

Internal and external effects on cognition

Evidence from memory training in very preterm-born children and cognition in patients with carotid artery stenosis before and after treatment

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This dissertation encompasses the following studies:

Study 1

Everts, R., **Wapp, M.**, Ritter, B. C., Perrig, W., & Steinlin, M. (2015). Effects of two different memory training approaches in very preterm-born children. *Advances in Pediatric Research* 2(13), 1-11. doi:10.12715/apr.2015.2.13

Study 2

Everts, R.* , **Wapp, M.***, Burren, Y., Kellner-Weldon, F., El-Koussy, M., Jann, K., Delameillieure Lenoir, J., Michel, P., & Schroth, G. (2014). Cognitive and emotional effects of carotid stenosis. *Swiss medical weekly* 144:w13970, 1-8. doi:10.4414/smw.2014.13970

Study 3

Wapp, M.*, Everts, R.* , Burren, Y., Kellner-Weldon, F., El-Koussy, M., Wiest, R., Federspiel, A., Michel, P., & Schroth, G. (2015). Cognitive improvement in patients with carotid stenosis is independent of treatment type. *Swiss medical weekly* 145:w14226, 1-7. doi:10.4414/smw.2015.14226

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Abstract

The present synopsis aims to integrate one study about memory training in very preterm-born children and two studies about cognition in patients with carotid artery stenosis before and after treatments.

Preterm-born children are at increased risk of cognitive deficits and behavioural problems compared with peers born at term. This thesis determined whether memory training would improve cognitive functions in school-age very preterm-born children. Memory strategy training produced significant improvements in trained and non-trained cognitive functions; a core working memory training revealed significant effects on short-term memory and working memory tasks. Six months after training, children in both training groups showed better working memory performance than children in the waiting control group. This is evidence that memory training – an external influence on cognition – induces plastic changes in very preterm-born children.

Patients with carotid artery stenosis are known to be at increased risk of cognitive impairment. We showed that patients with symptomatic or asymptomatic carotid artery stenosis were at higher risk for cognitive deficits than expected in a normative sample. This thesis seeks to link cognitive plasticity to internal factors like carotid stenosis. An external factor, which influences blood flow to the brain is the nature of the carotid artery stenosis treatment. Research on the effects of carotid artery stenosis treatment on cognition has produced inconsistent results. We found significant improvement in frontal lobe functions, visual memory and motor speed one year after treatment independent of the treatment type (best medical treatment, carotid artery stenting, carotid artery endarterectomy); providing evidence for ‘treatment-induced’ cognitive plasticity.

Baseline performance was negatively associated with improvement in various cognitive functions after training in very preterm-born children and after treatment in patients with carotid artery stenosis.

The present synopsis aims to integrate these findings into the current and relevant literature, and discuss consequences as well as methodological considerations resulting from the studies constituting the thesis at hand.

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Outline of the thesis

The first article included in this thesis is entitled „Effects of two different memory training approaches in very preterm-born children”. The second and third articles included adults with carotid artery stenosis. The second article is called “Cognitive and emotional effects of carotid stenosis” and the third is called “Cognitive improvement in patients with carotid stenosis is independent of treatment type”, which reviewed the cognitive functioning of those patients one year after treatment. The focus of this doctoral thesis is on cognitive functions of very preterm-born children and patients with carotid artery stenosis.

Chapter 1 provides a definition of prematurity and describes deficits in cognitive functions in preterm-born children. Our study about memory training in very preterm-born children is then linked to the current literature. Further, two different memory trainings, a memory strategy training and a core working memory training, are discussed as external influences on cognition. Chapter 2 integrates the findings of the second and third article about patients with carotid stenosis in the recent literature. In the following, the stenosis itself is described as an internal influence and the treatment as an external influence on cognition. Lastly, revascularisation methods and medical treatments are described shortly and cognitive functioning after treatment is summarised. Chapter 3 addresses the topic of plasticity. The findings of all three studies are linked to the concept of cognitive plasticity. The chapter is divided into two parts: Training-induced plasticity, and stenosis- and treatment-induced plasticity. In chapter 4, the main focus is on methodological considerations such as different test batteries, different follow-up schedules, randomisation, gain scores, inclusion criteria, as well as individual characteristics such as age at investigation, risk factors, motivation, and baseline performance. Moreover, limitations of the studies and future implications are discussed. Finally, chapter 5 summarises the most important points of this thesis.

1. Preterm-born children

In 2014, 85'287 children were born in Switzerland, of whom 0.4% were born extremely prematurely (gestational age: 22-27 weeks), 0.6% were born very prematurely (28-31 weeks) and 6.2% were born prematurely (32-37 weeks) (Bundesamt für Statistik, 2015). These frequencies are in line with worldwide estimates of rates of preterm birth in the year 2010 (Blencowe et al., 2012). The rise in number of premature births may be explained by the increased maternal age, increased use of reproductive technologies and hence higher rates of multiple gestations (Goldenberg, Culhane, Iams, & Romero, 2008). Improved neonatal care and changes in perinatal management have increased survival rates and reduced severe medical complications at birth, which are most common in extremely and very preterm-born children (Moster, Lie, & Markestad, 2008; Rügger, Hegglin, Adams, & Bucher, 2012).

Children born prematurely nevertheless remain vulnerable to many complications of prematurity. The lower the gestational age, the higher the mortality rate and likelihood of complications (Blencowe et al., 2012). Neurodevelopmental disorders (e.g. cerebral palsy, visual and hearing impairments, mental retardation and other disorders of the central nervous system) are also more common in children born prematurely (Behrman & Butler, 2007). A large cohort study by Moster and colleagues showed that preterm-born children are at increased risk of cerebral palsy and that the risk of having medical disabilities in adulthood was negatively associated with gestational age at birth. Furthermore, even without medical disabilities, gestational age at birth is negatively associated with income, participation in higher education and the likelihood of finding a life partner and/or having children (Moster et al., 2008). The last weeks of pregnancy are crucial for brain formation: cerebral white matter develops, the neuronal structure of the thalamus and the basal ganglia is established, and synapses are organised and proliferate. It is therefore unsurprising that prematurity has a clear impact on brain development (Volpe, 2010). Yet, the most common consequence to premature birth is global cognitive delay (Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015). Effects of prematurity on cognition are discussed in the next section.

1.1 Cognition in preterm-born children

Despite improvements in neonatal care over the past 30 years, preterm-born children are at increased risk of cognitive deficits and behavioural problems compared with peers born at term (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Anderson & Doyle, 2003; Anderson, 2014; Kerr-Wilson, Mackay, Smith, & Pell, 2012). General cognitive ability, typically measured with IQ tests, is about 12 IQ-points lower in children born prematurely. There is a trend towards a negative relationship between the severity of cognitive deficits and gestational age at birth (Anderson, 2014; Kerr-Wilson et al., 2012) and there is evidence that IQ differences persist until adolescence (Narberhaus et al., 2007). However, more specific measures are needed for detecting specific cognitive deficits (Anderson, 2014). It is known that children born prematurely are more likely to have impairments in executive functions such as working memory, cognitive flexibility, verbal fluency, and attention compared with their full-term peers (Aarnoudse-Moens et al., 2009; Mulder, Pitchford, Hagger, & Marlow, 2009; van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008). Preterm-born children also score significantly lower in tests of mathematics and in language abilities than peers born at full term, regardless of socioeconomic status (Aarnoudse-Moens et al., 2009; Aarnoudse-Moens, Oosterlaan, Duivenvoorden, van Goudoever, & Weisglas-Kuperus, 2011; Barre, Morgan, Doyle, & Anderson, 2011; van Noort-van der Spek, Franken, & Weisglas-Kuperus, 2012).

Given the problems described above it is not surprising that extremely and very preterm-born children perform worse on standardised measures of academic attainment than peers born at term (Hutchinson, De Luca, Doyle, Roberts, & Anderson, 2013; Johnson et al., 2009). At 5 years of age, very preterm-born children have school readiness difficulties (Roberts, Lim, Doyle, & Anderson, 2011). A substantial proportion of children born extremely prematurely will go on to need full-time special education (Johnson et al., 2009; Wolke, 2011). Unfortunately, in children with very low birth weight these educational disadvantages persist into early adulthood (Hack et al., 2002). We therefore aimed to determine whether memory training would improve cognitive functions in very preterm-born children.

1.2 Memory training: External influences on cognition

The participants in Study 1 were children aged 7 to 12 years who had been born very prematurely (below 32 weeks of gestational age) and/or children with very low birth weight (below 1500g). For simplicity all these children are referred to hereafter as ‘very preterm-born children’. We assessed various aspects of cognition: episodic memory, working memory, short-term memory span, fluid intelligence, inhibition, cognitive flexibility and processing speed; reading and arithmetic skills and every day memory were also evaluated. We trained the participants with two different memory trainings and compared the described cognitive aspects of cognition to a waiting control group. The aim was to determine whether two types of memory training improved various aspects of cognitive functioning after six weeks of training and at a six-month follow-up (Everts, Wapp, Ritter, Perrig, & Steinlin, 2015).

There are descriptions of a wide variety of cognitive training programmes in the current literature. These training programmes can be considered as external influences on cognition. One approach is to improve various cognitive aspects and academic performance by training internal strategies – referred to as ‘memory strategy training’ – i.e. teaching participants to use effective approaches to encoding, maintenance and retrieval (Morrison & Chein, 2011). Other training programmes use intensive working memory practise – referred to as ‘core working memory training’ – a technique for increasing working memory capacity. Setting improvement in working memory as a goal is reasonable; working memory is important for everyday challenges. The ability to encode and process task relevant information actively and to hold information in a temporary mental storage for a short period of time is important for many cognitive tasks and for academic success (Baddeley, 1996, 2012; Klingberg, 2010). Enhancing working memory is therefore a plausible approach for improving academic performance, not only for children with cognitive deficits but also for children without notable impairment. We used the ‘Memo-Training’, which consists of teaching and practising five different memory strategies (chaining, rehearsal, similarities, imagination, symbolic coding) in an adaptive manner (Everts & Ritter, 2013), and a computerised adaptive core working memory training consisting of three cognitive

training tasks (safari task, farm task and dot location; Buschkuehl, Jaeggi, Kobel, & Perrig, 2007).

The goal of all training programmes is transferable improvement. This means improvement in performance on tasks or domains that were not part of the intervention. Improvement in skills that were trained and in performance in closely related tasks which place structurally similar cognitive demands to those used in the training is referred to as ‘near transfer’, whereas ‘far transfer’ is the generalisation of improvements to performance on tasks that were not part of the intervention, in structurally different cognitive domains. Transfer is seen as a continuum and may occur through cognitive mechanisms, neural mechanisms or both of them together (Jaeggi & Buschkuehl, 2014).

A long time ago, Holbrook wrote a book entitled ‘How to strengthen the memory; or, natural and scientific methods of never forgetting’ which nicely describes the effects of repetition, association and the use of brief synopses (Holbrook, 1886) – all strategies which are still used in memory strategy training today. Nowadays, memory strategy training is often used in adult neurorehabilitation (for meta-analyses see Cicerone et al., 2005, 2011) and there has been some research on the effect of strategy use on working memory span (Turley-Ames & Whitfield, 2003). Core working memory training, on the other hand, has long been used in healthy people of all ages and in many neuropsychiatric conditions (Klingberg, 2010). There is a huge body of evidence from memory training research. This synopsis, however, focuses on research in memory training in children, particularly children born prematurely.

