consequently, non-parametric tests were used over all variables, hence mean rank scores are reported in the supplementary table. To unify scores from different tests, z-scores were calculated for each individual test score. Cognitive impairment was defined according to the standard of many clinical institutions: deficient cognitive performance was defined if a cognitive test score was more than 1 standard deviation below the mean of the normative sample given in the test manual. The patient group was compared with the norms given in the respective test manual by using Chi-Square Test. Mann-Whitney-U Test was used to compare two subgroups (e.g., symptomatic vs. asymptomatic, women vs. men, collaterals vs. no collaterals). Kruskal-Wallis-Test was applied to detect group differences among three subgroups (degree of stenosis, side of stenosis, circle of Willis). Spearman's correlation was performed to define the strength of the association between cognitive performance and: (1) emotional state (2) number of risk factors, and (3) the time between symptoms and cognitive assessment. The numbers of patients (n) was inconsistent due the fact that some tests were only performed in patients ≥ 70 years or < 70 years (e.g., visual memory: signs and Rey-Figure; see table 4).

Results

A total of 68 patients (52 male, 16 female; mean age 68.7 years, range 51.3–85.3 years) were included based on the aforementioned inclusion criteria. Reasons for drop-out were stenosis grade $< 70\%$ (n = 13), intracranial instead of extracranial stenosis (n = 5), severe stroke (n = 2) and missing neuropsychological data (n = 6). For demographic and medical characteristics see tables 2 and 3.

Table 3: Patient demographics and medical characteristics.

		n	%
Gender	male	52	76.5
	female	16	23.5
Education Level	1	14	20.6
	2	47	69.1
	3	7	10.3
Handedness	right	55	80.9
	left	3	4.4
	both	10	14.7
Side of Stenosis	right	29	42.7
	left	27	39.7
	bilateral	12	17.6
Degree of Stenosis	70% to near occlusion	40	58.8
	near occlusion	12	17.6
	total occlusion	16	23.5
Collaterals	complete	5	7.3
	hypoplastic	18	26.5
	incomplete	45	66.2
Symptoms	symptomatic	23	33.8
	asymptomatic	45	66.2

Note: Education Level 1 = < 9 years, 2 = 9–12 years, 3 = > 12 years

Overall, 30% of patients showed impairment in processing speed (Stroop Naming, Symbols), 32% in interference control (Stroop Interference), 26% in word production (Boston Naming), 30% in verbal episodic memory (Word Rey learning), 33% in visual episodic memory (Signs learning and recall), 50% in visuospatial abilities (Rey Figure copy, 31% in late recall), 38% in motor speed of the dominant hand and 34% of all patients showed impaired motor speed of the non-dominant hand. In all these tests significantly more patients showed impairment than expected in a normative sample. The differences between the observed and expected frequency of impairment were statistically significant (see table 4). Patients showed significantly more often anxiety but less often depressive symptoms than expected in a normative sample (table 4). Positive correlations between processing speed (Symbols) and emotional state (anxiety $r = .26$, $p = .029$; depression $r = .27$, $p = .027$) as well as between verbal fluency and emotional state (anxiety $r = .26$, $p = .035$; depression $r = .32$, $p = .008$) were observed.

The degree of stenosis did not affect any cognitive domain (Supplementary table). Patients with bilateral stenosis ($n = 12$) showed slowest processing speed (Stroop Reading; Supplementary table). Asymptomatic patients ($n = 45$) showed significantly faster processing speed (trail making test, TMT A) and dominant hand motor speed than symptomatic patients ($n = 23$; Supplementary table). Presence of collaterals did not influence cognitive performance, not even if degree of stenosis was considered. Risk factors

for CAS (table 2) were related to cognitive performance level. Patients with hypertension ($n = 46$) showed significantly worse motor speed (non-dominant hand) than patients without hypertension ($U = 306.0$, $p = .049$). Patients with atrial fibrillation ($n = 5$) performed significantly worse in the domains of processing speed (Symbols, $U = 46.0$, $p = .009$), visuospatial ability (Rey Figure copy, $U = 3.5$, $p = .034$) and motor speed (non-dominant hand, $U = 53.5$, $p = .021$). Patients with hypercholesterolemia ($n = 48$) performed significantly better than patients without hypercholesterolemia in verbal and visual episodic memory (Words Rey learning, $U = 329.0$, $p = .041$; Words Rey late recall, $U = 277.0$, $p = .006$; Rey Figure late recall, $U = 82.0$, $p = .025$). With regard to the risk factors diabetes mellitus, coronary artery disease, thrombophilia and smoking, groups did not differ in any cognitive domain. There was a significant negative correlation between the number of risk factors and motor speed (dominant hand $r = -.34$, $p = .007$; non-dominant hand $r = -.42$, $p = .001$).

