Baseline Vascular Cognitive Impairment Predicts the Course of Apathetic Symptoms After Stroke: The CASPER Study

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Objective: *To examine the influence of vascular cognitive impairment (VCI) on the course of poststroke depression (PSD) and poststroke apathy (PSA).* **Methods:** *Included were 250 stroke patients who underwent neuropsychological and neuropsychiatric assessment 3 months after stroke (baseline) and at a 6- and 12-month follow-up after baseline. Linear mixed models tested the influence of VCI in at least one cognitive domain (any VCI) or multidomain VCI (VCI in multiple cognitive domains) at baseline and domain-specific VCI at baseline on levels of depression and apathy over time, with random effects for intercept and slope.* **Results:** *Almost half of the patients showed any VCI at baseline, and any VCI was associated with increasing apathy levels from baseline to the 12-month follow-up. Patients with multidomain VCI had higher apathy scores at the 6- and 12-month follow-up compared with patients with VCI in a single cognitive domain. Domain-specific analyses showed that impaired executive function and slowed information processing speed went together with increasing apathy levels from baseline to 6- and 12-month follow-up. None of the cognitive variables predicted the course of depressive symptoms.* **Conclusion:** *Baseline VCI is associated with increasing apathy levels from baseline to the chronic stroke phase, whereas no association was found between baseline VCI and the course of depressive symptoms. Health professionals should be aware that apathy might be absent early after stroke but may evolve over time in patients with VCI.* (Am J Geriatr Psychiatry 2018; 26:291–300)

Key Words: Stroke, depression, apathy, vascular cognitive impairment

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Highlights

- Previous studies have shown associations between global VCI and affective symptoms. In addition, we studied the influence of domain-specific VCI on poststroke depression and apathy.
- VCI in at least one cognitive domain is associated with increasing apathy levels from 3 to 15 months after stroke.
- VCI in multiple cognitive domains is associated with higher levels of apathy in the chronic stroke phase compared with VCI in a single domain.
- Health professionals should be aware that symptoms of apathy might be absent early after stroke but evolve over time in patients with VCI.

INTRODUCTION

Apathy and depression are frequent neuropsychiatric symptoms after stroke, with prevalences ranging from 28% to 40%,[1,2] and both are associated with poor quality of life[3,4] and long-term prognosis.[5] Cross-sectional studies have indicated that vascular cognitive impairment (VCI) is associated with poststroke depression (PSD),[6] and according to longitudinal studies VCI also predicts long-term depressive symptoms.[7–10] VCI is frequent after stroke, ranging from mild cognitive impairment to dementia, and is highly age-related, with an overall prevalence of 22% up to 15 years after stroke.[11]

Many studies that have examined the association between VCI and PSD were cross-sectional and classified cognitive impairment based on a screening instrument for global cognition.[8,12] Only few studies have assessed different cognitive domains.[13,14] According to a systematic review, including five cross-sectional studies and one prospective study with assessments of multiple cognitive domains, impairments in the domains executive function, memory, language, and processing speed were associated with depression 3 months after stroke.[15] In a 6-month follow-up study patients with visual memory disorders, neglect, and language impairment were at risk to develop depressive symptoms.[7] One important limitation was that these studies did not consider the role of other neuropsychiatric symptoms like apathy.

Poststroke apathy (PSA) is a disorder of diminished motivation that shows large overlap with PSD[16] and is associated with more severe cognitive impairment.[17,18] According to a meta-analysis of eight cross-sectional and two prospective studies,[1] PSA was associated with lower Mini-Mental State Examination (MMSE)[19] scores. Few studies examined the association between PSA and cognitive functioning with a more extensive neuropsychological assessment.[17,20]

Thus, previous studies indicate that both apathy and depression are associated with VCI, but prospective studies with domain-specific information on cognitive impairment are scarce. In addition to any VCI, insight into which specific cognitive domains are involved might be valuable as well, because domain-specific information on cognition has been shown to be a good predictor of other outcomes like long-term cognitive and functional impairment.[21,22] Therefore, the present study aimed to unravel the relations between VCI, domain-specific cognitive symptoms, PSD, and PSA after stroke by examining the influence of any VCI, degree of VCI, and domain-specific VCI on the course of PSD and PSA over a period of 12 months.