1.2.1 Memory strategy training

Previous studies of memory strategy development have shown that younger children do not typically use memory strategies spontaneously and that they do not benefit from memory strategy training, as they are not able to apply them to improve memory performance (so called utilisation deficiencies). In older children utilisation deficiencies decrease and the use of memory strategies is clearly beneficial (Bjorklund, 1997; Schlagmüller & Schneider, 2002). The ‘overlapping wave model’ posits that preferred strategies change over time and several strategies are used at one time instead of step-like or linear progression in strategy use (Chen & Siegler, 2000; Siegler, 1996). In our study we therefore introduced

different strategies and allowed children to choose what strategy they would use in the training.

The strategic allocation hypothesis differentiates between individuals with high and low working memory span. The authors have suggested that one explanation for differences in working memory spans is that individuals with a high working memory span are more strategic (Engle, Cantor, & Carullo, 1992). This hypothesis is supported by some studies which showed that people with a high working memory span are more likely to use strategies like clustering or chaining (McNamara & Scott, 2001; Rosen & Engle, 1997). If the hypothesis is valid, one might expect memory strategy training to increase working memory span in children with known working memory problems.

To date, there has been little research on memory strategy training in children. In healthy undergraduates and in healthy school-age children, the use of a rehearsal strategy increased working memory span (St Clair-Thompson, Stevens, Hunt, & Bolder, 2010; Turley-Ames & Whitfield, 2003). One study reported that training in imagination and rehearsal improved performance on mathematical tasks as well as working memory (Witt, 2011). Chaining has also been shown to improve short-term memory (McNamara & Scott, 2001). An intervention based on ten different memory strategies which was designed for use in children with memory disorders resulted in a significant improvement in learning and memory in the intervention group (Lepach & Petermann, 2009). Training in rehearsal and organization strategies improved learning and memory in children with cerebral infarction (Yerys et al., 2003). In children with fetal alcohol spectrum disorder, which is associated with poor working memory, rehearsal training improved language comprehension and verbal working memory relative to a control group (Loomes, Rasmussen, Pei, Manji, & Andrew, 2008). Home-based rehearsal training increased verbal memory span in children with Down's syndrome (Conners, Rosenquist, Arnett, Moore, & Hume, 2008). To summarise, memory strategy training in children seems to be an effective way to improve various cognitive functions.

To the best of our knowledge our study is the first to examine long-term effects of memory strategy training in very preterm-born children. Our memory strategy training produced significant improvements in trained functions (episodic memory, short-term memory) and in other non-trained functions (working

memory, arithmetic) relative to controls. After six months the improvement in episodic and working memory remained significant (Everts, Wapp, et al., 2015). Our results corroborate earlier findings in children and highlight the importance of teaching memory strategies also to very preterm-born children to improve their cognitive performance.

1.2.2 Core working memory training

In healthy preschool- and school-age children, core working memory training is known to improve working memory performance, but there is also evidence for improvement in academically important skills such as reading and mathematics (e.g. Bergman Nutley et al., 2011; Blakey & Carroll, 2015; Loosli, Buschkuehl, Perrig, & Jaeggi, 2012; Studer-Luethi, Bauer, & Perrig, 2015) and even in fluid intelligence (Jaeggi, Buschkuehl, Jonides, & Shah, 2011). Children with poor working memory benefit from working memory training, showing improvements in mathematics as well as working memory (Holmes, Gathercole, & Dunning, 2009). There are also, however, studies failing to detect some of the reported effects of core working memory training (Karch, Strobach, & Schubert, 2015; Redick et al., 2012). A recent review concluded that working memory training produces limited benefits that are restricted to tasks that are very similar to the trained task and found no evidence of transfer to reading and maths (Redick, Shipstead, Wiemers, Melby-Lervåg, & Hulme, 2015). A lot of research on memory training is also done in children with attention deficit hyperactivity disorder (ADHD), because working memory impairments are common in this population. After core working memory training, children with ADHD showed significant improvements in working memory and other executive functions. Additionally, parents reported a reduction in ADHD symptoms (Beck, Hanson, Puffenberger, Benninger, & Benninger, 2010; Klingberg et al., 2005). However, the results have been difficult to replicate. A meta-analysis and a randomised clinical trial of core working memory training in school-age children with ADHD found improvements on the trained working memory performance, but not in other cognitive functions (Chacko et al., 2013, 2014).

To date only a small number of studies have investigated the effects of working memory training in preterm-born children. In children aged 5-6 years with very low birth weight, and children aged 14-15 years with extremely low

birth weight, computerised core working memory training significantly improved performance on the trained working memory tasks and on other memory tests (Grunewaldt, Løhaugen, Austeng, Brubakk, & Skranes, 2014; Løhaugen et al., 2011). Our study corroborates these results. We found significant short-term effects of core working memory training on short-term memory and working memory tasks. The near transfer effect (improvement in working memory task) remained significant even at the six-months follow-up (Everts, Wapp, et al., 2015). Similarly to our study, a meta-analysis concluded that working memory training in children often produced near transfer effects but that there was no evidence for far transfer (Melby-Lervåg & Hulme, 2013). Our results are consistent with the conclusion of a review by Redick and colleagues, namely that it is difficult to achieve stable far transfer effects with core working memory training (Redick et al., 2015).

1.2.3 Training effects

Our study is consistent with earlier studies, showing short-term near and far transfer effects, especially after memory strategy training. The results indicate that training induces plastic changes in children, a finding which is discussed in more detail in chapter 3. The factors underlying transfer of working memory training are not yet fully understood. Dunning and Holmes (2014) suggested that the improvement in untrained working memory tasks following working memory training is mediated by spontaneous, implicit changes in strategy use. They found a significant increase in use of grouping strategies after adaptive core working memory training, which was not seen in either the active or passive control groups (Dunning & Holmes, 2014). Familiarity with the stimuli and the setting and the expectation as a result of training (i.e. a placebo effect) could also account for the observed cognitive improvements following memory training (Chein & Morrison, 2010; Green, Strobach, & Schubert, 2014). These findings do not, however, explain why children's performance improves on some tasks but not others.

It is obvious, that training should improve trained aspects. It seems self-evident that a cello player who practises playing the cello will play it better than someone who does not practise the cello whatsoever. An individual who practises playing the cello may also get better at reading music, playing another bowed string instrument, and develop a more sensitive ear for music. The more similar

the processes underlying training and performance, the more likely it is that training in one task will transfer to another (Jaeggi & Buschkuhl, 2014). But if our hypothetical cello player doesn't play for a long time the trained function may disappear or require reactivation, perhaps in the form of booster training. Similar processes may account for the difficulty that researchers have had in detecting stable, long-term effects of memory training. In recent years an intense debate has arisen about the long-term behavioural and educational impact of brief interventions (Gathercole, 2014; Melby-Lervåg & Hulme, 2013; von Bastian & Oberauer, 2014). The 'use it or lose it' principle suggests that long breaks in training may erode training effects. However some researchers argue that consolidation of transfer after training requires a certain amount of time (Holmes et al., 2009). Studies showing transfer effects only in follow-up – referred to as 'sleeper effects' – are even more difficult to interpret (Jaeggi & Buschkuhl, 2014). In training studies it is particularly difficult to measure cognitive improvement as well as transfer and to compare studies. These issues are discussed in more detail in chapter 4.

Very preterm-born children are at increased risk of cognitive deficits. Memory training can improve various cognitive functions and induce plastic changes. The next chapters discuss the effects of carotid stenosis in adult patients as well as treatments of carotid stenosis on cognitive plasticity.

2. Patients with carotid artery stenosis

Patients with carotid artery stenosis (narrowing of the inner surface of the carotid artery) are at high risk of reduced cerebral blood flow and ipsilateral stroke. Atherosclerotic stenosis of the internal carotid artery causes 10-15% of all strokes (Bonati et al., 2015; Flaherty et al., 2013). Ischemic stroke is a major public health problem and the incidence increases steadily with age. In Europe it is the second leading cause of death, in the United States it is the third (Naylor, 2015). The known risk factors for carotid artery stenosis are smoking, hypertension, diabetes, hyperlipidaemia, coronary artery disease, male sex, and advanced age (de Weerd et al., 2010; Greco et al., 2013). Carotid artery stenosis is predominantly caused by atherosclerosis (Chatzikonstantinou, Wolf, Schaefer, & Hennerici, 2012) and is usually classified as symptomatic or asymptomatic. Carotid artery stenosis is defined as symptomatic if the patient has suffered a minor stroke or transient ischemic attack (TIA) resulting in motor, sensory, speech or visual impairment. Patients without symptoms are defined as asymptomatic. Unfortunately, cognitive functioning is not taken into account when classifying patients with carotid artery stenosis. Estimates of the prevalence of moderate carotid artery stenosis (stenosis between 50% to 70%) in the general population range from 0-22.5% and estimates of the prevalence of severe carotid artery stenosis (stenosis above 70%) range from 0-1.7% (de Weerd et al., 2010). In Germany 1-3% of all adults have an extracranial carotid artery stenosis (below 50%) and in people aged 65 years and older the prevalence of moderate carotid artery stenosis is higher, at 6-15% (Eckstein et al., 2012). The participants in Study 2 were patients with symptomatic or asymptomatic severe extracranial internal carotid artery stenosis aged 51-85 years (Everts et al., 2014).

2.1 Cognition in patients with carotid stenosis

Patients with carotid artery stenosis are known to be at increased risk of cognitive impairment (Baracchini et al., 2012; Sztriha, Nemeth, Sefcsik, & Vecsei, 2009). A systematic review of cognition in patients with symptomatic and asymptomatic carotid artery stenosis noted that 11 out of 15 studies reported cognitive deficits in symptomatic patients compared with those of control persons or with norms, and

all 3 studies of asymptomatic patients found cognitive deficits in this population (Bakker, Klijn, Jennekens-Schinkel, & Kappelle, 2000). Patients with asymptomatic stenosis, which is considered as clinically silent, also show deficits in cognitive performance (Johnston et al., 2004; Landgraff, Whitney, Rubinstein, & Yonas, 2010; Mathiesen et al., 2004). A review of 10 studies concluded that asymptomatic carotid stenosis was not only a risk factor for stroke, but may be also an independent risk factor for cognitive deficits (Chang et al., 2013). However, most of the described studies relied on screening tests to assess cognitive status (Folstein, Folstein, & McHugh, 1975) and such tests do not differentiate between the various different cognitive functions. It is important to use separate tasks to test specific cognitive functions (Sztriha et al., 2009).

In Study 2 we found evidence for cognitive impairment in patients with carotid artery stenosis. More specifically, we showed that patients with symptomatic and asymptomatic carotid artery stenosis were at higher risk for cognitive deficits than expected in a normative sample. In our sample patients showed deficits in higher-order cognitive functions such as executive functions, word production, and verbal and visual memory (Everts et al., 2014). These results are in line with earlier studies showing deficits in executive functions, verbal and visual memory, visuospatial tasks, and language (Bossema et al., 2006; Landgraff et al., 2010).