Cognitive performance was controlled for additional influencing variables. In symptomatic patients, a longer time interval between stroke or TIA and neuropsychological assessment was correlated with faster processing speed (Symbols: $r = .48$, $p = .031$). Patients with a higher education level showed better interference control (Stroop Interference $H(2) = 7.5$, $p = .023$ and better verbal fluency $H(2) = 11.1$, $p = .004$). Women performed significantly better than men in visual learning (Signs learning, $U = 38$, $p = .034$), visual recognition (Signs recognition, $U = 40.0$, $p = .034$), visual recognition (Signs recognition, $U = 40.0$, $p = .034$).

Table 4: Significant differences between observed and expected cognitive impairments.

Neuropsychological test		N° of patients with impairment	N° of subjects expected to show impairment [#]	Chi-Square (χ^2)	p	
<i>Executive functions</i>						
Processing Speed	Stroop naming	21	10	14.3	<.001	***†
	Stroop reading	11	10	0.1	.731	
	Symbols	18	11	5.3	.021	*
	TMT A time	2	11	8.8	.003	** ‡
Interference Control	Stroop interference	22	10	17.0	<.001	***†
Shifting	TMT B time	15	10	3.0	.084	
<i>Language</i>						
Word production	Boston naming	18	11	5.3	.021	*
Verbal fluency	Animal naming	7	11	1.7	.188	
<i>Verbal Memory</i>						
Episodic memory	Word rey learning	21	11	10.8	.001	**
	Word rey recognition	7	11	1.7	.188	
	Word rey late recall	16	11	2.7	.100	
Short term memory	Digit span	15	11	1.7	.188	
<i>Visual Memory</i>						
Episodic memory	Signs learning	10	5	6.0	.014	*
	Signs recognition	3	5	1.0	.327	
	Signs late recall	10	5	6.0	.014	*
	Rey figure copy	18	6	28.0	<.001	***†
	Rey figure immediate recall	6	6	0.0	1.000	
	Rey figure late recall	11	6	5.0	.025	*
<i>Emotional State</i>						
Anxiety	HADS	17	11	3.9	.048	*
Depression	HADS	4	11	5.3	.021	*‡
Motor Speed	PPD dominant hand	24	10	23.3	<.001	***†
	PPD non-dominant hand	21	10	14.4	<.001	***†

Note: * $p < .05$, ** $p < .01$, *** $p < .001$: significantly worse than expected in a normative sample; [#] according to the test manual; † p remains significant after Bonferroni correction; ‡ significantly better than expected in a normative sample; observed cognitive impairment ≤ -1 SD; TMT A: Trail making test Part A; TMT B: Trail making test Part B; PPD: Purdue Pegboard; HADS: Hospital Anxiety and Depression Scale

= .030) and visual recall (Signs recall, $U = 38.5$, $p = .037$). Handedness was related to cognitive performance with ambidextrous patients showing best performance in interference control (Stroop interference: $H(2) = 6.7$, $p = .033$), word production (Boston Naming: $H(2) = 8.2$, $p = .016$) and processing speed (TMT A: $H(2) = 7.0$, $p = .031$).

Discussion

The present study presents evidence that patients with CAS of $\geq 70\%$ may be at higher risk for cognitive impairment in some executive domains, word production, verbal and visual memory and motor speed. Surprisingly, processing speed was less often impaired in patients with CAS. Anxiety was increased more often than expected in a normative sample. Bilateral and symptomatic stenosis was related to slower processing speed but the degree of stenosis did not influence cognitive performance and anxiety level.

