Long-Term Cognitive Impairment After First-Ever Ischemic Stroke in Young Adults

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Background and Purpose—Up to 14% of all ischemic strokes occur in young adults (<50 years). Poststroke cognitive performance is a decisive determinant of their quality of life. However, virtually no studies report on cognition after young stroke, especially not on the long term. This long-term perspective is important because young patients have a long life expectancy during which they start forming a family, have an active social life, and make decisive career moves. We aimed to evaluate the long-term cognitive outcome.

Methods—All consecutive patients between January 1, 1980, and November 1, 2010, with a first-ever young ischemic stroke were recruited for cognitive assessment, using a matched stroke-free population as a reference. Composite Z scores for 7 cognitive domains were calculated and the ANCOVA model was used (Bonferroni correction). A below average performance was defined as >1.0 SD below the age-adjusted mean of the controls and cognitive impairment as >1.5 SD.

Results—Two hundred seventy-seven patients and 146 matched controls completed cognitive assessment (mean follow-up, 11.0 years, SD, 8.2; age, 50.9 years, SD, 10.3). Long-term cognitive outcome after an ischemic stroke was worse in most cognitive domains compared with a nonstroke population. Up to 50% of the patients had a below average performance or cognitive impairment. Deficits in processing speed, working memory, and attention were most common.

Conclusions—Even 11 years after ischemic stroke in young adults, a substantial proportion of patients must cope with permanent cognitive deficits. These results have implications for information given to patients and rehabilitation services. (Stroke. 2013;44:1621-1628.)

Key Words: cognitive impairment ■ cohort study ■ stroke in young adults

Abstract

Approximately 10% to 14% of all ischemic strokes occur in young adults (aged 18–50 years).1–7 The incidence of stroke in young adults is rising, which is a major concern.8 Their outcome is usually considered fairly good because these patients usually have a good motor recovery,9,10 and outcome after stroke is usually assessed with rating scales that predominantly measure motor performance.11 However, poststroke outcome is also very much dependent on cognitive performance after stroke. Surprisingly, there are only a few studies that addressed cognitive outcome on the short term (4–12 months)12,13 and none on the long term. Although these short-term studies found somewhat lower cognitive performance in patients with ischemic stroke compared with controls, that may still very well be compatible with the common observation of gradual cognitive recovery, which may continue for ≥1 year after stroke.14,15

Because life expectancy of most of these patients exceeds by far 1 year,16 patients need to be informed about their cognitive prognosis, not only on the short term, but also particularly for the coming decades, as they are in a period of life in which they start forming a family, have an active social life, and make decisive career moves. It is exactly this long-term perspective that is currently missing. The aim of the present study was to investigate the long-term cognitive performance after a first-ever young ischemic stroke.

Study Design

This study is part of the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study a large cohort study which investigates causes and consequences of stroke in young adults.17 The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study and the recruitment of controls. The present study comprises all consecutive patients with a first-ever ischemic stroke of presumed arterial origin, aged 18 to 50 years, admitted to Radboud University Nijmegen Medical Center from January 1, 1980, to November 1, 2010. This hospital is a large academic center, receiving patients

Received January 11, 2013; final revision received March 1, 2013; accepted March 19, 2013.

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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.111.000792
from both the direct environment and serving as a tertiary referral center. Our hospital is the only academic medical center in our region.

Patients were identified through a prospective registry of all consecutive young ischemic stroke patients that has been kept at the department since the 1970s with a standardized collection of baseline, clinical characteristics, and neurological examination. Ischemic stroke was defined as focal neurological deficit persisting >24 hours. The diagnosis of ischemic stroke and lesion location was based on medical records and radiological findings.

The diagnostic techniques have been improved during a 30-year period and to minimize bias, all initial diagnoses were reviewed by a panel of 2 experts from a pool of 4 (F.-E.d.L., E.J.v.D., R.M.A., L.J.D.) and in cases of disagreement, a consensus meeting was held to adjudicate the event.

Primary exclusion criteria for patients with ischemic stroke in the FUTURE study were cerebral venous sinus thrombosis and retinal infarction. There were additional exclusion criteria for cognitive assessment on the basis of the neurological examination, which was also a part of the FUTURE study (Figure 1).

Controls were recruited among patients’ spouses, relatives, or social environment. They had to be aged ≥18 years without a history of transient ischemic attack or stroke. The control group and patient group were matched for age, sex, and level of education. Controls were all living independently, none fulfilled the clinical criteria of dementia. They were recruited from the same environment as patients.

Written informed consent was obtained from all participants.