METHODS

Patient Population

The Cognition and Affect after Stroke: a Prospective Evaluation of Risks, or CASPER, study is a prospective clinical cohort study examining predictors of VCI, PSD, and PSA. The study was approved by the Medical Ethics Committee of Maastricht University Medical Center. Ischemic and hemorrhagic stroke patients who were admitted to the Stroke Unit of Maastricht University Medical Center or Zuyderland Medical Center (The Netherlands) were approached for participation between June 2013 and August 2015. Stroke was defined as a clinical stroke syndrome. Exclusion criteria were no written informed consent, insufficient knowledge of the Dutch language, age <40 years, too severe aphasia to understand the study procedure, an Informant Questionnaire on Cognitive

Decline in the Elderly (IQ-CODE)[23] score ≥3.60, MMSE[19] score <15, presence of neurologic or psychiatric diseases other than depression that are known to affect cognition, prestroke dementia, pre-existing cognitive impairment, mental retardation, blindness, history of stroke less than 3 years or residual symptoms from previous stroke, and postsurgery stroke/postanoxic encephalopathy (for details see Douven et al.).[24] Eligible patients were enrolled in the study after they signed informed consent.

At baseline (T0; approximately 3 months after stroke to avoid confounding effects caused by the acute stroke state), neuropsychological assessment and neuropsychiatric questionnaires were administered by a trained research (neuro)psychologist to the stroke patients according to a standardized protocol and were repeated at a 6-month (T1) and 12-month (T2) follow-up. In the present study only baseline data from the neuropsychological assessment were considered.

Neuropsychological and Neuropsychiatric Assessment

The MMSE was administered to assess global cognition. Specific neuropsychological tests were assessed covering three major cognitive domains: verbal memory, information processing speed, and executive function. The memory domain was measured with the Dutch adaptation of the Rey Verbal Learning Test (immediate and delayed recall).[25] Information processing speed was measured with the Trail-Making Test Part A[26] and the Digit Symbol Substitution Test, a subtest of the Wechsler Adult Intelligence Scale-III.[27] Executive function was measured with the Trail-Making Test Part B (mental flexibility)[26] and the 1-minute fluency test (animals and professions categories).[25] Test scores were converted to z scores, adjusted for age, sex, and highest level of education based on available norms.[27–30] Compound scores were calculated for each domain by averaging the z scores of the tests within this domain. For each cognitive domain patients were classified as no VCI (compound z score > –1.0) or VCI (compound z score ≤ –1.0), based on International Society for Vascular Behavioural and Cognitive Disorders criteria.[31] Patients with an impairment in at least one cognitive domain were classified as having any VCI. These patients were further divided into patients with an impairment in multiple cognitive domains (multidomain VCI) and in patients with an impairment in only a single cognitive domain (single-domain VCI).

The Montgomery-Åsberg Depression Rating Scale (MADRS),[32] which ranges from 0 to 60, was used as outcome measure of depressive symptoms, with a higher score representing a higher level of depressive symptoms. The MADRS was used because it is sensitive to change in symptom severity over time.[32] The Apathy Evaluation Scale (AES-C) was administered to evaluate the presence and severity of apathy.[33] Total scores range from 18 to 72, with a higher sum score representing a higher degree of apathy symptoms. The clinician-rated version was used because it has been rated as the most valid apathy instrument.[34] The IQ-CODE was administered to the informant of the stroke patient to detect possible prestroke dementia and was rated retrospectively (past 5 years before the index stroke).[23]

Statistical Analyses

Baseline differences were tested using χ^2 tests for qualitative variables and t tests for quantitative variables or Mann-Whitney U test if variables were not normally distributed. The influence of any VCI on the course of depression and apathy was assessed using linear mixed random-effects models, which account for the fact that repeated measurements are correlated within individuals. The models included a random intercept and random slope with an unstructured covariance structure because this resulted in the best fit according to likelihood ratio tests. A group (0 = no VCI, 1 = any VCI) by time (T0, T1, T2) interaction was added to study differences in rate of change between the groups.