Our detailed cognitive results show that in case of CAS, complex higher-order cognitive functions such as processing speed and interference control are likely to decline first, since these require a large amount of cognitive capacity. The findings of our study are in agreement with earlier reports (using some of the same neuropsychological tests as the present study), in which deficits in executive functions, verbal and visual memory, and visuospatial tasks were detected in both symptomatic and asymptomatic patients be-

fore carotid endarterectomy [19]. In routine neurological practice, assessment of frontal lobe functions is lacking, since higher order executive functions are not included in the commonly used mini mental state examination [20]. Hence, impairment of executive functions is likely to be missed.

Our data as well as that in previous studies [21] suggest that cognition and emotion are intertwined. We detected a low positive correlation between executive functions (processing speed, verbal fluency) and the degree of anxiety and depression. Considering the low correlation coefficients, data has to be interpreted with caution. Still, low executive performance may relate to an increased risk for emotional disturbances. Despite the link between cognition and emotion, the emotional state is rarely assessed in patients with carotid artery disease. The increased anxiety of our patients sample may occur due to fearfulness about the treatment procedure or concern regarding their general health status. After treatment of CAS with revascularisation techniques, the emotional state is likely to improve (see [22]). We present evidence of the importance of evaluating not only cognitive functions but also the emotional state when screening patients with CAS in order to adequately prepare them for the coming treatment procedure and discussing concerns and worries.

According to our study results, cognitive performance is impaired independent of the degree of stenosis. However,

Supplementary Table: Mean Rank scores across all neuropsychological tests.												
Neuropsychological test		Degree of stenosis				Condition			Side			
		>70%	near occl	total occl	p	sympt	asympt	p	right	left	bilat	p
		n = 40	n = 12	n = 16		n = 23	n = 45		n = 29	n = 27	n = 12	
<i>Executive Functions</i>												
Processing Speed	Stroop naming	34.5	30.5	33.5	.818	30.3	35.2	.313	38.6	31.4	26.0	.126
	Stroop reading	35.0	32.5	30.7	.735	34.5	32.9	.649	40.0	30.7	24.3	.036*
	Symbols	34.9	31.5	33.5	.869	30.1	36.1	.232	34.8	35.1	29.7	.693
	TMT A time	34.1	32.9	37.0	.975	27.0	37.4	.040*	34.2	35.5	30.1	.725
Interference Control	Stroop interference	34.9	24.0	37.3	.150	30.4	35.2	.337	35.6	32.7	30.1	.676
Shifting	TMT B time	31.6	31.6	31.2	.998	27.6	33.4	.240	30.9	36.7	21.6	.070
<i>Language</i>												
Word production	Boston naming	32.6	37.5	36.9	.639	31.7	35.9	.395	38.0	33.2	29.0	.367
Verbal fluency	Animal naming	35.4	31.6	34.6	.845	28.7	37.5	.083	34.7	34.9	32.9	.954
<i>Verbal Memory</i>												
Episodic memory	Word rey learning	33.2	41.1	32.9	.436	34.7	34.4	.958	37.6	34.7	26.5	.255
	Word rey recognition	33.6	44.8	29.0	.082	36.9	33.3	.447	37.3	35.6	25.5	.177
	Word rey late recall	33.0	40.2	33.9	.532	37.7	32.9	.335	39.4	32.6	27.4	.149
Short term memory	Digit span	34.9	31.9	35.6	.872	36.4	33.5	.577	36.5	37.5	23.0	.083
<i>Visual Memory</i>												
Episodic memory	Signs learning	14.9	18.1	14.6	.751	16.7	15.07	.651	13.9	16.9	15.5	.670
	Signs recognition	15.0	17.6	14.9	.777	17.6	14.8	.397	15.9	14.6	19.5	.705
	Signs late recall	15.5	18.2	12.2	.524	17.6	14.8	.432	15.2	16.3	11.5	.758
	Rey figure copy	17.3	20.9	19.3	.722	19.4	17.9	.672	20.0	18.9	15.9	.631
	Rey figure immediate recall	19.8	18.2	16.5	.706	20.6	17.2	.339	20.7	19.2	14.5	.334
	Rey figure late recall	19.5	17.3	17.5	.847	19.1	18.1	.768	19.2	20.7	15.1	.438
<i>Emotional State</i>												
Anxiety	HADS	33.4	34.8	37.0	.829	29.7	37.0	.151	34.5	34.6	34.4	.999
Depression	HADS	37.2	27.2	33.2	.292	32.3	35.6	.516	35.2	33.9	34.2	.970
Motor Speed	PPD dominant hand	34.6	29.2	27.3	.373	25.2	35.4	.036*	33.5	34.4	23.8	.223
	PPD non-dominant hand	32.3	26.2	33.1	.590	26.9	33.9	.151	34.2	31.4	25.8	.403