Cognitive Assessment
Neuropsychological tests were administered between November 2009 and the end of 2011. They covered the main cognitive domains and these tests have been previously applied in large-scale epidemiological studies in cerebrovascular disease.18,19 Strict instruction protocols were used to assess cognitive performance and researchers were trained. The following cognitive domains were examined: processing speed (the written administration of the Symbol-Digit Modalities Test, Abbreviated Stroop Color Word Test, parts I and II), visuoconstruction (Rey–Osterrieth Complex Figure—copy trial), working memory (Paper and Pencil Memory Scanning Test), immediate memory (Rey–Osterrieth Complex Figure—immediate recall and the total number of words immediately recalled in the 3-trial version of the Rey Auditory Verbal Learning Test), delayed memory (delayed recall on the Rey–Osterrieth Complex Figure and the Rey Auditory Verbal Learning Test), attention (Verbal Series Attention Test), and executive functioning (Verbal Fluency and Stroop Interference). To account for speed-accuracy trade-off on the Stroop test, Paper and Pencil Memory Scanning Test, and Verbal Series Attention Test, composite scores were calculated [accuracy(%)/reaction time].20 Stroop Interference was computed by dividing the composite Stroop part III score by the mean of the composite scores of parts I and II. To prevent potential bias in scoring the Rey–Osterrieth Complex Figure, 2 researchers independently rated 10% of the complex figures in both patients and controls, with high inter-rater reliability using the Spearman correlation coefficients (Copy: \( r_s = 0.90 \); Immediate recall: \( r_s = 0.97 \); Delayed recall: \( r_s = 0.95 \)). Detailed information on the neuropsychological examination is described extensively elsewhere.17

Other Measurements
Age, sex, level of education, depressive symptoms, and fatigue were considered possible confounders. Level of education was scored with a Dutch scoring system (1=less than primary school; 7=university degree).21
<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Characteristics of the Study Population and Patients With Ischemic Stroke Who Refused Cognitive Assessment</th>
</tr>
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<tr>
<td><strong>Participants With Ischemic Stroke (n=277)</strong></td>
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</tr>
<tr>
<td>Men (%)</td>
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<tr>
<td>Follow-up duration</td>
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<tr>
<td>&lt;10 y (%)</td>
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<tr>
<td>≥10 y (%)</td>
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<tr>
<td>Lesion location</td>
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<tr>
<td>Supratentorial stroke (%)</td>
</tr>
<tr>
<td>Left (%)</td>
</tr>
<tr>
<td>Right (%)</td>
</tr>
<tr>
<td>Bilateral (%)</td>
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<tr>
<td>Infratentorial stroke (%)</td>
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<tr>
<td>Age at follow-up examination</td>
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<td>Education</td>
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<td>NIHSS score at admission</td>
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<tr>
<td>Barthel Index at follow-up</td>
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<tr>
<td>Good outcome (BI, ≥85) (%)</td>
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<tr>
<td>Modified Ranking Scale at follow-up</td>
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<tr>
<td>Good outcome (mRS, 0–1) (%)</td>
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<tr>
<td>Marital status at follow-up</td>
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<tr>
<td>Married (%)</td>
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<tr>
<td>Widowed (%)</td>
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<tr>
<td>Divorced (%)</td>
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<tr>
<td>Never married (%)</td>
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<tr>
<td>Employment status at follow-up*</td>
</tr>
<tr>
<td>Working (%)</td>
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<tr>
<td>Unemployed (%)</td>
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<tr>
<td>Retired (%)</td>
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<tr>
<td>MMSE at follow-up</td>
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<tr>
<td>HADS—depressive symptoms</td>
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<tr>
<td>TOAST</td>
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<tr>
<td>Large-artery atherosclerosis (%)</td>
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<tr>
<td>Cardiac source of embolism (%)</td>
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<tr>
<td>Small-vessel occlusion (lacune) (%)</td>
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<tr>
<td>Stroke of other determined pathogenesis (%)</td>
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<tr>
<td>Multiple pathogenesis (%)</td>
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<tr>
<td>Stroke of undetermined pathogenesis (%)</td>
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<tr>
<td>Vascular medical history</td>
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<tr>
<td>Myocardial infarction (%)</td>
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<tr>
<td>Recurrent stroke (%)</td>
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<tr>
<td>Vascular risk factors</td>
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<tr>
<td>Hypertension (%)</td>
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<tr>
<td>Diabetes mellitus (%)</td>
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<tr>
<td>Dyslipidemia (%)</td>
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<tr>
<td>BMI at follow-up (%)</td>
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</tbody>
</table>