In a second set of random-effects models we examined whether patients with multidomain VCI differed from patients with single-domain VCI. Next, analyses were performed to assess the influence of domain-specific VCI on the course of depression and apathy, using a group (0 = normal cognition, 1 = impaired cognition) by time (T0, T1, T2) interaction. The null hypothesis of no difference in rate of change over time between the groups was tested with a χ^2 test of homogeneity (two degrees of freedom) to see whether there was a significant group-by-time interaction. All analyses were corrected for age at baseline, sex, and highest level of education. Baseline apathy score was added to the model with depression as the outcome

measure to correct for a possible effect of comorbid apathy on depression, and vice versa.

All statistical analyses were performed with Stata version 13.1 for Mac OS X (StataCorp LP, College Station, TX). An alpha level of 0.05 (two-sided) was used for all analyses.

RESULTS

Of the 250 stroke patients initially included at baseline, 4 patients were excluded from the analyses (for 3 patients compound z scores were missing for all three cognitive domains and for 1 patient the performance on neuropsychological tests was considered unreliable because of mild aphasia). Of the 246 remaining patients, 212 (86%) completed T1. At T2, 13 patients dropped out (11 refused, 2 had died), and 19 patients who did not participate at T1 re-entered at T2, resulting in 218 patients (89%) completing T2 (see Supplementary Figure S1). Patients lost to follow-up were older and had any VCI more often than patients who completed all measurements (see Supplementary Table S1).

Patient characteristics of the remaining 246 patients included in the analyses are summarized in Table 1, separately for patients with (N = 113) and without any VCI (N = 133). Patients with any VCI were significantly less educated, had a lower MMSE score, had a higher IQ-CODE score, and had higher levels of depression and apathy at T0 compared with patients without VCI (Table 1). The frequencies of patients performing normal or impaired on the three cognitive domains and the average z scores on each domain separately are shown in Supplementary Table S2. Compound z scores for memory, information processing speed, and executive function were missing for four, one, and one patients at baseline, respectively, because they were cognitively or physically incapable to complete the tests. These patients were not excluded from the whole study but only from the particular domain-specific analysis.

Influence of Baseline Cognitive Impairment on the Course of Depression

The results for change in depression score over time according to baseline cognition are shown in Table 2.