Note: occl. = occlusion; sympt. = symptomatic; asympt = asymptomatic; bilat = bilateral; * $p < 0.05$ significant group differences (Kruskal-Wallis test); TMT A: Trail making test Part A; TMT B: Trail making test Part B; PPD: Purdue Pegboard; HADS: Hospital Anxiety and Depression Scale

the small sample size of the subgroups asks for caution when interpreting these results. Nevertheless, in line with our results, a previous study found no association between the intima-media thickness of the common artery and cognition, even when adjusting for vascular risk factors [5]. These data suggest that the intima-media thickness is more likely to be a marker for underlying risk factors and generalised atherosclerosis than a direct cause of cognitive impairment.

Impairment of left-hemisphere functions such as language is expected to occur more often in patients with left-hemisphere stenosis while impairment of visuospatial abilities relates to right-hemisphere stenosis [6, 11]. In our study, no such association was observed, as was also shown in some older studies [23, 24]. A possible explanation for the missing structure-to-function relationship is the presence of efficient collateral blood supply, allowing for good cognitive functions even in brain regions with reduced blood flow. However, despite the small sample size of the subgroups, the present study suggests no influence of the presence of collateral blood supply on cognitive performance. Hence, the CAS might be a marker for vascular disease and its risk factors, and therefore not be directly associated with cognitive performance itself.

Our results indicate that the absence of neurological events does not guarantee normal cognitive performance in patients with CAS. Also in previous studies including asymptomatic patients with CAS [4, 25], significantly lower attention, processing speed, learning, reasoning, memory and motor functions was reported independent of the presence of brain lesions. Cognitive impairment in asymptomatic patients may be a marker for an increased risk for stroke [26] and for progression to dementia [27], institutionalisation and mortality [28]. Many asymptomatic patients with CAS are therefore not truly 'normal' from a neuropsychological point of view.

Cerebrovascular risk factors were related to worse cognitive performance in our study. Interestingly, hypercholesterolemia was associated with better verbal and visual episodic memory. We suggest that it is not the risk factor of hypercholesterolemia *per se* that influences episodic memory, but rather the pharmaceutical treatment of this risk factor. Statins are often given to treat hypercholesterolemia (in 87% of our sample). A possible positive effect of statins on episodic memory was previously suggested in a study of 37 elderly patients, all treated with statins for >15 years [29]. Patients receiving long-term statin therapy exhibited better verbal episodic memory than controls, and this association became even more pronounced with longer statin therapy. Our study results support the potential positive effect of statins on verbal and visual episodic memory.

Mechanisms underlying cognitive impairment in patients with CAS remain uncertain. Carotid stenosis may act as a marker of intracerebral atherosclerosis leading to micro-circulatory disturbances that are likely to influence cognitive performance. Small-vessel disease and lacunar infarctions arising from silent micro-embolism (which has been noted with carotid stenosis of >70%) affecting subcortical structures and deep white matter is additionally suggested to have an impact on cognitive performance. Silent infarctions are detected in 15 to 19% of patients with asymptomatic

stenosis [30]. Spontaneous cerebral emboli are associated with a decline of cognitive performance in patients with dementia [31] and may have influenced cognitive performance in our patients. In patients with CAS, atrophy of the corpus callosum is suggested to be associated with cognitive impairment and with changes in haemodynamic features [1]. Cortical disconnection may be an important factor in the development of cognitive impairment in patients without large cortical lesions.

When interpreting the present findings, one has to consider that our results are based on a heterogeneous group of patients with carotid artery stenosis which increases the generalisability of results. However, only patients with enough time for a neuropsychological assessment before treating the CAS were included. Hence, there might be a bias towards less severe cases of patients with CAS.