(Continued)
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Participants With Ischemic Stroke (n=277)</th>
<th>Refusals† (n=138)</th>
<th>P Value‡</th>
<th>Controls (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current (%)</td>
<td>78 (28.2)</td>
<td>NA</td>
<td>...</td>
<td>38 (26.0)</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>129 (46.6)</td>
<td>NA</td>
<td>...</td>
<td>55 (37.7)</td>
</tr>
<tr>
<td>Never (%)</td>
<td>70 (25.3)</td>
<td>NA</td>
<td>...</td>
<td>53 (36.3)</td>
</tr>
<tr>
<td>Alcohol (&gt;2 U/d) (%)</td>
<td>19 (6.9)</td>
<td>NA</td>
<td>...</td>
<td>14 (9.6)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD), number (%), or median (Q1–Q3). Missing data in participants with ischemic stroke: lesion location=0.4%, education=1.1%, NIHSS at admission=0.7%, marital status=1.1%, employment status: 2.5%, MMSE=2.9%, HADS depression=1.1%, CIS-20R=1.1%, BMI=3.2%, alcohol=0.4%. Missing data in the controls: employment status=1.1%, BMI=1.4%, missing data in the refusals: NIHSS at admission=1.4%.

Bl indicates Barthel Index; CIS-20R, Checklist Individual Strength; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*The proportion of patients with ischemic stroke with baseline employment (n=231) and who were unemployed, still employed, or retired at follow-up. Controls: employment status at follow-up.
†Patients with ischemic stroke who refused to participate in the FUTURE study (n=96)+ patients who participated in the FUTURE study, but refused to visit the research center (n=42).
‡Comparisons between participants with ischemic stroke and those who refused cognitive assessment.
§Student t test.
‖Pearson χ² test.
#Mann–Whitney U test.

Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale, and fatigue was assessed using the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R). Marital status (married, divorced, widowed, and never married) at follow-up was reported. Employment status at follow-up was defined as the number of patients who worked/studied at the time of their event and were unemployed, still employed, or retired at follow-up assessment. Employment status of controls was defined as employed, unemployed, and retired at follow-up assessment. Functional outcome during follow-up visit was evaluated using the Barthel Index and modified Rankin Scale. A good functional outcome was defined as an modified Rankin Scale score of 0 to 1 and a Barthel Index of ≥85.

Furthermore, assessment of both the pathogenesis (Trial of Org 10172 in Acute Stroke Treatment) and severity (National Institutes of Health Stroke Scale) was performed retrospectively in all cases using a validated approach because these scales did not exist at the time when a substantial proportion of the patients experienced their qualifying event.

We assessed vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking [current/former/never], current alcohol use (>2 U/dl) and vascular disease (myocardial infarction and recurrent stroke) on the basis of medical history using a standardized, structured questionnaire, and the use of medication. Whenever a myocardial infarction or recurrent stroke was suspected, information retrieved was verified and adjudicated by physicians. The body mass index at follow-up was calculated as weight (kg) divided by height (m) squared.

### Statistical Analysis

Baseline characteristics were presented as means (±SD), median (Q1–Q3), or number of cases (%). All statistical analyses were performed with IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY). Baseline characteristics in young participants with ischemic stroke and patients with ischemic stroke who refused cognitive assessment were compared using a Pearson χ² test, Mann–Whitney U test, or Student t test when appropriate. To adjust for multiple comparisons in all analyses a Bonferroni correction was applied (P values <0.0071 were considered significant because there were 7 pairwise comparisons for each analysis).

The mean raw cognitive test scores (±SD) for each test were calculated. The Rey Complex Figure—Copy trial showed a left skewed distribution; therefore, this variable was transformed (e²) to obtain a normal distribution to use in all subsequent analyses. For the purpose of data reduction, across-domain comparison, and statistical considerations, raw test scores were converted to Z scores, using the mean and SD of the controls. Z scores of tests assigned to the same cognitive domain were averaged and were used in all subsequent analyses as composite Z score or domain score. If 1 test of a particular domain was missing, the domain score was occasionally based on the remaining tests of that domain (always<5.1%).

A 1-way ANCOVA model was used for each cognitive domain with a 2-level factor adjusting for age, sex, level of education, depressive symptoms, and fatigue severity. All P values reported were 2-sided and confidence intervals were calculated at the 95% confidence interval.

Linear regression was used to explore the effect of differences in follow-up duration and performance on cognitive domains adjusting for age, sex, level of education, depressive symptoms, and fatigue. Results were reported as standardized β coefficients.