TABLE 1. Baseline Characteristics of the Study Sample by VCI Status

Characteristics	Total Sample (N = 246)	No VCI (N = 133)	Any VCI (N = 113)	p	t/Mann-Whitney U or χ^2 (df)
Mean age, yr (SD)	67.6 (11.9)	66.3 (11.4)	69.1 (12.2)	0.063	−1.869 (244)
Male sex, N (%)	158 (64.2)	91 (68.4)	67 (59.3)	0.137	2.216 (1)
Education, N (%)					
Low education	102 (41.5)	42 (31.6)	60 (53.1)	<0.01	12.296 (2)
Middle education	86 (35.0)	52 (39.1)	34 (30.1)		
High education	58 (23.6)	39 (29.3)	19 (16.8)		
Mean time since stroke, mo (SD)	2.9 (0.5)	2.9 (0.4)	3.0 (0.5)	0.287	−1.068 (244)
First-ever stroke, N (%)	230 (93.5)	125 (94.0)	105 (92.9)	0.736	0.114 (1)
Ischemic stroke, N (%)	231 (93.9)	128 (96.2)	103 (91.2)	0.096	2.765 (1)
History of depression, N (%)	55 (22.4)	35 (26.3)	20 (17.7)	0.106	2.613 (1)
Family history of depression, N (%)	34 (13.9)	20 (15.2)	14 (12.4)	0.533	0.389 (1)
Mean MADRS score (SD)	6.1 (5.8)	5.3 (5.2)	7.0 (6.4)	0.036	−2.100[a]
Mean AES-C score (SD)	26.5 (8.0)	25.3 (7.8)	28.0 (8.0)	<0.01	−2.675 (244)
Mean IQ-CODE score (SD)	3.2 (0.3)	3.2 (0.2)	3.2 (0.4)	0.047	−1.984[a]
Mean MMSE score (SD)	28.2 (1.7)	28.8 (1.3)	27.4 (1.8)	<0.01	6.637[a]
VCI groups, N (%)					
Single-domain VCI	58 (24.2)	0 (0.0)	58 (54.2)	n.a.	n.a.
Multi-domain VCI	49 (20.4)	0 (0.0)	49 (45.8)	n.a.	n.a.
Impaired memory	47 (19.4)	0 (0.0)	47 (43.1)	n.a.	n.a.
Impaired information processing speed	78 (31.8)	0 (0.0)	78 (69.6)	n.a.	n.a.
Impaired executive function	56 (22.9)	0 (0.0)	56 (50.0)	n.a.	n.a.

Notes: Missing values: 8 for MADRS, 11 for IQ-CODE, 3 for MMSE, 1 for family history of depression, 6 for multidomain VCI, 4 for impaired memory, 1 for impaired information processing speed, and 1 for impaired executive function. Univariate analyses were performed with χ^2 test for categorical variables and Student's t test (or Mann Whitney U test if applicable) for continuous variables. SD: standard deviation.

[a]z Statistic from a Mann-Whitney U test.

TABLE 2. Mean Differences (and 95% Confidence Intervals) in Baseline Depression and Apathy Score and in Rate of Change (Slopes) from Baseline to Follow-Up Between Patients with and Without Impairment in Cognitive Functioning

	Time										
	Baseline			Change T0 – T1			Change T0 – T2				
Parameter	Difference	95% CI	p[a]	Change	95% CI	p[a]	Change	95% CI	p[a]	VCI by Time[b]	p
MADRS											
Any VCI	0.95	−0.34,2.24	0.149	0.50	−1.03,2.03	0.520	−1.21	−2.86,0.43	0.149	4.67	0.097
Multidomain VCI[c]	0.01	−1.91,1.93	0.994	0.28	−2.06,2.62	0.817	1.44	−1.11,3.98	0.268	1.36	0.508
Memory	0.50	−1.11,2.11	0.543	0.83	−1.18,2.83	0.418	0.47	−1.68,2.61	0.671	0.66	0.720
IPS	1.29	−0.13,2.72	0.075	0.22	−1.42,1.86	0.792	−1.49	−3.26,0.29	0.101	4.29	0.117
EF	0.49	−1.03,2.00	0.527	0.42	−1.41,2.25	0.655	−0.58	−2.61,1.44	0.574	1.03	0.597
AES-C											
Any VCI	1.14	−0.71,2.99	0.227	1.24	−0.55,3.03	0.175	2.34	0.23,4.44	0.030	4.76	0.092
Multidomain VCI[c]	2.55	−0.19,5.29	0.068	0.32	−2.41,3.05	0.817	1.89	−0.25,4.01	0.251	1.54	0.464
Memory	0.81	−1.49,3.11	0.489	1.00	−1.34,3.35	0.402	1.61	−1.13,4.35	0.249	1.39	0.499
IPS	2.22	0.19,4.26	0.032	0.39	−1.53,2.31	0.689	2.27	−0.00,4.55	0.050	4.53	0.104
EF	0.94	−1.23,3.10	0.397	1.44	−0.69,3.58	0.185	3.32	0.77,5.86	0.011	6.54	0.038

Notes: Results of random effects models adjusted for age at baseline, sex, and highest level of education. Analyses with MADRS score as outcome were additionally corrected for AES-C score, and vice versa. CI: confidence interval; EF: executive function; IPS: information processing speed.