2.2 Carotid stenosis: an internal influence on cognition

There are two possible mechanisms underlying the cognitive changes observed in patients with carotid artery stenosis. First, reduced blood flow in the carotid artery as a result of the stenosis causes a reduction in cerebral blood perfusion; the more severe the stenosis, the greater the decline in cognitive functioning (Alexandrov, 2007; Scherr et al., 2012). This explanation is corroborated by a number of studies. During induced cerebral hypoperfusion with internal artery balloon occlusion tests, patients with loss of cerebral blood flow showed an impairment in sustained attention which was reversed when the carotid occlusion was removed (Marshall et al., 2001). Chronic hypoperfusion resulting from carotid atherosclerosis lead to brain atrophy (Avelar et al., 2015; Kin et al., 2007), which may lead to a decline of cognitive functions. The second explanation is that carotid atherosclerosis may

result in cerebral micro-emboli which produce silent infarcts and white matter lesions which may be responsible for a decline in cognitive functioning (Avelar et al., 2015; Demarin, Zavoreo, & Kes, 2012; Dempsey, Vemuganti, Varghese, & Hermann, 2011). In contrast, a study which investigated cerebral blood flow and severity of stenosis showed that more severe stenosis was indeed associated with cognitive deficits, but that this effect was independent of white matter lesions (Scherr et al., 2012). Another large study in asymptomatic patients suggested that poor performance on tasks assessing attention, psychomotor speed, and memory is independent of magnet resonance imaging (MRI) lesions such as white matter hyperintensities, or cortical or lacunar infarcts (Mathiesen et al., 2004). Of course other factors play also an important role in influencing cognition, for example good collateral arteries can efficiently supply brain areas until a certain level (Sztrika et al., 2009) and the location of a stroke or cerebral emboli is a factor in the resulting cognitive deficits. Stenosis of the carotid artery may thus be regarded as an internal factor influencing the blood flow to the brain and a cause of stroke, TIA, or micro-emboli, which might produce a decline in cognitive functioning. As Holbrook noted as early as 1886: “If the blood is deficient, then the memory is, for the time, feeble; if the blood is modified in any way, the memory will also be modified.” (Holbrook, 1886, p. 15).

In patients with carotid artery stenosis it is assumed that stenosis severity is negatively associated with performance on cognitive tests. It is also assumed that the laterality of stenosis plays a role regarding performance in tests requiring a hemisphere-specific function. There is some debate about the importance of laterality. For example, patients with left-side stenosis are expected to show more severe language impairments than patients with right-side stenosis. One study reported that patients with left-side stenosis showed deficits in verbal fluency whereas patients with right-side stenosis had more difficulty with a visual recognition task. This dissociation was only observed in patients with reduced cerebrovascular reactivity (Silvestrini et al., 2009). In Study 2 we found no severity- or laterality-related differences in any aspect of cognition (Everts et al., 2014). A study by Landgraff and colleagues showed that in asymptomatic patients visuospatial/constructional deficits are related to right-sided stenosis. But they only detected language deficits in patients with moderate stenosis and occlusions and not in patients with severe stenosis (Landgraff et al., 2010). Another study of

asymptomatic patients only found cognitive impairments in patients with left-side stenosis; intima-media thickness of the carotid artery was associated with cognitive impairment independent of stenosis laterality (Johnston et al., 2004). Further studies should take into account haemodynamic parameters and lesion load when assessing the effects of stenosis. At present it is not clear if the stenosis itself represents an independent risk factor for cognitive impairment or if underlying factors cause the decline.

Even though cognitive impairment in patients with carotid artery stenosis is known in the literature, in clinical praxis cognitive deficits are mostly unrecognised (Berman et al., 2012). The negligence is even worse in asymptomatic patients (Martinić-Popović, Lovrenčić-Huzjan, & Demarin, 2012). Patients with cognitive deficits who clinically present with dizziness, subjective weakness, or blurry vision are classed as asymptomatic, even if they have severe stenosis. Therefore the classification in symptomatic or asymptomatic patients is critical (Lanzino, Rabinstein, & Brown Jr, 2009). It is still not standard practise to take cognitive functioning into account when making decisions about the treatment of patients with carotid artery stenosis (Landgraff et al., 2010). The instruments commonly used to assess cognitive functioning in routine clinical practise, such as the mini-mental state examination (Folstein et al., 1975), do not encompass higher-order cognitive functions. In order to make adequate treatment decisions it is important to be able to identify patients experiencing cognitive decline and to monitor their higher-order cognitive functions.

2.3 Medical treatment and revascularisation: External influences on cognition

One of the external factors which influence the blood flow to the brain is the nature of the carotid artery stenosis treatment (best medical treatment, carotid artery stenting, carotid artery endarterectomy). The goal of all treatments for carotid artery stenosis is improvement in cerebral blood flow and stroke prevention.

2.3.1 Treatments

Two revascularisation interventions are commonly used in the management of patients with carotid artery stenosis. Carotid artery stenting (CAS) was developed

in the 1990s and has emerged as an alternative to carotid artery endarterectomy (CEA) (Bonati et al., 2015). Both procedures are used to treat blockage or narrowing of the carotid artery. During endarterectomy the internal carotid artery is incised and the plaque is removed surgically. Carotid stenting is a minimally invasive procedure in which a catheter is inserted into the carotid artery and a stent is placed in the opened area to prevent the re-closing or narrowing of the artery (Gahremanpour, Perin, & Silva, 2012). The main medical therapies for carotid artery stenosis are anti-platelet therapy to prevent blood clots, cholesterol-lowering drugs e.g. statins and antihypertensive agents; smoking cessation and physical exercise are also recommended (Sobieszczyk & Beckman, 2006; Wapp et al., 2015).

The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) is a randomised trial based on a sample of over 2500 patients with symptomatic or asymptomatic extracranial carotid artery stenosis. It showed that there was no difference between patients receiving CAS and patients receiving CEA with respect to risk of stroke, myocardial infarction or death (Brott et al., 2010). Another randomized clinical trial, the International Carotid Stenting Study (ICSS), involving 50 centres across the world and over 1700 patients with symptomatic carotid artery stenosis, indicated that CEA and CAS lower the long-term risk of stroke. Both methods produced similar long-term functional outcomes and similar reduction in risk of stroke (Bonati et al., 2015).

2.3.2 Cognitive outcomes of treatment

Research on the effects of carotid artery stenosis treatment on cognition has produced inconsistent results. A review of 32 studies by De Rango and colleagues (2008) concluded that there was no clear evidence that either CAS or CEA influenced neurocognition. Larger studies with greater statistical power are needed to draw firm conclusions about cognitive outcomes of treatment (De Rango et al., 2008). A review of 22 studies by Berman and colleagues noted that 8 found improvements in cognition, 11 reported mixed results and 3 found a decline in cognitive functioning (Berman, Pietrzak, & Mayes, 2007). More recent studies have also produced mixed results and concluded that CEA and CAS have similar cognitive outcomes (for a recent review see Plessers, Van Herzeele, Vermassen, & Vingerhoets, 2014).

In Study 3 we investigated 58 patients; 20 received CEA, 10 CAS and 28 received best medical treatment. One year after the intervention all treatment groups showed similar improvements in various aspects of cognition, namely interference control, verbal fluency, word production, verbal recognition, short-term memory, visual recognition and visual recall. None of the functions we tested was worse at the one-year follow-up (Wapp et al., 2015). Other studies have also reported improvements in visuospatial function, memory and language and mean cognitive performance six months or twelve months after revascularisation (e.g. Baracchini et al., 2012; Lal et al., 2011; Ortega et al., 2013). However, there are also studies which have found mixed results after CAS (Grunwald et al., 2010), no cognitive change (De Rango et al., 2008) or even a cognitive decline after CEA and CAS (e.g. Altinbas et al., 2011; Wasser et al., 2012).

Improvements in cognition following revascularisation are attributed to the improvement in cerebral blood flow (Ghogawala et al., 2013) while cognitive decline after revascularisation is often attributed to clinically silent ischemic lesions, general anaesthesia (used in CEA) and temporary interruption of blood flow (CEA and CAS) (De Rango et al., 2008).

It is important to evaluate the differential effects of carotid stenosis treatment on cognitive functions. Not only because it is an effective form of treatment against cognitive decline even in asymptomatic patients, but also because the chances of cognitive improvement vary between the outcomes of the different reperfusion methods, which has to be taken into account when estimating the risks and benefits of treatments.

3. Cognitive plasticity

Cognitive research often refers to the concept of plasticity. Over 120 years ago, James mentioned brain-matter plasticity in his book ‘The Principles of Psychology’ (James, 1890). Today, plasticity is defined as an adaptive neural response to learning, training and environmental enrichment (Anderson, Spencer-Smith, & Wood, 2011). Neuroplasticity used as an umbrella term is a fundamental property of neurons and the nervous system at all levels (from the highest behavioural level to the lowest genetic level) and across all species. Plasticity – whether during development, provoked through diseases or by external factors – is therefore the basis of all neuroscience (Shaw & McEachern, 2001). There are close relationships among neuronal activation, connectivity, and volumetric changes in brain and behaviour, achievement in school and employment and various cognitive functions. Structural brain changes can reflect changes in behaviour and cognition (Kolb & Whishaw, 1998). Neuronal and cognitive plasticity are intertwined, cognitive plasticity can stimulate neuronal plasticity and neural plasticity can in turn strengthen cognitive plasticity (Greenwood & Parasuraman, 2010). “Plasticity is an intrinsic property of the central nervous system, reflecting its capacity to respond in a dynamic manner to the environment and experience via modification of neural circuitry” (Anderson, Spencer-Smith, & Wood, 2011, p. 2197) or more simply, “brain plasticity refers to the brain’s ability to change structure and function” (Kolb & Whishaw, 1998, p. 43).

In the present thesis, plasticity is defined as an individual’s latent cognitive potential or cognitive capacity to adapt under certain specified conditions (Willis, Schaie, & Martin, 2009). Cognitive plasticity relates to the ability to change – for better or worse – on a behavioural level. It is important to stress at this point that despite some researchers claiming that plasticity can only be measured at the neuronal level, changes in cognition also represent a form of plasticity. Modification of cognitive functioning as a result of internal and external influences can also be defined as plasticity. Of course, measurements of changes in cognition are only indirect measures of plasticity. They are, however, an important indicator for intervention induced changes.

3.1 Training-induced plasticity

In most studies, cognitive plasticity, or reserve capacity, is operationalised as an improvement in performance on a given cognitive task following training (Fernández-Ballesteros et al., 2012). In regard to the described cognitive improvements after memory training in very preterm-born children, our data corroborate the existence of training-induced plasticity in the brains of very preterm-born children (Everts, Wapp, et al., 2015). The child's brain is highly plastic on cortical layers (Gogtay et al., 2004). The dynamic changes in brain structures which occur during childhood result in increased neuronal efficiency and faster network connections (Bryck & Fisher, 2012), this rapid maturation allows children to learn rapidly. The young brain is more responsive to remedial education and enrichment than the adult brain (Huttenlocher, 2002), for example children gain more from mnemonic practise than older adults. This finding strengthens the hypothesis that neuronal structures supporting memory are more plastic during infancy than in old age (Brehmer, Li, Muller, von Oertzen, & Lindenberger, 2007). While the sparse evidence for far-transfer of memory training does not speak for 'global' plasticity it is still possible that training does have specific effects on cognition because certain structures and neuronal processes react highly specifically and selectively to training (Gathercole, 2014). A pilot study by Everts and colleagues (2015) investigating a subsample of the described very preterm-born children in Study 1 could demonstrate high training-induced neural plasticity. They found that children who obtained memory training showed a significant decrease in fronto-parietal brain activation during a visual working memory task immediately after memory training in comparison to untrained controls. The children who showed the greatest improvement in working memory also showed the greatest reduction in fronto-parietal activation. These findings suggest that the child's brain is capable of training-related neuroplasticity (Everts, Mürner-Lavanchy, Schroth, & Steinlin, 2015).

Nevertheless, not only the child's brain is plastic. Cognitive plasticity changes across the life span (Brehmer et al., 2007; Lövdén, Brehmer, Li, & Lindenberger, 2012; Willis, 2010) and there is an association between cognitive plasticity and cognitive aging (Noack, Lövdén, Schmiedek, & Lindenberger, 2009). The notion that plasticity decreases or is lost altogether with age is

debatable, and in recent years there has been increasing interest in possible ways of slowing down the progression of age-related changes in cognition and the brain (Green, Strobach, & Schubert, 2014; Greenwood & Parasuraman, 2010). Healthy individuals show remarkable training-induced plasticity across the life span (Karbach & Schubert, 2013). Development remains modifiable or plastic throughout life span although there are limitations during various periods of development (Huttenlocher, 2002; Willis, 2010).

