General conclusions and discussion
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Limitations of this study

A number of limitations of this study need to be considered when interpreting the data. With respect to the selection of participating subjects a selection bias towards the less severe stroke patients may have occurred. The GPs might have spared the study from the most severe stroke patients by not submitting them for the study. Moreover, a substantial number of patients (32%) either refused, was too disabled to participate or died before first assessment. Between the first and second measurements 20 percent of the patients dropped out of the study. On average these patients represented the more severely disabled and older individuals.

Overall, the size of the patient group as well as the control group can be considered adequate, but the division in subgroups caused relatively small sample sizes. Although 300 GPs participated in the present study, it was also necessary to recruit patients admitted to the Stroke Unit (SU) from the University Hospital Groningen, in order to create a large enough patient group with sufficient statistical power. The criteria for unilateral, clinically first-ever, ischemic strokes, with no other psychiatric or neurological diseases were very strict and the number of patients that met these criteria was smaller than we anticipated. From the 235 patients that were submitted, 194 were sent in by their GP, and 41 were included by the SU (for details see chapter two).

With respect to the neuropsychological test data, missing data decreased the statistical power in some analyses. The missing data are the result of logistic problems or technical failure on one hand, or are caused by patients who refused to further co-operate after the first half of the neuropsychological assessment on the other hand. The patients who did not complete the test battery at T1 did not differ in age or education from those who did, but they scored significantly lower on the dementia-screening test (CST).

A CT scan was made in most patients within a few days after stroke in this study. Therefore not much detailed information about lesion site and volume was available. The main objectives of this study did not directly involve questions about lesion site and size. However, more detailed information about the lesion characteristics would have been very useful in explaining some of the results that were found.

Impact of stroke on cognition

The first main goal of this study was to examine the impact of a clinically first-ever unilateral ischemic stroke on cognitive functioning in a community-based patient group. It was clearly demonstrated that stroke can lead to impaired cognitive functioning in this patient group that receives little or no (para)medical care as these patients are generally expected to recover well. As is usually the case in patient groups, much variation between the individual patients was found.
Moreover, cognitive impairment did not affect memory functioning in the elder subjects of the study group or speed of information processing as much as we had expected based on earlier stroke studies (Hochstenbach, Mulder, Van Limbeek, Donders, & Schoonderwaldt, 1998, Tatemichi, et al., 1994). The most probable explanation for these different findings is twofold. First, the examined patient group was a relatively less affected group since the majority of these patients was community-based and not selected from a hospital or rehabilitation setting, like in most other studies. Moreover, selection bias at the level of the GPs may have occurred and stroke severity may have been related to refusal to participate. Second, it is likely that our control group performed not as well on the neuropsychological tests as the control subjects in other studies. Contrary to the recruitment of control subjects in most other (stroke) studies, enrolment of our control subjects and patients groups was based on the GP’s request. These patient groups were matched on age, gender and socio-economic region. As shown in chapter two, the two groups were comparable with respect to co-morbidity as well. Often, ‘normal’ control subjects are recruited by advertisements, thus attracting the more than average motivated volunteers.