[a]P-values are the result of χ^2-tests with df = 1.

[b]Overall interaction between cognition (normal, impaired) and time (baseline, 6-month follow-up, 12-month follow-up, as indicated by χ^2, df = 2).

[c]Compared with single-domain VCI.

The overall interaction between cognition group and time was not significant in any of the analyses (Table 2). Also, no differences in rate of decline of depressive symptoms were observed within individual time intervals (T0 to T1 or T0 to T2).

Any VCI

No significant difference in depression score was found between patients with and without any VCI at T0 or at follow-up (Table 2, Figure 1A). Of the patients who had available compound z scores on all three cognitive domains (N = 240), we compared patients with single-domain VCI (N = 58) with patients with multidomain VCI (N = 49). No significant difference in depression score was found between the two groups at T0 or at follow-up (Table 2, see Supplementary Figure S2).

Domain-Specific

At T0 no significant difference in depression score was found between patients with or without impairment in memory (Table 2, Figure 2A), information processing speed (Table 2, Figure 2B), or executive function (Table 2, Figure 2C).

Influence of Baseline Cognitive Performance on the Course of Apathy

The results for change in apathy score over time according to baseline cognition are shown in Table 2. The overall interaction between cognition group and time was not significant in any of the analyses, except for executive function (Table 2). In addition, group differences in rate of change between individual time-intervals were observed.

Any VCI

At T0 the difference in apathy scores between patients with and without any VCI was not significant (Table 2) but became significant at T1 (t(245) = 2.45, p = 0.015) and T2 (t(245) = 3.28, p = 0.001), with higher apathy levels in patients with any VCI (Figure 1B). In line with this, time-stratified analyses showed a significant increase in apathy scores from T0 to T2 in patients with any VCI ($\chi^2 = 4.74$, df = 1, p = 0.030). No significant difference in apathy score was found between patients with multidomain VCI and single-domain VCI at T0 (Table 2), but this group difference became significant at T1 (t(239) = 1.97, p = 0.049) and at T2 (t(239) = 2.76, p = 0.006), although time-stratified

FIGURE 1. **Effect of any VCI on the course of depression and apathy. [A] Course of depression scores by any VCI. [B] Course of apathy scores by any VCI. Based on random effects analysis with random intercept, random slope, and unstructured correlation matrix, adjusted for age at T0, sex, level of education, group, and group by time interaction. Analyses with MADRS score as outcome were additionally corrected for AES-C score, and vice versa. Predicted mean scores are estimated marginal means for cognition group by time, with all covariates fixed at their means. Error bars represent 95% confidence intervals around the predicted means. Higher mean scores indicate a higher level of depression and apathy, respectively.**