3.2 Stenosis- and treatment-induced plasticity

It is a bold endeavour, but this thesis represents an attempt to link cognitive plasticity to internal factors like carotid stenosis and external factors such as stenosis treatment. Study 2 showed that carotid stenosis, or the underlying causes of stenosis, has a negative influence on cognitive plasticity. The cognitive functions most affected by carotid stenosis (processing speed and interference control) are complex higher-order cognitive functions, which require a large cognitive capacity (Everts et al., 2014). It is not surprising that higher order association cortices are the first to be affected by reductions in cerebral blood flow. Higher cortical functions are more malleable than motor and primary sensory functions (Huttenlocher, 2002). They seem to be more vulnerable to internal and external factors influencing the brain and thus cognition. A recent study found diffuse white matter abnormalities and gray matter atrophy ipsilateral to the stenosis in patients with carotid artery stenosis before treatment compared to healthy controls (Avelar et al., 2015). These changes in brain tissue may result due to chronic hypoperfusion and might be an explanation for cognitive decline in patients with carotid artery stenosis. After treatment of the stenosis – whether with best medical treatment, CAS or CEA – there is an improvement in various cognitive tasks, which suggests that the brain has the ability to positively adapt in cognitive aspects. Better cerebral blood flow seems to improve cognitive performance. It is not possible, however, to make a statement about neuronal plasticity on the basis of Study 3, which examined cognitive outcome following carotid artery treatment. We do not yet know how endovascular treatment – and the resulting enhanced cerebral blood flow – changes brain tissue or whether it has effects at synaptic level.

In summary, our studies support that internal as well as external factors on cognition leads to plasticity in children born prematurely and patients with carotid artery stenosis, respectively. However, plasticity is a widely used term and it is tempting to use it to explain cognitive changes in almost every context. It is important to define what is meant by 'plasticity'. Fluctuation and variability in performance can also generate changes in cognition. For this reason, Noack and colleagues stated that plasticity is a relatively long-lasting phenomenon that requires change in intrinsic capacity (Noack et al., 2009). It is therefore crucial to investigate the long-term effects of cognitive plasticity and the processes underlying them. In order to link cognitive and neuronal plasticity, future research on cognitive plasticity should include measurements of functional and structural changes in the brain.

4. Methodological considerations, limitations and implications

4.1 Methodological differences in studies

Differences in methodology should be taken into account when comparing studies. Publication bias is a problem in cognitive science literature (positive results are more likely to be published) and selective outcome or analysis reporting biases (only some of the analysed outcomes are reported) are ubiquitous. Methods for reducing publication bias include encouraging replications, study registration and accurate pre-specification (Ioannidis, Munafò, Fusar-Poli, Nosek, & David, 2014). Differences in the results of memory training studies and studies of cognitive functions in patients with carotid artery stenosis may be due to differences in patient characteristics (see 4.1 Individual differences) and methodology. The latter is discussed below.

The use of different neuropsychological tests makes comparing studies problematic. Most studies do not assess higher cognitive functions as they rely on instruments which assess general cognitive ability, mostly IQ-tests (studies of preterm-born children) or examinations like the mini-mental state (studies of patients with carotid artery stenosis). This emphasis on change in global cognitive function scores means that changes in specific cognitive domains might be neglected (Plessers et al., 2014). Sometimes researchers assess several groups investigating the same cognitive domains by using the same tests (e.g. clinical trials in schizophrenia: Green et al., 2004). This enables more precise comparisons between studies. It is also important to note that clinical assessments do not always capture problems which affect everyday living. We should also consider behavioural correlates of the various cognitive functions because, for example, the executive function deficits in children born very prematurely are different when assessed clinically using cognitive instruments and when assessed using behavioural instruments (Ritter, Perrig, Steinlin, & Everts, 2014).

A second point is that follow-up schedules vary widely across studies. The interval between intervention and follow-up may be an important determinant of the detectable changes in cognition. As already mentioned, there is no consensus about the use of follow-up assessments in memory training studies (Jaeggi & Buschkuhl, 2014; Redick et al., 2015). On the one hand, training effects may be

lost after a long break in training, on the other hand, it may take some time after training for transfer effects to be consolidated (Holmes et al., 2009). In Study 1, we found cognitive improvements immediately after training as well as at a six-month follow-up (Everts, Wapp, et al., 2015). In Study 3, there was a one-year interval between treatment of carotid artery stenosis and follow-up (Wapp et al., 2015) – longer than is typical for such studies. Follow-up assessments are typically conducted between one day and six months after intervention and only a minority of studies report outcomes after twelve months (Plessers et al., 2014; De Rango et al., 2008). In patients with carotid artery stenosis the improvements in cognition seem to be greater at later follow-ups. We are not able to make a statement about cognitive changes occurring immediately after treatment on the basis of our study. It is recommended that postoperative testing should be carried out at least three months after treatment to detect lasting effects (Plessers et al., 2014).

Randomisation is another point to mention. In our memory training study children were randomly assigned to the memory strategy training group, the core working memory training group or the waiting control group. But randomisation can potentially create problems such as group differences in baseline performance. A possible solution to this problem is a randomised block design, where subjects are classified on the basis of their pre-test performance and then randomly assigned to the subgroups (Green et al., 2014). In our study of carotid artery stenosis treatments, treatment group allocation was not random, but based on the clinical decision of the treating physicians (Wapp et al., 2015). A control group would have strengthened the study by providing a control for spontaneous improvements and practise effects. In memory training research the relative merits of active and passive control groups are debated. It is difficult to control for the amount of contact, familiarity with the setting and expectancy effects with a passive control group. Using raters who are blind to group assessment may also help to reduce research bias in intervention studies (Green et al., 2014; Jaeggi, Buschkuhl, Shah, & Jonides, 2014; Morrison & Chein, 2011; Redick et al., 2015).

It is also important to consider methodological differences in the assessment of training benefits. Several methods of calculating the increase in working memory span have been used in core working memory studies. Different memory-training studies use different methods to calculate a ‘training gain’ score. For

example, some authors calculated the last minus the first training-session working memory span (Buschkuhl et al., 2008; Jaeggi, Buschkuhl, Jonides, & Perrig, 2008), others calculated the percentage increase in working memory span (Chein & Morrison, 2010). One research group used the highest three spans from the last three training days and the highest three spans from days two to four. Overall, participants trained each day over five weeks (Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009), others did not even report how gain scores were calculated (Olesen, Westerberg, & Klingberg, 2004). One reason for the differences in calculation of gain is that gain may not be a good indicator of the effectiveness of training. In core working memory training, the increase in working memory span may not be reflected in performance on other cognitive tasks. Von Bastian and Oberbauer (2013) have noted that the effects of memory training can be explained in two ways. First, an increased working memory capacity may lead to enhanced performance in various cognitive domains sharing variance with working memory. Second, transfer may be the result of the more efficient use of available working memory capacity as a result of use of specific strategies or automatization (von Bastian & Oberauer, 2014).

The choice of inclusion criteria is another important issue. In our memory training study we included only children who were born prematurely; had no or mild cerebral lesions; no or mild periventricular leukomalacia; were without chronic illness or medical problems which might influence development or pervasive developmental disorders (e.g. autism); had normal or corrected-to-normal vision and hearing and an IQ above 85 as measured by neuropsychological assessment (Everts, Wapp, et al., 2015). This last criterion may have resulted in underestimation of the population's true level of impairment. Including children with IQ below 85, however, would have reduced the validity of our results due to a larger heterogeneity of the study sample. In our studies of patients with carotid stenosis we included only patients with no major stroke; no progressive cerebral pathology and with enough time for the neuropsychological assessment before the intervention (Everts et al., 2014; Wapp et al., 2015). This last point created a selection bias towards less severe cases. Plessers and colleagues have argued that researchers should report inclusion criteria clearly, especially those relating to the inclusion or exclusion of stroke patients (Plessers et al., 2014). The next

subchapter discusses individual factors which should be considered when choosing inclusion criteria and interpreting findings.

4.2 Individual characteristics

Individual characteristics are usually neglected in intervention research (Bürki, Ludwig, Chicherio, & de Ribaupierre, 2014; von Bastian & Oberauer, 2014). Nevertheless, there are individual factors in plasticity and hence cognition which are of great clinical relevance. Since there is an almost endless list of factors concerning individual differences only the most commonly investigated individual factors in recent intervention research are discussed.

Age at time of investigation. Previous studies have shown that age contributes significantly to variance in cognitive performance in children born very prematurely or with very low birth weight. Young children (7-10 years) appear to have impairments in inhibition, working memory and shifting relative to controls, whereas older children (10-12 years) do not (Ritter, Nelle, Perrig, Steinlin, & Everts, 2013). This suggests that children born prematurely have caught up with their peers born at term by the age of 12 years, at the neural (Mürner-Lavanchy, Steinlin, Nelle, et al., 2014) and functional network level (Mürner-Lavanchy, Ritter, et al., 2014; Mürner-Lavanchy, Steinlin, Kiefer, et al., 2014) as well as in terms of cognitive performance (Ritter et al., 2013). Other research groups have also found evidence for catch-up in, for example, repetitive vocabulary (Luu, Vohr, Allan, Schneider, & Ment, 2011). Core working memory training studies report larger training-induced improvements in younger than older adults (for an overview see von Bastian & Oberauer, 2013). In Study 1, age was negatively correlated with gains in arithmetic in the memory strategy-training group. We also found a negative correlation between age and processing speed gain in the core working memory-training group. None of the other outcome variables were correlated with age (Everts, Wapp, et al., 2015). Studies of cognition in patients with carotid artery stenosis have found that older patients perform worse in cognitive tasks (Johnston et al., 2004), and that the cognitive outcome of revascularisation is worse in older patients (Mocco et al., 2006; Wasser et al., 2012). However, some studies have found that cognitive performance improves after CAS regardless of age, asymptomatic status and previous stroke events

(Ortega et al., 2013). In Study 2, we found no age-related differences in cognitive performance because we used age-adjusted normative test scores (Everts et al., 2014). In Study 3, we also found no age-related differences in pre-treatment cognition, but younger patients showed bigger improvements in word production, verbal recognition and recall, visual learning and short-term memory one year after treatment (Wapp et al., 2015). These results suggest that it is important to use age-matched controls or at least control for the effects of age when reporting on cognitive changes through training or medical treatment in pediatric or adult patients.

Risk factors. This section is not about maternal risk factors for preterm delivery (for an overview see Goldenberg et al., 2009), but about risk factors for cognitive impairment. As noted above, gestational age is negatively associated with educational achievement (Moster et al., 2008), and executive functions (Ritter, Nelle, Steinlin, & Everts, 2013). Preterm-born children with neurosensory impairment, and children growing up in a difficult socio-economic milieu are at higher risk of persistent cognitive deficits (Luu et al., 2011; Wolke, 2011). In children born prematurely, male sex is a predictor of general cognitive impairment and language impairment in early infancy, but not in middle childhood. It seems that as children mature perinatal risk factors gradually become irrelevant whilst environmental factors (e.g. parental education) become more important (Linsell et al., 2015). Genetic predispositions contribute to the inter-individual differences observed in training research (von Bastian & Oberauer, 2014), but consideration of genetic factors is beyond the scope of this thesis. The risk factors for carotid artery stenosis are smoking, hypertension, diabetes, hyperlipidaemia, coronary artery disease, male sex and advanced age (de Weerd et al., 2010; Greco et al., 2013). In our study risk factors were associated with cognitive performance before treatment. Motor speed was lower in patients with hypertension than in patients without hypertension and patients with atrial fibrillation had lower processing speed, lower visuospatial abilities and lower motor speed. On the other hand, patients with hypercholesterolemia had better verbal and visual episodic memory than patients without hypercholesterolemia (Everts et al., 2014). This finding may be due to the pharmaceutical treatment of hypercholesterolemia, as it has been reported that statins have a positive effect on episodic memory (Hyttinen et al., 2010).