### Below Average Performance and Cognitive Impairment

Because of the long-term follow-up, patients differed in age at follow-up cognitive assessment. Obviously, age has an influence on cognitive performance apart from stroke. To account for differences in age, age-adjusted Z scores for each neuropsychological test were calculated using the mean and SD of the controls in 3 different strata of age at follow-up: 20 to 40, 40 to 60, and 60 to 80 years. Next, Z scores of cognitive tests assigned to the same cognitive domain were averaged.
The frequency of a below average performance (>1.0 SD below age-adjusted mean of controls) and cognitive impairment (>1.5 SD) was determined.15

A Pearson χ² test (or Fisher exact test when an expected cell count was <5) was used to investigate differences between patients and controls in the proportion of participants with cognitive impairment.

Lesion Location and Cognitive Outcome

The frequency of cognitive impairment or a below average performance for each cognitive domain in patients with supratentorial infarction (left versus right) and infratentorial infarction was determined. The proportion of patients with cognitive impairments were compared with controls using a Pearson χ² test (or Fisher exact test when an expected cell count was <5).

Recurrent Stroke

All above described analyses were conducted including and excluding patients with a recurrent stroke to investigate whether patients with recurrent events influenced the results.

Results

The study population consisted of 277 participants with ischemic stroke and 146 controls (Figure 1). Basic demographic and clinical characteristics of the study population are described in Table 1 and neuropsychological test scores are presented in Table 2. Mean age of patients was 40.0 years (SD 7.7) at stroke onset; 55.6% was women. Mean follow-up of the study population was 11.0 years (SD 8.2), whereas 48.0% had a follow-up of ≥10 years. Participants did not significantly differ on basic demographic and clinical characteristics from patients with ischemic stroke who refused to participate or who did participate in the FUTURE study but did not want to visit the research center (Table 1).

Patients with ischemic stroke had a worse cognitive performance on 6 cognitive domains after a mean follow-up of 11 years compared with controls (processing speed: F(1,406)=35.4, \( P<0.0001 \); working memory: F(1,407)=41.7, \( P<0.0001 \); immediate memory: F(1,412)=14.0, \( P=0.0002 \); delayed memory: F(1,408)=17.7, \( P<0.0001 \); attention: F(1,396)=28.6, \( P<0.0001 \); executive functioning: F(1,409)=17.2, \( P<0.0001 \) (Figure 2).

Follow-up Duration

In patients with ischemic stroke longer follow-up duration was associated with a lower immediate memory (β=−0.23; \( P=0.001 \)), delayed memory (β=−0.30; \( P<0.0001 \)), and executive functioning score (β=−0.22; \( P=0.004 \)).

Below Average Performance and Cognitive Impairment

Patients with ischemic stroke showed a substantially higher proportion of patients with a below average performance (<1.5 SD composite Z score<−1 SD) or cognitive impairment (>1.5 SD) compared with controls (Figure 3A). Up to 50% of all patients with ischemic stroke had a below average performance or cognitive impairment. Cognitive impairments were frequent among patients, affecting ≤34.5%. Deficits in processing speed, working memory, and attention were most common.

Lesion Location and Cognitive Outcome

One patient could not be classified as supratentorial or infratentorial infarction (infarction in basal ganglia or brainstem). Seven patients with bilateral supratentorial infarction were excluded from the analysis because the number of patients was too small for further analyses. The results showed that patients with a left supratentorial infarction had the worst cognitive outcome, ≤45.5% of patients had cognitive impairments on the long term (Figure 3B).

Recurrent Stroke

After exclusion of patients with a recurrent stroke (n=30), there was no longer a significant negative relation between follow-up duration and executive functioning score in patients with ischemic stroke.

Discussion

This study showed that a substantial proportion of young patients with ischemic stroke after a mean follow-up of 11...
years showed a worse cognitive performance on a wide range of cognitive domains compared with a matched stroke-free population. Patients with a left supratentorial infarction had the worst cognitive outcome.

Strong elements of our study include a large sample size in a single center, with a high response rate. We used extensive neuropsychological testing rather than a short cognitive screen, and we included a representative control group as a reference for neuropsychological examination.

However, some methodological issues need to be addressed. First, the study was not community based, but hospital based and, therefore, our sample may not represent all young stroke survivors in our catchment area. However, we think that our population with stroke is representative to the wider Dutch population. Those who survive usually visit a university medical center during the course of their disease. Furthermore, the age and sex standardized prevalence of stroke in our region equals that of the age and sex standardized prevalence of stroke in the Netherlands. We, therefore, think that our cohort has a good external validity. This is also underlined by the fact that we included all consecutive cases admitted to our hospital.

Second, cognitive data of patients who refused to participate obviously were lacking, but their baseline characteristics did not differ from participants in the present study, making a selection bias unlikely.