**Speed of information processing**

In the present study mental slowness subjectively appeared to be the main cognitive change due to the stroke as experienced by the patients as well as their partners (for detailed information see dissertation A.C. Visser-Keizer, Chapter 3). One of the expectations at the start of this study involved the central role that speed of information processing would play on other cognitive domains and ultimately on stroke outcome at the level of daily life. These expectations were based on the literature pertaining to patients with closed head injury (Spikman, Van Zomeren, & Deelman, 1996; Van Zomeren & Deelman, 1976) and normal ageing (Salthouse, 1996). However, slowed speed of information processing did not appear to be a general factor in the stroke patients. To date, few research papers have been published that focussed on mental speed after stroke. Stroke studies that did involve mental speed usually did not use a reaction time paradigm that distinguished between movement times and decision times. For example, Hochstenbach and co-workers (1998) demonstrated that 70% of their stroke patients had slowed information processing capacities, but the tests they used were dependent on motor functions. In the present study basic slowness in decision time was confined to patients in the subacute phase with a lesion in the right hemisphere, and most pronounced in the contralesional decision times. The left hemispheric stroke patients were, like the right hemispheric stroke patients, slower than control subjects on the cognitively more demanding tasks for speed of information processing, but they showed no basic visuomotor slowness. This apparently specific right hemisphere deficit was discussed in terms of the theory postulated by Mesulam (2000). In this model it is suggested that the right
hemisphere is responsible for spatial attention in both sides of the visual field, while the attentional capacities of the left hemisphere are mainly restricted to the contralateral visual field. Hence, deficits in spatial attention after left hemisphere damage would be less likely, because of the bilateral function of the right side of the brain. Even though we did not find the ubiquitous impact of stroke on speed of information processing as we had expected, mental speed did play a role in several outcome factors. First of all, slower speed of information processing was related to decreased reasoning performance. No identical relation was found for the patients and the control subjects involving the basic visuomotor decision times. These were related to reasoning performance in the patients, but not in the control group subjects. The data indicate that visuomotor slowing was a more important predictor of decreased reasoning capacities than stroke per se. Second, speed of information processing was, at least to some extent, related to depressive mood both in the subacute and chronic phases after stroke. Furthermore, more improvement of activity level between three and fifteen months post onset was associated with better reasoning performance and faster mental speed at three months post-stroke. Finally, when the patients with and without asymptomatic pre-stroke brain lesions were compared, at 15 months post-stroke basic speed of information processing was the only cognitive domain in which the groups differed; the patients with asymptomatic lesions were slower. In the subacute phase none of the cognitive domains differed between the two patient groups.

**Side of stroke**

Much effort is invested in the development of a neuropsychological test battery that allowed us to compare the performance of left and right hemispheric stroke patients. When necessary new tests were constructed (The Couples Test and the cognitive reaction time tasks), or existing tests were adapted (the visuomotor reaction time tasks and the Snijders-Oomen Non-verbal Learning Test-R 5 ½ -17). Remarkably few lateralisation effects were found. Besides the above mentioned right hemisphere sensitivity to basic slowness of information processing no differences in reasoning performance, nor in verbal (Names) versus non-verbal (Faces) memory, were observed. Several factors play a role in this finding. For one, it is very difficult to make an exact distinction between verbal and non-verbal tests. Hence, non-verbal tests can be non-verbal in the sense that they do not require a verbal response, but one can never rule out that verbal strategies are the most efficient despite the non-verbal modality of the test-material (even for example nonsense figures). Moreover, in the present study we used tests with at least some ecological validity, like remembering names and faces. In tests like these various aspects of the memory process are involved, memory processes that are related to various structures located bilaterally in the brain (Cabeza & Nyberg, 2000). It requires the implementation of more experimental designs to unravel laterality effects, but in the present clinical study we showed that laterality effects are not as
likely to occur in stroke patients on neuropsychological tests as is generally assumed. In addition the lack of laterality effects found in cognitive functioning, depressive mood did not appear to be related to side of stroke nor was the relation between depressive mood and cognitive functioning. In the literature the relation between side of stroke and depression is still subject to debate. In agreement with our present findings, a recent meta-analysis by Carson and colleagues (2000) was also unable to confirm the hypothesis that the occurrence of depression after stroke is related to the side of the stroke.