Motivation. Only few memory training studies investigate the impact of motivational factors. Jaeggi and colleagues (2014) reported that the engagement level of participants who did not complete the training study decreased over time, whereas engagement levels remained stable in participants who completed the training sessions. Moreover, it has been reported that self-reported engagement correlates with training gain (Jaeggi et al., 2014). In our memory training study, motivation was positively associated with visual short-term memory gain score in both training groups (Everts, Wapp, et al., 2015). The positive association between motivation and cognitive performance change should be taken into account in further training studies.

Baseline performance. Pre-existing abilities influence the cognitive outcome of memory training and other interventions. Educational status, environment and the support of family, teachers and others also play an important role in individual performance. In very preterm-born children and in patients with carotid artery stenosis respectively, some similarities can be found regarding the improvements in various cognitive functions. In studies 1 and 3, baseline performance was negatively correlated with gain scores; in other words, the participants with the lowest performance before training or treatment gained most from the intervention (Everts, Wapp, et al., 2015; Wapp et al., 2015). Other studies have also reported that baseline performance influences response to an intervention (Diamond & Lee, 2011; Jaeggi et al., 2014; von Bastian & Oberauer, 2014); for example studies with older adults (Zinke et al., 2014) and children (Jaeggi et al., 2011) found that low baseline performance was associated with a greater cognitive improvement after training. Unfortunately most training studies do not report these aspects of the data (Bürki et al., 2014). We did not find a single study in patients with carotid artery stenosis which controlled for variance in baseline performance. It is strongly recommended that future studies should control for this factor.

To conclude, considering the number of individual factors which influence cognitive change, there is a need for more precise tools that take into account the variability within and between individuals. Latent growth curves are a useful way of visualising inter- and intra-individual change during training (Bürki et al., 2014). A recent review by Paraskevas and colleagues (2014) stated that no definitive conclusion could be drawn about the relative effects of CAS and CEA due to the described methodological considerations (Paraskevas, Lazaridis,

Andrews, Veith, & Giannoukas, 2014). Almost all reviews – whether about treatment of carotid stenosis, or memory training in children – discuss methodological problems and exclude some studies on the basis of methodological criteria. It is debatable whether the results of different training studies can be compared or not. Differences in training, samples, training duration and training intensity make it very difficult to come to general conclusions about the effectiveness of memory training. Studies of cognition in patients with carotid artery stenosis have to control for test-retest effects, perfusion at baseline and perfusion changes after intervention. Of course there is no ‘one size fits all’ methodology (Green et al., 2014), but this chapter has briefly summarised some of the different factors which should be taken into consideration in future studies.

5. Conclusion

The increasing number of studies about memory training in children and cognitive performance in patients with carotid artery stenosis underline the importance of both topics. The findings of the present thesis have implications for future memory training studies and intervention decisions for patients with carotid stenosis. Cognitive plasticity seems to be influenced by both internal and external factors.

The extant body of research provides evidence for the existence of training-induced cognitive plasticity. Our results highlight the importance of external factors such as memory training – especially memory strategy training – as a means of improving the cognitive performance of school-aged children born very prematurely. Interventions such as memory training are clinically highly significant as they have the potential to increase the working memory span and also enhance other school-relevant functions not only in children born prematurely, but also in children with various kinds of learning difficulties (Everts, Wapp, et al., 2015). Because memory training programmes have multiple components, it is difficult to determine which components are responsible for the reported cognitive changes. Training the brain is a difficult undertaking; new methodological approaches and rigorous designs may facilitate research into the effectiveness of cognitive interventions (Schubert, Strobach, & Karbach, 2014). Advances in neuroscience will also provide greater insight into the neural plasticity and may help to uncover the mechanisms underlying the observed cognitive changes (Bryck & Fisher, 2012). Although the mechanisms underlying transfer are not yet fully understood, there is no harm in using memory training (Jaeggi & Buschkuhl, 2014; Redick et al., 2015). There is only little evidence for far transfer effects, but if memory training makes someone believe that his or her memory has improved why would we not use memory training? At present there is only evidence that training has a positive and no negative impact on brain development, hence there is no reason not to train the brain.

There is some evidence for the existence of ‘stenosis-induced’ cognitive plasticity. Cognitive impairments are frequent in patients with carotid stenosis. Blockage or narrowing of the carotid artery has an impact on cognition and can therefore be seen as an internal influence on cognition. It is important to remember, however, that at present we do not know if the cognitive impairment

associated with carotid stenosis is due to the disease itself or to the risk factors for it (Everts et al., 2014). Nonetheless, from a clinical perspective it is important to identify patients showing signs of cognitive decline and monitor their higher-order cognitive functions. There is also evidence for ‘treatment-induced’ cognitive plasticity in patients with carotid artery stenosis; significant long-term improvements in frontal lobe functions and memory were found one year after treatment, independent of treatment type (Wapp et al., 2015). With the progressive ageing of the population it is becoming more and more important to understand cognitive functioning.

The thesis points out the importance of age as an individual factor influencing cognition. The important issue with respect to plasticity is whether there are sensitive periods in brain development during which interventions are more effective. Similarly, are there ‘critical periods’ or ‘windows of opportunity’ (Huttenlocher, 2002) for specific interventions? Further studies should consider this issue.

Last but not least, in both follow-up studies individuals with poor baseline performance profited most from interventions (Everts, Wapp, et al., 2015; Wapp et al., 2015); this highlights the significance of memory trainings in very preterm-born children and treatment in patients with carotid artery stenosis, especially in people with severe cognitive deficits. This pleasing finding is cause for optimism especially for individuals with more severe cognitive deficits resulting from premature birth or carotid artery stenosis.

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Statement of authorship

I hereby certify that this doctoral thesis has been composed by myself, and describes my own work, unless otherwise acknowledged in the text. All references and verbatim extracts have been quoted, and all sources of information have been specifically acknowledged. The work has not been accepted in any previous application for a degree. I am aware that otherwise, according to the article 36(1)(o) of the law of the 5th of September 1996, the senate is entitled to withdraw the title obtained by the present thesis.

Bern, January 2016

Manuela Wapp

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Study 1

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Effects of two different memory training approaches in very preterm-born children

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Abstract

Background: Little research has been conducted to assess the effect of using memory training with school-aged children who were born very preterm. This study aimed to determine whether two types of memory training approaches resulted in an improvement of trained functions and/or a generalization of the training effect to non-trained cognitive domains.

Methods: Sixty-eight children born very preterm (7-12 years) were randomly allocated to a group undertaking memory strategy training ($n=23$), working memory training ($n=22$), or a waiting control group ($n=23$). Neuropsychological assessment was performed before and immediately after the training or waiting period, and at a six-month follow-up.

Results: In both training groups, significant improvement of different memory domains occurred immediately after training (near transfer). Improvement of non-trained arithmetic performance was observed after strategy training (far transfer). At a six-month follow-up assessment, children in both training groups demonstrated better working memory, and their parents rated their memory functions to be better than controls. Performance level before the training was negatively associated with the training gain.

Conclusions: These results highlight the importance of cognitive interventions, in particular the teaching of memory strategies, in very preterm-born children at early school age to strengthen cognitive performance and prevent problems at school.

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Introduction

Children born very preterm (<32 weeks of gestation) and/or with very low birth weight (<1500g) show increasing survival rates thanks to advances in neonatal care. However, even in healthy preterm-born children, reading, writing, arithmetic, and attention are more often impaired than in children born at full term [1]. Scholastic problems can be related to

difficulties in learning and remembering information [2]. These observations highlight the need for a special memory-based training program to prevent school problems and strengthen cognitive performance in very preterm-born children.

Memory training research distinguishes between two different training approaches: restitution and substitution [3]. The restitution approach is based on the assumption that memory capacity can be

increased through intensive practice, and is often carried out using working memory training [4]. The substitution approach implies the use of internal strategies, namely memory strategies (such as rehearsal or chaining [5, 6]), in order to facilitate encoding, maintenance and recall of information. The aim of all memory training is to improve trained aspects of memory and structurally similar memory tasks (near transfer). In best case scenarios, memory training can also confer a generalization of the training effect to other non-trained, structurally different cognitive domains (far transfer).

Memory strategy training is often used in adult neurorehabilitation in order to enhance learning and the ability to remember after brain injury. However, it has been suggested that the use of memory strategies at early school age can also induce an improvement of verbal short-term memory, an increase in verbal learning [5], or amelioration of general knowledge and vocabulary [7]. Controversial study results exist as to whether memory strategy training induce a transfer effect. Some authors conclude that memory strategy training entails only a near transfer effect to structurally similar aspects of memory, and does not transfer to other memory domains or even cognitive domains unrelated to memory [8, 9]. Others present evidence to suggest there is indeed a far transfer of memory strategy training: in healthy young adults, the imagination strategy [10], the chaining strategy [6] and the rehearsal strategy [5] led to improvements of working memory. Likewise, teaching a combination of the rehearsal and organization strategies to school-aged children after stroke revealed a far transfer effect with improvements in non-trained verbal learning [11]. Both a near and far transfer effect was observed in a study teaching ten different memory strategies to children with memory problems; immediately after receiving the training they showed improvements in short-term memory and visual learning, but also an amelioration of general knowledge and vocabulary [7]. However, none of these studies has examined the long-term effect of memory strategy training after a few months.

Working memory is an important precondition for the attainment of school-relevant functions such as reading [12], arithmetic [13], executive control, and problem solving [14], and is closely related to general intelligence [15]. In line with the close association of

working memory with many higher order cognitive functions, working memory training studies claim improvement of working memory but also an improvement of non-trained functions such as fluid intelligence [16], reading performance [17, 18], arithmetic [19], attention [20] and executive functions [4, 21] in children and adults. Even three months after completion of working memory training, fluid intelligence is suggested to be increased [16], inferring that this type of training has a far transfer effect. However, just as for memory strategy training, the far transfer effect of working memory training is put into question; some studies have suggested that working memory training merely increases the trained function *per se* [19, 22].

The success of memory strategy training depends on certain influencing factors. Since age and experience help the child to choose the strategy that is most effective [23], the age range is central to training effect. Whether a child's intelligence has an influence on the training effect or not is unclear. Intelligent children might already apply memory strategies themselves before receiving memory strategy training and hence benefit less from this type of instruction. Additional factors such as motivation or number of training sessions are expected to influence the effect of memory training in children. The child's brain is in a process of rapid maturation and is therefore thought to possess particular plasticity, allowing for rapid learning within a short period of time. Thus, training effects in children are suggested to be stronger than in adults [24].

We hypothesize that, independent of the training approach, memory training activities lead to improvements in memory and non-trained functions (near and far transfer) in very preterm-born school-aged children immediately after receiving the training and at a six-month follow-up.

We will test this hypothesis by using a randomized, controlled and blinded study design. Evidence of a training effect would open up new opportunities to strengthen cognitive performance and prevent scholastic problems in very preterm-born children, but also in school-aged children with learning problems of other etiologies.