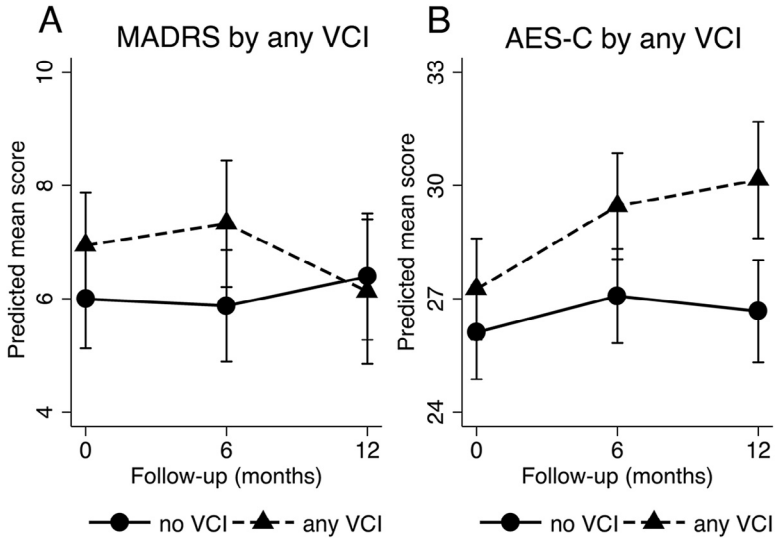


FIGURE 2. **Effect of baseline cognitive performance on the course of depression. [A] Course of depression scores by memory. [B] Course of depression scores by information processing speed. [C] Course of depression scores by executive function. Based on random effects analysis with random intercept, random slope, and unstructured correlation matrix, adjusted for age at T0, sex, level of education, group, and group by time interaction. Analyses were additionally corrected for AES-C score. Predicted mean scores are estimated marginal means for cognition group by time, with all covariates fixed at their means. Error bars represent 95% confidence intervals around the predicted means. Higher mean scores indicate a higher level of depression.**

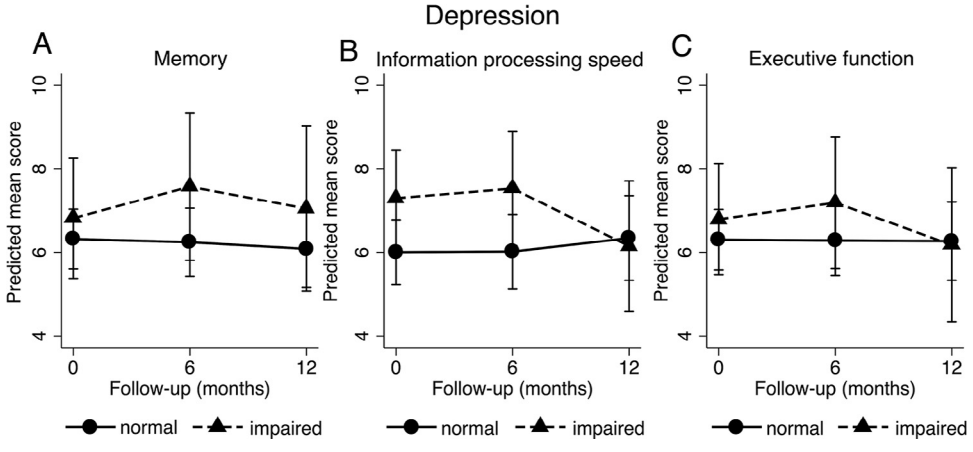
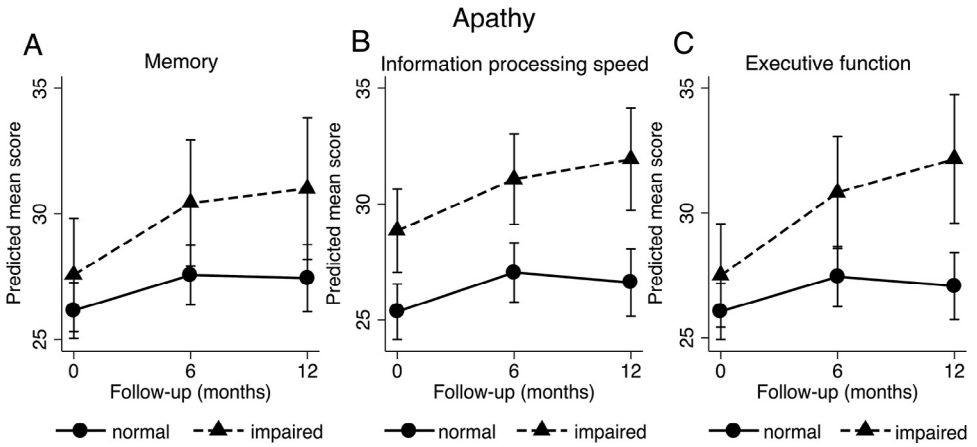