Aphasia & neglect

In the present study patients with aphasia or neglect demonstrated the poorest test performance in the cognitive domains: speed of information processing, learning and reasoning. The tests had been adjusted to take the influence of aphasia and neglect into account; nevertheless the test results were negatively associated with the presence of these specific disorders. Aphasia or neglect can be indices of adverse overall cognitive outcome after stroke, possibly because of the extent or volume of the infarct. In a recent study using MR perfusion-weighted imaging, a relation between neglect and aphasia battery scores, in right and left hemispheric stroke patients respectively, on one hand and volume of dysfunctional tissue on the other hand was demonstrated (Hillis, Wityk, Barker, Ulatowski, & Jacobs, 2003). Moreover, greater stroke volume has been associated with a higher probability of developing post-stroke dementia (Censori, et al., 1996; Pohasjavaraa, et al., 2000). In the present study insufficient data on lesion volume are available to further elaborate on this topic. On the other hand, the neuropsychological test procedures should still be administered for their adequacy in this patient group, despite the applied modifications. Hence, the effect of aphasia or neglect might dominate the cognitive domain that is actually tested.

Course of cognition

Within the subacute and chronic phases after stroke, cognitive functioning appeared to remain unchanged at least at the group level. Although some improvement was observed in several test scores, this improvement only exceeded the improvement found within the control subjects in one of the three reasoning subtests, the Mosaics. Thus, with the exception of the Mosaic test performance, improvement in test scores should be interpreted as a retest effect. At 15 months post stroke, the reasoning and explicit memory capacities of the patients are still impaired compared to the control subjects. However, speed of information processing no longer differed between the patients and the control subjects. Subjectively the patients experienced more cognitive changes due to the stroke in the chronic phase than they did at three months post stroke. This is probably the result of growing awareness of these invisible and chronic cognitive disorders,
which might have been overshadowed by the physical impairments in the beginning. Moreover, resuming daily activities in this phase might have confronted these patients with several unexpected disabilities. Thus, at about three to four months post stroke cognitive outcome at neuropsychological test level can be assessed fairly reliable, but the cognitive complaints may still increase.

**Impact of cognition on mood and daily life**

These subjectively experienced cognitive changes appeared to be related to depressive mood after stroke. Objective cognitive test scores and partners’ reports failed to confirm this relation with the exception of observer-rated depressive mood, which appeared to be related to speed of information processing at both times of measurement, and with reasoning at 15 months post stroke. No relation between self-rated depressive mood and cognitive functioning was found. Considering the lack of significant relations between (course of) cognitive test performance and (course of) depressive mood after stroke it is suggested that these are two separate phenomena that can independently occur after stroke. Still, as proposed by Gainotti and co-workers (1997, 2002), post stroke depression can be a reaction to the experienced changes, including the perceived cognitive changes.

Long term life satisfaction after stroke, on the other hand, can be predicted by memory functioning and reasoning performance in the subacute stage. Moreover, reasoning performance and speed of information processing were related to stroke outcome in terms of daily activity level.

**Clinical implications**

The present findings suggest that based on neuropsychological examination in the subacute stage, at about four months post-onset, a fairly good prediction can be made about expected cognitive stroke outcome. However, this applies to group level outcome; of course individual differences at subject level should be taken into account. Moreover, no typical profile for left and right hemispheric stroke patients was found, therefore a broad spectrum of neuropsychological tests should be used when examining stroke patients, irrespective of the side of the lesion. The Neuropsychology Section from the Dutch Professional Association of Psychologists (NIP) has suggested implementing specific neuropsychological test protocols for various neurological disorders. Soon the Stroke Protocol, proposed by some Dutch neuropsychologists, will be introduced on their website. Conducting a proper neuropsychological examination in stroke patients is important for several reasons:

- First, to examine the disabilities, and especially the abilities of the patients necessary to regain former activities or engage in new activities. In this sense neuropsychological examination is indispensable in formulating the optimal post stroke regime.
Second, properly explaining the results of the neuropsychological examination to the patient can be considered an important intervention in improving understanding by itself and may facilitate the patient in accepting the changes and adapting to them.

Third, the results from the neuropsychological examination provide important information to the spouses of the patient in order to better understand and cope with the impairments.