Among the limitations of the study is the likelihood of bias of study results due to multiple comparisons. Since some neuropsychological tests are inter-related, they may influence one-another (i.e. intercorrelation between different tests of executive functions such as processing speed measured with the TMT and motor speed). This is why the Bonferroni correction has to be critically questioned and is referred to in table 4. The degree of stenosis was not directly associated with cognitive performance level in our study. The variable 'degree of stenosis' was used as a categorical variable, divided in three categories, resulting in small sample size per category. Treating the variable as a continuous variable and correlating it with continuous cognitive performance scores might reveal different results. In this prospective study, we only included patients with enough time for a neuropsychological assessment before intervention; hence there might be a bias in patient selection.

Our results point towards a generally high sensitivity of standardised cognitive assessment tools – possibly higher than that of cerebral MR imaging – for detecting early signs of atherosclerosis. Since the blood supply to the brain is thought to be associated with cognitive functioning it would be interesting to quantify the blood supply by means of positron emission tomography (PET), dynamic susceptibility-weighted contrast-enhanced perfusion MR or even more specifically, arterial spin labelling, and to compare these data with cognitive functioning in a future study.

Recently it was proposed that treatment with transcervical carotid artery stenting with flow reversal leads to a significant increase in cognition, regardless of baseline risk factors (e.g. hypertension, diabetes mellitus, dyslipidemia). The increase was particularly evident in processing speed, language, memory, and visuospatial functions [3]. Other studies have not been able to draw a clear conclusion regarding the impact of interventions such as carotid endarterectomy [32] or carotid artery stenting [33] upon cognition. Since our data present no direct link between the degree of carotid stenosis or the presence of collaterals and cognitive impairment, it remains to be determined in a future study how carotid interventions such as revascularisation (i.e. stenting or endarterectomy) change neuropsychological performance levels. The present study contributes to more detailed knowledge about the cognitive and emotion-

al state of patients with carotid artery disease and may improve counselling, interpretation of symptoms and taking care of these patients.