FIGURE 3. Effect of baseline cognitive performance on the course of apathy. [A] Course of apathy scores by memory. [B] Course of apathy scores by information processing speed. [C] Course of apathy scores by executive function. Based on random effects analysis with random intercept, random slope, and unstructured correlation matrix, adjusted for age at T0, sex, level of education, group, and group by time interaction. Analyses were additionally corrected for MADRS score. Predicted mean scores are estimated marginal means for cognition group by time, with all covariates fixed at their means. Error bars represent 95% confidence intervals around the predicted means. Higher mean scores indicate a higher level of apathy.



analyses did not reach significance for differences in rate of change from T0 to T2 (Table 2, see Supplementary Figure S2).

Domain-Specific

At T0 no difference in apathy score was found between patients with and without impaired memory performance (Figure 3A), and there were no significant differences in rate of change over time (Table 2). In contrast, a significantly higher apathy score was found in patients with impaired information processing speed at T0 ($\chi^2 = 4.57$, df = 1, $p = 0.033$; Figure 3B), which remained significant at T1 ($t(244) = 2.46$, $p = 0.015$) and T2 ($t(244) = 3.86$, $p < 0.001$). Impaired information processing speed at baseline was not associated with increasing apathy scores from T0 to T2 ($\chi^2 = 3.83$, df = 1, $p = 0.0504$). No significant difference in apathy score was found between patients with and without impaired performance on executive function at T0 (Table 2), but patients with impaired performance on executive function showed higher apathy levels at T1 ($t(244) = 2.08$, $p = 0.038$) and at T2 ($t(244) = 3.35$, $p = 0.001$; Figure 3C). Indeed, the overall interaction between executive function and time on apathy scores was significant, and comparison of the time-specific slopes suggested that this effect was driven by a significant increase in apathy scores from T0 to T2 in patients with impaired executive function (Table 2).

DISCUSSION

This study examined the association between baseline VCI and the course of PSD and PSA symptoms over time. The results show that the association between VCI and course of PSA symptoms varies across time points and with number and type of cognitive domains that are affected. Levels of apathy increased over time in patients with any VCI and even more when multiple cognitive domains were affected. Change was most pronounced in those with impaired executive functioning and impaired information processing speed. None of the cognitive variables predicted course of depressive symptoms.

The observed association between impaired executive functioning and apathy is in line with previous findings of Almenkerk et al.,[35] who showed that executive dysfunction was associated with apathy in the chronic stroke phase. However, the present study had a prospective design showing that apathy scores

increased from the postacute to the chronic stroke phase. In addition, the results of the present study are supported by a recent study of Roussel et al.,[36] who reported that half of the stroke patients suffered from a dysexecutive syndrome, including apathy, according to criteria by Godefroy et al.[37] Similar results were also found in a recent cross-sectional study with lacunar stroke patients, in which apathy, not depression, was associated with impaired executive function and also with impaired information processing speed.[38]

In the current study baseline impairment in information processing speed was associated with higher levels of apathy at baseline, which remained stable throughout time, which is in line with results from the Sydney Stroke Study,[17] which also found a significant association between apathy and reduced information processing speed after 3–6 months. However, they did not provide results on long-term follow-up. Because patients with impaired information processing speed already showed higher levels of PSA at baseline, it might be possible that symptoms of PSA have a negative effect on information processing speed as well or that apathy and impaired information processing speed are both the result of underlying brain pathology, although this had not been examined in earlier studies. No association was found between apathy and memory impairment. However, in patients with VCI, memory is usually less affected compared with impairment in "frontal functions" like slowed processing speed and executive dysfunction,[39] and apathy is also considered to be strongly related to frontal lobe dysfunction,[40] which might explain the lack of association.