Methods

This study reports on a subset of data from the NEMO (NEuropsychology and meMOry) research project at the Children's University Hospital, Inselspital, Bern, Switzerland. The NEMO project examines cognitive development and training-induced changes in school-aged very preterm-born children. The ethics committee of the Children's University Hospital, Inselspital (Ethikkommission der Kinderkliniken Bern) and the regional ethics committee (Kantonale Ethikkommission Bern) approved the study protocol. All children and caregivers provided informed written consent prior to participation, consistent with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Participants

Very preterm-born children (<32 weeks of gestational age) and/or children with very low birth weight (<1500 g) born in the 1998-2003 cohort at the Children's University Hospital Bern were assessed within the scope of the NEMO research program. Inclusion criteria were: aged between 7 and 12 years, no or mild neonatal cerebral lesions (maximum hemorrhage grade I), no or mild periventricular leukomalacia (maximum grade II), no chronic illness (e.g. birth deformities, congenital heart defects, cerebral palsy or epilepsy), no medical problems potentially influencing development (e.g. meningitis, encephalopathy or traumatic brain injury), no pervasive developmental disorders (e.g. autism), normal or corrected-to-normal vision and hearing, and IQ >85 as measured by neuropsychological assessment. The latter criterion of having an IQ >85 was chosen so that the study sample would represent the largest population of preterm-born children, namely those with an IQ within the normal range [25], and to avoid cognitive heterogeneity impacting on the ability to generalize results. Inclusion was determined by revising medical files and by evaluating the first neuropsychological assessment. A total of 76 children fulfilled the inclusion criteria and were invited to the Children's University Hospital via a mailshot, which included an information booklet for parents and one for children. A total of 68 very preterm or very low birth weight children agreed to

participate in the study (35 boys, 33 girls; age mean, $M=9.56$ years, $SD=1.7$).

Study design

After a first neuropsychological assessment, a total of 68 children were randomly allocated to either the memory strategy training group ($n=23$), the working memory training group ($n=22$), or the control group ($n=23$). Randomization was carried out as per the standard operating procedure of the Clinical Trial Unit, University of Bern (between-subject factor: group). Randomization and allocation was performed using sealed randomization envelopes (Envelopock® Tamper Proof Evident Security Envelopes). The randomization process was stratified for age to achieve age-balanced groups.

Children underwent three neuropsychological assessments; time-point 1 (TP1) before the training or waiting control period; time-point 2 (TP2) immediately after training or waiting control period, and time-point 3 (TP3) six months after the training or waiting control period. Experienced clinical child neuropsychologists conducted all assessments; neuropsychologists blinded to the group allocation conducted assessment at TP2 and TP3. Mean time between TP1 and TP2 for the memory strategy training group was $M=70$ days (d), $SD=24$; for the working memory training group, $M=67$ d, $SD=18$; and for the control group, $M=64$ d, $SD=40$. Mean time between TP2 and TP3 for the memory strategy training group was $M=189$ d, $SD=20$; for the working memory training group, $M=185$ d, $SD=32$; and for the control group, $M=190$ d, $SD=30$.

Training procedure

Children randomly allocated to the memory strategy training group ($n=23$) received four weekly 60-minute 'Memo-Training' [26] sessions with a trained child neuropsychologist. These took place in a one-to-one setting at the Children's University Hospital. After each of the four training sessions, children practiced one of the memory strategies four times at home, resulting in an expected maximum of 16 homework sessions at 10 minutes per session. Memo-Training includes teaching and practicing of five

different memory strategies in an adaptive manner. It trains encoding and recall strategies in the episodic and semantic memory domain and is not expected to directly affect working memory, short-term memory or everyday memory. The following memory strategies were taught: chaining (creating a story with items to be recalled), rehearsal (internal or external repetition of items to be recalled), similarities (a combination of items to be remembered with known ideas or cues), imagination or visualization (lively imagination of the items to be recalled), and symbolic coding (symbolic notes of items to be remembered). The training tasks consisted of two difficulty levels; one for younger children (7-9 years) and one for older children (10-12 years) to achieve maximum individual adaptation and training involvement. The training procedure was the same for all participants, with a standardized order of instructional rounds and training tasks. The first two training sessions were used to introduce the child to the five memory strategies. During the third and fourth training sessions, the child was asked to choose between the five memory strategies to allow for autonomous strategy use and to stimulate meta-memory processes. A neuropsychological re-assessment was performed immediately after termination of the four-week memory strategy training ($n=23$), and at a follow-up assessment six months later ($n=22$).

Children randomly allocated to the working memory training group ($n=22$) undertook a computerized working memory training program (BrainTwister; www.braintwister.unibe.ch). This type of working memory training has previously been shown to improve working memory and fluid intelligence in adults [27,28], and reading performance in children [18]. The training was introduced to the children and their parents at the University Hospital in a 30-minute one-to-one setting, where installation and implementation of the training was explained and practiced. Over four weeks, two verbal and one visual working memory task were trained adaptively (mean 19.4 sessions) according to a training plan. The training plan allowed for a mingled task order. Each training task lasted four minutes, resulting in a total training time of 12 minutes. A neuropsychological re-assessment was performed immediately after termination of the four-week working memory

training program ($n=22$), and at a follow-up assessment six months later ($n=20$).

Children randomly allocated to the control group ($n=23$) underwent a neuropsychological assessment at TP1, then a passive waiting period of four weeks (no intervention). A neuropsychological re-assessment took place immediately after the waiting period (TP2, $n=23$), and again at six-month follow-up (TP3, $n=15$). After termination of the study protocol, children in the control group were free to choose between one of the two memory training approaches, or to have no further training.

Assessment procedure

Pre and post-test measures: At each time point, cognitive measures (Table 1) were assessed in the same order. If available, parallel versions of the neuropsychological tests were used at TP2 and TP3. Over all tests, raw scores were used for analyses of training effect. To examine the performance change between TP1 and TP2 (short-term effect) and TP1 and TP3 (long-term effect), we calculated a short-term gain score and a long-term gain score. The short-term gain score refers to the difference between performance at TP1 and TP2: $((TP2-TP1)/TP1)$. The long-term gain score is defined in the same way: $((TP3-TP1)/TP3)$. The higher the gain score, the stronger the changes between the two time points.

Motivation and number of homework sessions: In both training groups, the child's motivation was assessed before the second, third and fourth week of training. This was done using a self-generated motivation questionnaire consisting of four items (e.g. "Did you have fun doing the training?") 0=not at all to 5=very much), resulting in a possible total motivation score of 20. Furthermore, the sum of all homework sessions was counted using the child's training diary, in which the date and time of day of each training session was listed.

Socioeconomic status: Socioeconomic status was defined as the highest level of maternal education as assessed via a questionnaire (1=no graduation; 2=college; 3=college of higher order education; 4=university degree).

Table 1. Neuropsychological measures used to assess the training effect

| | Test | Measures/subtests used |
|-----------------------------------|---|---|
| Episodic memory D | Verbal Learning and Memory Test (VLMT) [39] | Word list: Verbal learning Verbal recall Verbal recognition |
| | BASIC Memory and Learning Test MLT (Battery for Assessment in Children) [7] | Patterns: Visual learning Visual recall Visual recognition |
| Working memory <i>e</i> | WISC-IV [40] | Letter-number sequencing |
| | BASIC Memory and Learning Test MLT (Battery for Assessment in Children) [7] | Spatial positioning |
| Short-term memory span D <i>e</i> | WISC-IV [40] | Digit span forward |
| | Corsi Block-Tapping Test [41] | Block tapping forward |
| Fluid intelligence | WISC-IV [40] | Matrices |
| Inhibition | Test Battery of Attention Performance (TAP) [42] | Selective attention (Go/NoGo) |
| Cognitive flexibility | Delis-Kaplan Executive Function System (D-KEFS) [43] | Color-Word Interference Test (number of mistakes) |
| Processing speed | WISC-IV [40] | Symbol search |
| Reading | ELFE [44] | Sentence reading |
| Arithmetic | WISC-IV [40] | Arithmetic |
| Everyday memory | Kognitive Probleme bei Kindern und Jugendlichen (KOPKIJ) [45] | Memory scale |

D This function is trained during memory strategy training

e This function is trained during working memory training

Statistical analysis

Data were analyzed with the Statistical Package for Social Sciences software for Windows, version 20 (SPSS, Chicago, Illinois). Because most of the variables were not normally distributed, non-parametric tests were calculated. Based on the directional hypothesis, tests were computed one-sided and a significance level of $p < 0.05$ was assumed. For multiple comparisons the Bonferroni method was used. Comparability of training groups with regards to cognitive performance at TP1 and demographical variables were calculated using the Chi-square or Wilcoxon rank-sum test. To determine the training effect, Wilcoxon rank-sum tests were calculated. For the short-term training effect, short-term gain scores for the control group were compared to the short-term gain scores for the memory strategy training group and the working memory training group, respectively. Long-term training effects were computed in the

same way, using long-term gain scores. To calculate the relationship between gain scores and age, IQ, motivation, and number of homework sessions, Spearman correlations were applied (for this correlation we used an absolute gain score, TP2-TP1, TP3-TP1 respectively).

Results

The control and training groups were comparable with regards to demographic variables at TP1 (see Table 2). Cognitive performance did not differ significantly between the three groups at TP1.

In the memory strategy training group, children completed an average of 13.3 homework sessions (SD=2.6; range 8-16). Mean motivation across all four memory strategy training sessions was 15.9 (SD=2.4; highest possible motivation score=20).

Table 2. Demographic data for the control and training groups

2a. Demographic data for the control and memory strategy training groups

| | Controls <i>n</i> =23 | Memory strategy training group <i>n</i> =23 | Total <i>n</i> =46 | χ^2/Z | <i>p</i> |
|------------------------|--------------------------|--|-----------------------|------------|----------|
| Sex (female) | 13 | 10 | 23 | 0.78 | 0.38 |
| Age, years | 9.34 (1.8) | 9.88 (1.6) | 9.6 | -0.98 | 0.33 |
| Gestational age, weeks | 29.5 (2.4) | 29.7 (2.1) | 29.6 | -0.13 | 0.89 |
| Birth weight, g | 1243.0 (389.9) | 1323.3 (394.7) | 1283.2 | -0.86 | 0.39 |
| IQ | 98.74 (11.8) | 103.30 (8.1) | 101.02 | -1.39 | 0.17 |
| SES | 2.70 (0.9) | 2.78 (0.9) | 2.74 | -0.39 | 0.70 |

2b. Demographic data of the control and working memory training groups

| | Controls <i>n</i> =23 | Working memory training group <i>n</i> =22 | Total <i>n</i> =45 | χ^2/Z | <i>p</i> |
|------------------------|--------------------------|---|-----------------------|------------|----------|
| Sex (female) | 13 | 10 | 23 | 0.55 | 0.46 |
| Age, years | 9.34 (1.8) | 9.45 (1.8) | 9.4 | -0.18 | 0.86 |
| Gestational age, weeks | 29.5 (2.4) | 29.2 (2.1) | 29.4 | -0.75 | 0.46 |
| Birth weight, g | 1243.0 (389.9) | 1298.3 (324.7) | 1270.0 | -0.69 | 0.49 |
| IQ | 98.74 (11.8) | 100.14 (9.8) | 99.4 | -0.55 | 0.59 |
| SES | 2.70 (0.9) | 2.68 (1.0) | 2.69 | -0.09 | 0.93 |

Note: Data are mean (SD); SES = socioeconomic status

On average, children in the working memory training group completed 20 training sessions (SD=2.4; range 15-25). Mean total motivation was 14.6 (SD=4.3).

Memory strategy training

Following memory strategy training, children showed significantly stronger improvement of trained functions (verbal/visual learning, visual recall and short-term memory; see Table 3) than the control group. Non-trained functions improved significantly more strongly in the training groups compared to the control group over the short-term (working memory: letter-number sequencing, spatial positioning, mental arithmetic). At the six-month follow-up assessment, improvement of verbal learning and working memory (letter-number sequencing), and parents' rating of their child's everyday memory functions remained

significantly stronger in the memory strategy training group compared to the control group.