Although we investigated a wide range of cognitive domains, agnosia or language comprehension were not included in our neuropsychological assessment. On the basis of the neurological examination, we considered the proportion of patients with these symptoms to be small and, therefore, we think that this has not largely influenced cognitive performance.

We found relatively low MMSE scores in both the patients and the controls, compared with others and healthy older adults. However, all controls lived independently and none fulfilled the clinical criteria for dementia. Furthermore, the diagnostic accuracy of the MMSE in detecting cognitive impairment is generally poor, especially outside the Alzheimer domain; hence, we think this finding is of little clinical relevance.

Longer follow-up, adjusted for age effects, was associated with a decrease in cognitive functioning in patients with ischemic stroke. Longer time interval might be associated with incident comorbidity that could in turn have negatively affected cognitive performance. Another explanation is that these patients are older and that, apart from the stroke, neurodegenerative pathology might have emerged that interacts with the cerebrovascular disease. A better understanding of this interaction is important as especially those with the longest follow-up are the oldest patients who might be at risk for further cognitive decline, because of this interaction of vascular lesions and neurodegenerative pathology.

Two studies have investigated cognitive performance in 24 and 40 young patients with ischemic stroke 4 to 12 months after stroke. Malm et al examined 24 patients with cerebellar infarcts and cognitive domains most affected were mental speed, cognitive flexibility, and working memory. We also found that an infratentorial infarction was associated with impairments in processing speed and working memory. Cao et al investigated 40 young patients with ischemic stroke and assessed other domains and found that language comprehension, reasoning, and verbal memory to be most affected. Processing speed was not assessed in these patients. Comparing our results with these 2 studies, we found similar deficits not only in verbal memory, working memory, and processing speed, but also in executive functioning and attention are common on the long term in patients with ischemic stroke. These 2 domains were not addressed in reported studies.

A substantial proportion ≤50% of young patients with ischemic stroke had below average cognitive performance or
impairment, despite the fact that the median of initial stroke severity was relatively mild. This highlights the influence of cerebrovascular lesions on cognitive performance, even decades after the stroke. It could also be that a severity rating scale, which includes predominantly motor signs (National Institutes of Health Stroke Scale), may underestimate the effect of stroke on other than motor symptoms. This would justify a basic careful neuropsychological examination of stroke patients in the (sub)acute phase of the disease.

Interestingly, a focal stroke on the long term seems to have a widespread impact on cognition, affecting multiple cognitive domains. Increasing evidence suggests that focal lesions can have a widespread, diffuse impact on brain network organization, which may explain the cognitive impairments attributable to dysfunction of the brain, remote from the site of the infarction.

The stroke in young adults seems to have a relatively better cognitive prognosis as compared with stroke in the elderly, as we found cognitive deficits in 20.4% to 34.8% of our young patients with ischemic stroke, whereas 31% to 77% was reported in elderly stroke survivors. This difference in cognitive prognosis is perhaps because of a better collateral blood supply with an attendant lower volume of the infarction, a more pronounced neuronal plasticity, and the absence of neurodegenerative pathology in younger adults.

Conclusions
In young patients with ischemic stroke, with in general a good motor recovery, long-term cognitive impairments are common. Given the importance of cognitive performance for poststroke quality of life, cognitive functioning should be monitored in clinical practice. This may also yield valuable information for treating rehabilitation services and return to work.

Acknowledgment
We thank all the patients, controls, and staff involved during execution of the research project.

Sources of Funding
This study was funded by the Dutch Epilepsy Fund (grant number 10–18).

Disclosures
None.
References


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Stroke. 2013;44:1621-1628; originally published online May 7, 2013;
doi: 10.1161/STROKEAHA.111.000792
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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The version of the article, “Long-Term Cognitive Impairment After First-Ever Ischemic Stroke in Young Adults” by Schaapsmeerders et al (Stroke. 2013;44:1621–1628) that published online ahead-of-print on May 7, 2013 contained an errors in Table 1 and Table 2.

Table 1 incorrectly indicated that all values in parentheses were percent values. Some of the variables were mean or median values, not percentages. A footnote to Table 1 was missing the number FUTURE study participants (n=96) this has been corrected to, read, “†Patients with ischemic stroke who refused to participate in the FUTURE study (n=96)+ patients who participated in the FUTURE study, but refused to visit the research center (n=42).

This has been corrected in the print and current online version of the article.

Table 2 had a typo in the legend stating that, “S, MP, DHN: Patients had to memorize the letters S, MP, DHN and find them among 20 distracting letters.” This has been corrected to S, MP, DHN: Patients had to memorize the letters S, MP, DHN and find them among 120 distracting letters.” This has been corrected in the print and current online version of the article.