The present results suggest that (any, multiple, or domain-specific) VCI is not associated with the level or course of PSD in the postacute or chronic stroke phase, which is in contrast with some earlier studies.[7,9] This discrepancy might be explained by the fact that cognitive impairment was determined in the acute stroke phase in these studies and also by differences in measurement instruments and criteria for defining cognitive impairment. However, the results of the present study are in agreement with a longitudinal study from Bour et al.[41] that looked into the 1-year course of PSD and also indicated that cognitive deficits at baseline did not predict the development of PSD in the first year after stroke, although this was only based on the MMSE score. The present results did not show an association between level or course of depression and impaired executive function at 3 months poststroke, which was in contrast with earlier studies indicating that depression and executive function are strongly linked after stroke.[13,14] Yet, a modest association was found between the course of apathy symptoms over time and executive function, so lack of adjustment for comorbid apathy in these earlier studies could be one explanation for this discrepancy.

The results of the present study support the hypothesis that PSA can develop as an independent syndrome[16] and may be associated with different risk factors than PSD, because in the present study VCI was only related to the course of apathy. An explanation could be that because apathy is a common behavioral symptom in patients with dementia, it might be more directly related to cognitive dysfunction[42] than depression, which may be more related to an initial psychological and emotional response to the stressful event of suffering from a stroke.[43] Neuropsychiatric symptoms after stroke might develop because patients have insufficient cognitive capabilities to cope with the consequences of the stroke, as a study with brain injury patients showed that depression and apathy were associated with different coping styles after brain injury.[44] VCI might possibly affect coping styles after stroke, thereby influencing the development of neuropsychiatric symptoms. Hence, being aware of the consequences of VCI in the postacute and chronic stroke phase, when patients are usually not engaged in rehabilitation care anymore, is important because not in the early stroke phase (0–3 months after stroke) but at a later stage (9–15 months), these patients are likely to develop symptoms of PSA. Professional caregivers should be aware of this, because PSA can have a negative impact on quality of life and clinical outcome after stroke. To get a better understanding of how cognitive deficits and neuropsychiatric symptoms affect each other, possibly in a bidirectional manner, the influence of apathy (and also depression) at baseline on long-term cognitive functioning should be studied in future studies as well.

Strengths of our study include the longitudinal design with serial assessments of cognition, depression, and apathy and with relatively low dropout. We used an extensive neuropsychological assessment covering several cognitive domains, and validated instruments were used to measure levels of depression and apathy. A limitation of the study is the

exclusion of patients with aphasia and other neurologic or psychiatric conditions because this made the study sample less representative of the general stroke population. In addition, of the eligible patients a substantial part refused to participate, and it is possible that particularly these patients may have had depressive or apathetic symptoms or cognitive complaints. Also, the frequency of any VCI was higher in the patients who dropped out compared with the patients who completed all assessments. Furthermore, it should be noted that there are many reasons for finding an association between VCI and PSA but not PSD. This could for example be due to differential reliability of the assessments, low prevalence of PSD, or low statistical power. Therefore, the results should be interpreted carefully. Finally, in some cognitive domains the impaired group was small in sample size, which could have resulted in lack of power in the random-effect models, thereby explaining the fact that we did find significant differences at certain time points but no significant interaction with time (except for any VCI and executive function). Thus, the present results showed relatively small but significant differences with respect to the course of apathy between patients with and without VCI after stroke. Nevertheless, these findings are of theoretical interest because they show that the impact of cognitive impairment on the development and course of PSA is likely to be different from PSD, which emphasizes the importance of distinguishing between symptoms of depression and apathy.

In conclusion, VCI was associated with increasing levels of apathy in the chronic stroke phase, which was strongest for impairments in executive function and information processing speed and for patients with impairments in multiple cognitive domains. Health professionals should be aware that neuropsychiatric symptoms, particularly apathy, might not be present in the early phase but evolve over time in patients with VCI.

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APPENDIX: SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at doi:10.1016/j.jagp.2017.09.022.

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