In the memory strategy training group, a negative correlation was detected between age at TP1 and the arithmetic gain score ($r=-.51$, $p=0.017$), with a higher gain score seen in younger children. Intelligence was positively correlated with the visual recall gain score (*visual recall*: $r=0.68$, $p=0.007$), and negatively correlated with the verbal working memory gain score (*letter-number-sequencing* $r=-0.432$, $p=0.039$). Motivation was positively correlated with the visual short-term memory gain score (*spatial positioning* $r=0.46$, $p=0.026$). Performance at TP1 related negatively to the strength of the gain score in various cognitive domains (see Table 4), indicating higher gain scores in children with low cognitive performance before the training. This relationship was even apparent when controlling for age at TP1.

Table 3. Short- and long-term training effects

| Neuropsychological measures | Memory strategy training vs. controls | | Working memory training vs. controls | |
|--------------------------------|---------------------------------------|------------------|--------------------------------------|------------------|
| | Short-term effect | Long-term effect | Short-term effect | Long-term effect |
| | Z | Z | Z | Z |
| Episodic memory | | | | |
| Verbal learning | -3.45***‡ | -2.75**‡ | -0.65 | -0.10 |
| Verbal recall | -0.94 | -0.20 | -0.57 | -0.01 |
| Verbal recognition | -1.02 | -0.21 | -1.27 | -0.05 |
| Visual learning | -3.06**‡ | -1.30 | -0.21 | -1.53 |
| Visual recall | -1.98* | -0.58 | -1.49 | -0.27 |
| Visual recognition | -1.01 | -1.21 | -1.45 | -1.45 |
| Working memory | | | | |
| Letter-number sequencing | -3.40***‡ | -3.52***‡ | -2.09* | -2.10* |
| Spatial positioning | -1.74* | -1.53 | -0.52 | -0.65 |
| Short-term memory span | | | | |
| Digit span forward | -0.64 | -0.14 | -1.04 | -0.17 |
| Block tapping forward | -2.18* | -0.85 | -2.06* | -0.65 |
| Fluid intelligence matrices | -0.20 | -0.99 | -0.46 | -1.52 |
| Inhibition selective attention | -1.62 | -1.10 | -0.05 | -0.69 |
| Cognitive flexibility | | | | |
| Colour-word interference | -0.40 | -0.65 | -0.76 | -0.32 |
| Processing speed | | | | |
| Symbol search | -0.96 | -0.65 | -1.61 | -1.08 |
| Reading | | | | |
| Sentence reading | -1.05 | -0.02 | -0.65 | -0.39 |
| Arithmetic | -2.32** | -0.01 | -1.01 | -0.67 |
| Everyday memory | -0.45 | -2.70***‡ | -0.22 | -1.91* |

Note: *p* one-sided, **p*<.05, ***p*<.01, ****p*<.001, ‡ remains significant after Bonferroni correction

Working memory training

Following working memory training, there was a significantly stronger improvement in trained functions (working memory, short-term memory; see Table 3) when compared to the control group. There were no significant group differences in the improvement of non-trained functions. At the six-month follow-up assessment, improvement of trained verbal working memory remained significantly stronger, and parents' rating of their child's everyday memory functions was significantly better in the training group compared to the control group.

In the working memory training group, age at TP1 was negatively correlated with processing speed gain score (*symbol search*: $r=-0.44$, $p=0.044$), indicating

higher gain scores in younger children. Intelligence was positively correlated with the visual learning gain score (*visual learning*: $r=0.64$, $p=0.002$), and negatively correlated with the arithmetic gain score ($r=-0.48$, $p=0.032$). Motivation was positively associated with visual short-term memory (short-term gain score; *block tapping forward* $r=0.46$, $p=0.031$). Performance at TP1 was negatively correlated with various short and long-term gain scores (see Table 4), with higher gain scores in children with low cognitive performance, even when controlling for age at TP1.

In both training groups, neither the number of training or homework sessions, nor socioeconomic status was associated with short and long-term gain scores.

Table 4. Correlations between short-term gain score and performance before training (TP1)

| Measures | Memory strategy training | Working memory training | Control group |
|---|--------------------------|-------------------------|---------------------|
| | Short-term GS x TP1 | Short-term GS x TP1 | Short-term GS x TP1 |
| Word list: Verbal learning | -0.33 | -0.44* | -0.17 |
| Verbal recall | -0.80***‡ | -0.55** | -0.81***‡ |
| Verbal recognition | -0.61***‡ | -0.49* | -0.20 |
| Patterns: Visual learning | -0.39 | -0.09 | -0.37 |
| Visual recall | -0.80***‡ | -0.63***‡ | -0.55** |
| Visual recognition | -0.33 | -0.15 | -0.26 |
| Letter-number sequencing | -0.74***‡ | -0.07 | -0.32 |
| Spatial positioning | -0.51* | -0.14 | -0.47* |
| Digit span forward | -0.01 | -0.58** | -0.67***‡ |
| Block tapping forward | -0.44* | -0.28 | -0.50** |
| Matrices | -0.33 | -0.01 | -0.47* |
| Selective attention (Go/NoGo) | -0.69***‡ | -0.62***‡ | -0.57** |
| Colour-word interference test (number of mistakes) | -0.65***‡ | -0.72***‡ | -0.40 |
| Symbol search | 0.15 | -0.36 | -0.18 |
| Sentence reading | -0.14 | -0.37 | -0.54* |
| Arithmetic | -0.62***‡ | -0.33 | -0.03 |

Note: p one-sided, * $p < .05$, ** $p < .01$, *** $p < .001$, ‡ remains significant after Bonferroni correction

Discussion

Following two different memory training approaches, children who were born very preterm showed improvements in memory functions over both the short and long term, independent of the type of training.

In more detail, children who undertook a course of memory strategy training sessions exhibited a near and far transfer effect, with immediate improvement of trained aspects of memory (verbal and visual learning and recall, visual short-term memory), and improvement of non-trained cognitive domains (working memory, mental arithmetic). At the six-month follow-up assessment, improvements in trained functions (verbal learning) and non-trained domains were still present (verbal working memory, parental rating of everyday memory performance), whereas no performance changes occurred in the control group, neither at short nor at long term

Children following a program of working memory training presented a significant improvement in trained functions (verbal working memory, visual

short-term memory). Non-trained functions did not improve after the training. At the six-month follow-up assessment, improvement of verbal working memory remained significant, and parents' rating of their child's everyday memory functions was better in the working memory training group compared to the control group.

To summarize, these results show an immediate effect of memory training on cognitive domains that are structurally related to trained functions (near transfer). Following memory strategy training, there was even an improvement of structurally unrelated tasks such as mental arithmetic (far transfer). Long-term training effects occurred in different memory domains after both types of training.

Transfer effect

Why did a far transfer effect to structurally different cognitive domains only occur after memory strategy training? We assume that participants generalize the skills learned during memory strategy training to other cognitive domains, especially where multiple

memory strategies were used [5, 7]. In memory strategy training studies applying only one memory strategy, no transfer effect to non-trained cognitive domains occurred [8]. Where multiple memory strategies were used, a far transfer effect is more likely to occur [7, 11]. Support for this assumption is given when considering meta-memory; knowledge and consciousness about one's own memory processes. Memory strategy training requires children to recall different memory strategies, and then to autonomously apply the most applicable strategy to the situation at hand. Hence, our memory strategy training strains meta-memory to a high extent. Meta-memory is known to be a precondition for learning and applying memory strategies [29]. Pre-school children have only basic meta-memory skills, whereas at the age of around 12 years, meta-memory is suggested to be fully developed and considered a good predictor for memory performance [23]. We therefore suggest that the effect of memory strategy training coincides with an improvement of meta-memory.

Low performers are high gainers

It is of great clinical relevance to determine factors that influence the training effect. Our analysis showed that, in particular, children who had low cognitive performance before the training program improved their performance through memory training. In other words, our study revealed that low performers are high gainers, independent of the memory training approach. The influence of performance level on the training effect has been shown in previous studies using working memory training activities [16, 30]. For memory strategy training, we assume that low performers benefit more because they have not yet spontaneously applied memory strategies to solve a task, whereas high-performers might have already referred to memory strategies, thus enabling high cognitive performance levels.

Plasticity of the child's brain

Children tend to show greater neural and behavioral plasticity than adults [31], and hence training-induced plasticity is expected to be enhanced in the developing brain. A study by Brehmer *et al.* (2007),

compared training-induced plasticity across the lifespan [10]. The authors taught healthy young (9-12 years), middle-aged (20-25 years), and older participants (65-78 years) a modified version of the 'method of loci, a memory strategy applied to encode and retrieve words through location cues. In line with current views from lifespan psychology [24], children profited more from memory strategies than older adults [10]. Also after working memory training, Brehmer *et al.* (2012) showed that training and transfer gains were somewhat greater for younger than for older adults in some tasks, but comparable across age groups in other tasks [32]. Our data support the notion of high functional plasticity in children: a four-week training course led to an improvement in different aspects of cognition in children who were born very preterm. A subgroup of the present study population underwent functional magnetic resonance imaging to detect the cerebral visual working memory network before and after the training or waiting period. Interestingly, results show a significant decrease of neural activity within the fronto-parietal working memory network in both memory training groups whereas no neural changes occurred in the control group [33]. These pilot data point towards a training-related decrease of brain activation, independent of the training approach and clearly highlight the high training-induced plasticity of the child's brain during development. In a future study, it would be interesting to compare the effect size of memory training approaches, and the magnitude of the transfer effect across lifespan.

In previous studies we have shown that our very preterm study population presents a maturational spurt at around the age of 7-12 years, which does not occur in the healthy term-born control sample. On a cognitive [34] but also on a neural [35] and functional network level [36,37] group differences were significantly more pronounced between our preterm and control samples at a younger (7-8 and 9-10 years) age than at an older (11-12 years) age. The observation of a maturational catch-up at early school-age in very preterm-born children might be associated with high training-induced plasticity after our rather short memory training programs. Whether the training effect would be similar in term-born control children, where maturational changes are less salient at early school-age, remains to be determined.

Limitations

Studies of memory training are not as rigorous as standardized clinical trials. Although individual measures such as motivation or number of homework sessions were assessed, there always remains some inter-individual variance. The training and homework sessions implied enhanced attention and care from parents and trainers, which might influence the child's cognitive performance level indirectly (e.g. through increased self-confidence or strengthening of the child-caregiver relationship), and hence favor the training groups as opposed to the control group. This variance must be considered when interpreting results of memory training studies. The present study only included very preterm-born children with an IQ >85 and few-to-no neonatal complications. Hence, data cannot be generalized to any preterm sample. Furthermore, the optimal duration and spacing of memory training sessions, and the role of reward have yet to be determined. Memory training might be more useful in association with ecological tasks [38], or ongoing low-level training over the months and years.

Conclusions

Memory training is an effective way to improve different aspects of memory at early school-age, but - particularly in the case of memory strategy training - also helps to improve non-trained cognitive domains in children who were born very preterm. However, the child's cognitive performance level before undertaking training significantly influences the training's success, with low performers being high gainers, independent of the training approach. Consequently, these data emphasize the need to educate parents, teachers and therapists on how to introduce memory training activities to children who were born very preterm, but also to children with various kinds of learning difficulties in order to decrease the risk of academic problems.