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References

- 1 Yamauchi H, Fukuyama H, Nagahama Y, Katsumi Y, Dong Y, Konishi J, et al. Atrophy of the corpus callosum associated with cognitive impairment and widespread cortical hypometabolism in carotid artery occlusive disease. *Arch Neurol*. 1996;53(11):1103–9. PubMed PMID: 8912483.
- 2 Rao R. The role of carotid stenosis in vascular cognitive impairment. *Eur Neurol*. 2001;46(2):63–9. doi: 50765. PubMed PMID: 11528153.
- 3 Ortega G, Alvarez B, Quintana M, Ribo M, Matas M, Alvarez-Sabin J. Cognitive improvement in patients with severe carotid artery stenosis after transcervical stenting with protective flow reversal. *Cerebrovasc Dis*. 2013;35(2):124–30. doi: 10.1159/000346102. PubMed PMID: 23406878.
- 4 Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bonna KH. Reduced neuropsychological test performance in asymptomatic carotid stenosis: The Tromso Study. *Neurology*. 2004;62(5):695–701. PubMed PMID: 15007116.
- 5 Johnston SC, O'Meara ES, Manolio TA, Lefkowitz D, O'Leary DH, Goldstein S, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. *Ann Intern Med*. 2004;140(4):237–47. PubMed PMID: 14970146.
- 6 Landgraff NC, Whitney SL, Rubinstein EN, Yonas H. Cognitive and physical performance in patients with asymptomatic carotid artery disease. *J Neurol*. 2010;257(6):982–91. doi: 10.1007/s00415-009-5449-z. PubMed PMID: 20099067.
- 7 Iddon JL, Sahakian BJ, Kirkpatrick PJ. Uncomplicated carotid endarterectomy is not associated with neuropsychological impairment. *Pharmacol Biochem Behav*. 1997;56(4):781–7. PubMed PMID: 9130305.
- 8 Bakker FC, Klijn CJ, Jennekens-Schinkel A, Kappelle LJ. Cognitive disorders in patients with occlusive disease of the carotid artery: a systematic review of the literature. *J Neurol*. 2000;247(9):669–76. PubMed PMID: 11081804.
- 9 Spencer MP, Reid JM. Quantitation of carotid stenosis with continuous-wave (C-W) Doppler ultrasound. *Stroke; a journal of cerebral circulation*. 1979;10(3):326–30. PubMed PMID: 462521.
- 10 Alexandrov AV. The Spencer's Curve: clinical implications of a classic hemodynamic model. *J Neuroimaging*. 2007;17(1):6–10. doi: 10.1111/j.1552-6569.2006.00083.x. PubMed PMID: 17238866.
- 11 Silvestrini M, Paolino I, Vernieri F, Pedone C, Baruffaldi R, Gobbi B, et al. Cerebral hemodynamics and cognitive performance in patients with asymptomatic carotid stenosis. *Neurology*. 2009;72(12):1062–8. doi: 10.1212/01.wnl.0000345015.35520.52. PubMed PMID: 19307539.
- 12 Rockwood K, Eby E, Hachinski V, Hogan D. Presence and treatment of vascular risk factors in patients with vascular cognitive impairment. *Arch Neurol*. 1997;54(1):33–9. PubMed PMID: 9006411.
- 13 Altinbas A, van Zandvoort MJ, van den Berg E, Jongen LM, Algra A, Moll FL, et al. Cognition after carotid endarterectomy or stenting: a randomized comparison. *Neurology*. 2011;77(11):1084–90. Epub 2011/09/02. doi: 10.1212/WNL.0b013e31822e55b9. PubMed PMID: 21880992.
- 14 Cohen J. A power primer. *Psychological bulletin*. 1992;112(1):155–9. Epub 1992/07/01. PubMed PMID: 19565683.
- 15 Staikov IN, Arnold M, Mattle HP, Remonda L, Sturzenegger M, Baumgartner RW, et al. Comparison of the ECST, CC, and NASCET grading methods and ultrasound for assessing carotid stenosis. European Carotid Surgery Trial. North American Symptomatic Carotid Endarterectomy Trial. *J Neurol*. 2000;247(9):681–6. PubMed PMID: 11081806.
- 16 Ryan DJ, Byrne S, Dunne R, Harmon M, Harbison J. White matter disease and an incomplete circle of Willis. *Int J Stroke*. 2013. doi: 10.1111/ijls.12042. PubMed PMID: 23521864.
- 17 Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971;9(1):97–113. PubMed PMID: 5146491.
- 18 Salmaso D, Longoni AM. Hand preference in an Italian sample. *Percept Mot Skills*. 1983;57(3 Pt 2):1039–42. PubMed PMID: 6664783.
- 19 Bossema ER, Brand N, Moll FL, Ackerstaff RG, de Haan EH, van Doornen LJ. Cognitive functions in carotid artery disease before endarterectomy. *J Clin Exp Neuropsychol*. 2006;28(3):357–69. doi: 10.1080/13803390590935318. PubMed PMID: 16618625.
- 20 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–98. PubMed PMID: 1202204.
- 21 Brosch T, Scherer KR, Grandjean D, Sander D. The impact of emotion on perception, attention, memory, and decision-making. *Swiss medical weekly*. 2013;143:w13786. Epub 2013/06/07. doi: 10.4414/smww.2013.13786. PubMed PMID: 23740562.
- 22 Berman L, Pietrzak RH, Mayes L. Neurocognitive changes after carotid revascularization: a review of the current literature. *J Psychosom Res*. 2007;63(6):599–612. doi: 10.1016/j.jpsychores.2007.06.009. PubMed PMID: 18061750.
- 23 Boeke S. The effect of carotid endarterectomy on mental functioning. *Clin Neurol Neurosurg*. 1981;83(4):209–17. PubMed PMID: 6276069.
- 24 Hemmingsen R, Mejsholm B, Vorstrup S, Lester J, Engell HC, Boysen G. Carotid surgery, cognitive function, and cerebral blood flow in patients with transient ischemic attacks. *Ann Neurol*. 1986;20(1):13–9. doi: 10.1002/ana.410200104. PubMed PMID: 3527038.
- 25 Benke T, Neussl D, Aichner F. Neuropsychological deficits in asymptomatic carotid artery stenosis. *Acta Neurol Scand*. 1991;83(6):378–81. PubMed PMID: 1887760.
- 26 Ferrucci L, Guralnik JM, Salive ME, Pahor M, Corti MC, Baroni A, et al. Cognitive impairment and risk of stroke in the older population. *J Am Geriatr Soc*. 1996;44(3):237–41. PubMed PMID: 8600190.
- 27 Desmond DW, Moroney JT, Sano M, Stern Y. Incidence of dementia after ischemic stroke: results of a longitudinal study. *Stroke; a journal of cerebral circulation*. 2002;33(9):2254–60. PubMed PMID: 12215596.
- 28 Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. *Neurology*. 2000;54(2):447–51. PubMed PMID: 10668712.
- 29 Hyttinen L, TuulioHenriksson A, Vuorio AF, Kuosmanen N, Harkanen T, Koskinen S, et al. Long-term statin therapy is associated with better episodic memory in aged familial hypercholesterolemia patients in comparison with population controls. *Journal of Alzheimer's disease: JAD*. 2010;21(2):611–7. doi: 10.3233/JAD-2010-091381. PubMed PMID: 20571223.
- 30 Brott T, Tomsick T, Feinberg W, Johnson C, Biller J, Broderick J, et al. Baseline silent cerebral infarction in the Asymptomatic Carotid Atherosclerosis Study. *Stroke; a journal of cerebral circulation*. 1994;25(6):1122–9. PubMed PMID: 8202968.
- 31 Purandare N, Voshaar RC, Morris J, Byrne JE, Wren J, Heller RF, et al. Asymptomatic spontaneous cerebral emboli predict cognitive and functional decline in dementia. *Biol Psychiatry*. 2007;62(4):339–44. doi: 10.1016/j.biopsych.2006.12.010. PubMed PMID: 17531959.
- 32 Lunn S, Crawley F, Harrison MJ, Brown MM, Newman SP. Impact of carotid endarterectomy upon cognitive functioning. A systematic re-