A common experience in clinicians’ daily practice is that standard neuropsychological tests are not always suitable for stroke patients due to language disorders, visuospatial problems or motor impairments (Gerritsen, Visser-Keizer, & Deelman, 2002). In the present study we attempted to overcome this limitation as much as possible. The data from our measurements showed that indeed decision reaction times and movement times constitute two separate factors. We therefore stress the importance of this distinction in order to enable reliable conclusions about the patients’ mental speed. Moreover, we demonstrated the feasibility, validity, and reliability of the Snijders-Oomen Non-verbal Intelligence Test (SON-R 5½ - 17, Snijders, Tellegen, & Laros, 1989) in stroke patients as well as non-stroke older adults (Gerritsen, Berg, & Deelman, 2001). In chapter five normative data of 132 stroke free older adults are presented.

Considering the prevalence of both objective and subjective cognitive changes and the impact of these changes on mood and daily life, each Stroke Unit should have a staff neuropsychologist on their team, or should at least be able to consult one. Van Zandvoort and co-workers (2001) demonstrated that patients could well be tested neuropsychologically early after stroke. Between 4 and 20 days post stroke, 77% of the patients were able to complete the majority of their test battery.

In all stages after stroke patients and / or their partners should have the possibility to enter a neuropsychological rehabilitation programme. One of the neuropsychological programmes available is cognitive rehabilitation, in which patients are taught new strategies in order to better compensate for their cognitive deficits. Cognitive rehabilitation is evidence-based (Cicerone, et al., 2000; Deelman & Berg, 2002), and still an important research topic. Another, more holistic approach, has been administered in clinical practice for years, but so far no randomised clinical trials have been conducted to demonstrate its perceived benefits. Recently, Judd (1999) introduced the term ‘neuropsychotherapy’ to describe this form of rehabilitation that is tailored to the individual and involves the combination of emotional, behavioural and cognitive changes as a result of brain damage. Moreover, training of caregivers, mostly spouses, has demonstrated an improvement of psychosocial outcome in care givers as well as the stroke patients after one year, and a reduction in health and social services related costs (Kalra et
al., 2004). Although all rehabilitation centres in the Netherlands employ psychologists that are specialised in the field of neuropsychology and/or rehabilitation psychology, the availability of neuropsychological treatment to stroke patients as well as their partners needs considerable improvement. Especially the relatively less affected patients, who presently receive little or no rehabilitation, are a suitable group that may benefit significantly from cognitive rehabilitation and/or neuropsychotherapy. The Dutch College for General Practitioners (Nederlands Huisartsen Genootschap, NHG) has developed a new stroke care standard that acknowledges, among other issues, the need for stroke patients and their caregivers for education in all stages after stroke (Verhoeven, et al., 2003 CONCEPT).

**Implications for future research**

More suitable neuropsychological tests for stroke patients are needed. For example there are still few non-verbal memory tests available that actually measure learning capacity and are not entirely visuospatial derived or rely solely on recognition. The Couples Test that was developed in this study could be a promising test, but has some practical disadvantages: it is a difficult test, especially for older people and it takes much time to complete (about half an hour for each sub test). Although it was not evaluated systematically it was felt that subjects actually disliked the test. Further research aimed at the modification of this test may lead to the development of a feasible instrument with a parallel verbal and non-verbal modality.

The impact of silent brain infarcts and white matter lesions on the course of cognitive recovery after stroke should be studied in larger groups focusing especially on speed of information processing and using both cognitive and radiological longitudinal assessment.

The effectiveness and optimal content of neuropsychological treatment programmes for stroke patients and their partners should be investigated further. Moreover, short care programmes, involving cognitive education and counselling for stroke patients and their partners, which can be applied shortly after stroke, should be developed. When a patient is discharged from the hospital, a neuropsychologist could indicate whether such a programme should be applied. The programme should be able to contribute to a better reintegration and may prevent some of the insecurity and frustration people experience after stroke.
References


General conclusions and discussion