- view of the literature. *Cerebrovasc Dis.* 1999;9(2):74–81. doi: 15901. PubMed PMID: 9973649.
- 33 Feliziani FT, Polidori MC, De Rango P, Mangialasche F, Monastero R, Ercolani S, et al. Cognitive performance in elderly patients undergoing carotid endarterectomy or carotid artery stenting: a twelve-month follow-up study. *Cerebrovasc Dis.* 2010;30(3):244–51. doi: 10.1159/000319066. PubMed PMID: 20664257.
- 34 Delis DC, Kaplan JH. *Delis-Kaplan Executive Function System.* San Antonio, TX: The Psychological Corporation; 2001.
- 35 von Aster M NA, Horn, R. Wechsler Intelligenztest für Erwachsene WIE. Übersetzung und Adaption der WAIS-III von David Wechsler [German adaption of the WAIS-III]. Pearson Assessment. Frankfurt, Germany; 2006.
- 36 CERAD-Plus Memory Clinic, University hospital Basel. 2009. <http://www.memoryclinic.ch/content/view/37/47/>
- 37 Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol.* 1999;14(2):167–77. PubMed PMID: 14590600.
- 38 Helmstaedter C LM, Lux S. VLMT Verbaler Lern- und Merkfähigkeitstest [Verbal learning and attention test]. Belz Test GmbH, Göttingen; 2001.
- 39 Rey A. *L'examen clinique en psychologie* [The clinical examination of psychology]: Press Universitaire de France. Paris, France; 1964.
- 40 Rey A. *Manuel du test de copie d'une figure complexe de A. Rey* [Manual for testing copying of the Rey Figure]. Centre de Psychologie Appliquée. Paris, France; 1959.
- 41 Meyers J MK. *Rey complex figure test and recognition trial: Professional manual.* PAR, Inc.; 1995.
- 42 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361–70. PubMed PMID: 6880820.
- 43 Hinz A, Schwarz R. [Anxiety and depression in the general population: normal values in the Hospital Anxiety and Depression Scale]. *Psychother Psychosom Med Psychol.* 2001;51(5):193–200. doi: 10.1055/s-2001-13279. PubMed PMID: 11417357.
- 44 Strauss E, Sherman EMS, Spreen O, Spreen O. *A compendium of neuropsychological tests: administration, norms, and commentary.* 3rd ed. Oxford; New York: Oxford University Press; 2006. xvii, 1216 p. p