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Study 2



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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 | Delis-Kaplan Executive Function System (D-KEFS; [34]) | | | |
| | Stroop reading | | | | |
| | 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 Salmaso & 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.

| | | 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 ^a | 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; ^a 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 | .989 | 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 asympto-

matic 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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Cognitive improvement in patients with carotid stenosis is independent of treatment type

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Summary

Treatment of carotid artery stenosis decreases the long-term risk of stroke and may enhance cerebral blood flow. It is therefore expected to have the potential to prevent cognitive decline or even improve cognition over the long-term. However, intervention itself can cause peri-interventional cerebral infarcts, possibly resulting in a decline of cognitive performance, at least for a short time. We investigated the long-term effects of three treatment methods on cognition and the emotional state one year after intervention.

In this prospective observational cohort study, 58 patients with extracranial carotid artery stenosis ($\geq 70\%$) underwent magnetic resonance imaging and assessment of cognition, mood and motor speed before carotid endarterectomy ($n = 20$), carotid stenting ($n = 10$) or best medical treatment ($n = 28$) (i.e., time-point 1 [TP1]), and at one-year follow-up (TP2). Gain scores, reflecting cognitive change after treatment, were built according to performance as $(TP2 - TP1)/TP1$.

Independent of the treatment type, significant improvement in frontal lobe functions, visual memory and motor speed was found. Performance level, motor speed and mood at TP1 were negatively correlated with gain scores, with greater improvement in patients with low performance before treatment.

Active therapy, whether conservative or interventional, produces significant improvement of frontal lobe functions and memory in patients with carotid artery disease, independent of treatment type. This effect was particularly pronounced in patients with low cognitive performance prior to treatment.

Key words: carotid artery stenosis; cognitive function; emotional state; endarterectomy; stenting; best medical treatment

Introduction

Cognitive performance is an important outcome measure of carotid artery treatment and affects patient well-being and quality of life. High-grade stenosis of the carotid artery is associated with cognitive impairment [1], even when there is no evidence of infarction on magnetic resonance imaging (MRI). Likely mechanisms for such cognitive effects are multiple and include embolisation and chronic or intermittent hypoperfusion distal to the stenosis. Interestingly, some patients display normal cognitive performance despite severe carotid artery disease [1]. At present, carotid artery disease is usually treated with carotid endarterectomy (CEA), carotid artery stenting (CAS) or best medical treatment (BMT).

Reports on the effect of carotid artery treatment on cognition are inconsistent. Some studies claim an increase of cognitive performance after CEA in certain cognitive domains [2, 3], others propose a cognitive decline [4, 5], and some describe no performance change after CEA [6]. Recent reviews [7–9] concluded that neither CEA nor CAS clearly affected cognition in general and that there were no differences in overall cognitive functioning after CEA or CAS. However, a definitive conclusion regarding the effect of CAS versus CEA on cognitive function is impossible owing to heterogeneity in definition, method, timing of assessment and type of cognitive tests.

Time at follow-up varied widely across studies, with follow-up ranging from 24 hours to 12 months [8]. More time between carotid stenosis treatment and follow-up as-

assessment is reported to be associated with greater cognitive improvement [10, 11]. Therefore, the time-window between treatment and follow-up might be a crucial factor for evaluating cognitive change after carotid stenosis treatment.

Regarding the emotional state of patients with carotid artery disease, several studies indicate an improvement after treatment of carotid stenosis: lower depression scores were observed after CAS [12] and better mental health scores were observed after CEA [13]. These improvements are likely due to the emotional relief of a reduced risk of stroke and psychological relief after uncomplicated treatment [6].

In this study, we compared the long-term effects of different invasive revascularisation methods (CEA, CAS) and BMT on cognition, and describe for the first time in the literature the long-term effects of three different treatment methods on the emotional state of patients with carotid artery disease. Findings of cognitive or emotional long-term improvements would support the efficacy of carotid artery disease treatment.

Methods

Cohort and study design

Between 2009 and 2012, specialised interdisciplinary clinical teams at two university hospitals recruited 95 in- or outpatients with significant carotid stenosis ($\geq 70\%$) on any noninvasive examination (Doppler, computed tomography angiography or magnetic resonance [MR] angiography). Patients were considered symptomatic if a minor stroke [14], retinal ischaemia or transient ischaemic attack (TIA) with motor, sensory, speech or visual impairment had occurred within 3 months prior to inclusion. Asymptomatic patients were defined as having no previous minor stroke or TIA. Patients had to consent to the study and be able to undergo a standardised cognitive assessment and an MRI examination before possible treatment of carotid artery disease (time point 1; TP1, as described elsewhere [1]) and at one-year follow-up (time point 2; TP2). A one-year follow-up period was chosen to gain insight into the long-term outcome of patients after noninvasive treatment of carotid artery disease.

Exclusion criteria were: major stroke, carotid stenosis $< 70\%$, significant handicap at the time of inclusion as measured by a modified Rankin Scale score > 2 , progressive cerebral pathology (such as tumour, multiple sclerosis, Alzheimer's disease), and standard exclusion criteria for MRI investigations. Local ethics committees of the responsible centres approved the study protocol. Written informed consent was obtained from all patients prior to study inclusion.

Clinical assessment

The degree of carotid artery stenosis was determined based on Duplex ultrasound. Peak systolic velocities of > 125 cm/sec were graded as stenosis of $\geq 70\%$, which is equivalent to a stenosis of $\geq 70\%$ according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) [15, 16]. If Duplex data were unavailable, data from digital subtraction

angiography, computed tomography angiography or MR angiography were used to grade stenoses, also according to NASCET criteria [15]. High resolution 1.5 Tesla MRIs were analysed to score the severity of white matter hyperintensities (Fazekas rating scale, Age-Related White Matter Changes (ARWMC) scale [17–19]) and to document structural brain lesions caused by trauma, haemorrhage, old infarction, infection or tumour, in particular in symptomatic carotid artery disease (table 1). On T1 weighted images the relative white and grey matter volumes were calculated (Statistical Parametric Mapping 8, SPM8; www.fil.ion.ucl.ac.uk/spm/ for MATLAB R2009a, MathWorks, Natick, MA, USA). 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 et al. 2013 [20]: classical complete, hypoplastic and incomplete circle of Willis. For details regarding the association between the collateralisation and cognitive assessment at TP1 see [1]. The National Institute of Health Stroke Scale (NIHSS) was assessed to evaluate the neurological status of the patients. Vascular risk factors were assessed by physicians during an interview (see table 1).

Cognitive assessment

The cognitive assessment comprised 13 cognitive domains (printed below in italics). In the domain of executive functions, *interference control* (Stroop Interference [21]), *processing speed* (Symbols [22]), and *verbal fluency* (Animal Naming; [23]) were assessed. *Word production* was assessed with the Boston Naming Test [23]. Furthermore, different memory domains such as *verbal learning, recall and recognition* (Word Rey Learning Tests; [24]), *short term memory* (Digit Span Test; [22]) and *visual learning, recall and recognition* (for patients > 70 years Signs; [25]; for patients < 70 years Rey Figure [26]) were assessed. *Motor speed* (Purdue Pegboard; [27]) and *emotional state* (Hospital Anxiety and Depression Scale [28]) were assessed (high scores represent high anxiety and/or depression). In all tasks higher scores reflect better performance, except for interference control, where lower scores indicate better performance. For a detailed description of cognitive performance before treatment see [1].

Therapy

Decisions about whether and which method of treatment was applied (CEA, CAS, BMT) were taken independently of the study and were up to the treating physicians and patients. In both centres, published European guidelines were followed [29]. There was a lower threshold to intervene (CEA or CAS) in patients with recent symptoms related to the stenosis, male patients, and high grade stenosis. In both centres, CEA is generally preferred in symptomatic and elderly patients. BMT included an antiplatelet agent, statin treatment to attain a low density lipoprotein cholesterol level ≤ 2.6 mmol/l, antihypertensive treatment to attain a blood pressure $< 140/90$ mm Hg (diabetics: $< 130/85$), strict control of hyperglycaemia if diabetic, counselling for smoking cessation, and basic information about weight control, regular physical exercise, and balanced nutrition.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics 20.0. For all cognitive, motor speed and emotional state tests, raw scores were used for the analyses. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. The majority of the variables (except interference control and verbal learning, recognition and recall) were not normally distributed. Consequently, and also because of the different group sizes, non-parametric statistics were used to evaluate all variables. Two-sided probabilities are reported for all statistical tests. The Bonferroni method was used to counteract type I error caused by multiple comparisons [30]. Mann-Whitney-U tests were analysed to identify group differences between symptomatic and asymptomatic patients according to the MRI. To detect group differences among the three treatment groups (CEA, CAS, BMT) with regard to patient characteristics, the Kruskal-Wallis test was applied. Differences between cognitive performance at TP1 and TP2 were calculated using the Wilcoxon signed-rank test. Changes in cognitive performance between TP1 and TP2 are presented as relative gain scores, and approximate effect sizes are reported as r . The relative gain score is defined as $((TP2-TP1)/TP1)$. Gain score differences were analysed with Kruskal-Wallis tests (treatment groups, education level, side of stenosis) or Mann-Whitney-U tests (sex, condition). To analyse the relationship between age, performance level at TP1 and gain scores, Spearman correlations were performed. Sample size varied across different cognitive tasks due to the fact that some tasks were only performed in patients ≥ 70 years (visual memory: Signs Learning Test) or in patients < 70 years (visual memory: Rey figure).

Results

Of 95 patients who were initially recruited into the study at the two hospitals, 37 were excluded because of stenosis grade $< 70\%$ ($n = 13$), intracranial instead of extracranial stenosis ($n = 5$), infarction larger than a third of the middle cerebral artery territory ($n = 3$), severe stroke ($n = 2$), or missing cognitive data ($n = 6$). One year after the first assessment, two patients had died and six patients did not want to continue in the study. Therefore, 58 patients were retained for further analyses (43 male, 15 female; mean age 69.4, range 51.4–85.3 years). There was no effect of age (over all raw scores Spearman correlations $p > 0.05$), sex (Kruskal-Wallis tests $p > 0.05$) or education (Mann-Whitney-U tests $p > 0.05$) on gain scores. The number of symptomatic or asymptomatic patients, sex, age, vascular risk factors, relative grey and white matter volume, hyperintensity, NIHSS scores and cognitive performance at TP1

showed no significant differences between treatment groups (table 2). White matter hyperintensities, and grey and white matter volumes, did not differ between symptomatic and asymptomatic patients (table 1).

For all groups combined, mean time between cognitive assessment and follow-up examination was 389 days (standard deviation [SD] 38, range 306–519 days). At time of treatment, 36 patients were asymptomatic. Among the 22 patients with symptomatic carotid artery stenosis, 44.5% had a TIA, 22.2% suffered from a minor stroke and 33.3% had retinal ischaemia. In symptomatic patients, the time interval to stroke or TIA had no influence on the gain scores in all cognitive tasks.

In the total group of patients, the mean score of all 13 cognitive tasks increased between TP1 and TP2. Significant improvement of cognitive performance occurred in 8 out of 13 cognitive tasks (61.5%) and in motor speed (dominant hand: $Z = -2.16$, $p = 0.031$, table 3). Emotional state did not improve significantly between TP1 and TP2 (anxiety: $Z = -1.15$, $p = 0.249$; depression $Z = -0.06$, $p = 0.950$).

Cognitive assessment at TP1 was performed in 20 patients before CEA (34.5%), in 10 patients before CAS (17.2%) and in 28 patients before BMT (48.3%). Patients of the CAS group improved in all cognitive tasks after one year; this was statistically significant in 4 of 13 tasks ($p < 0.05$). Patients with CEA also improved in all cognitive tasks; this was statistically significant in 2 of 13 tasks ($p < 0.05$). Patients with BMT improved in 11 of 13 cognitive tasks; this was statistically significant in 3 of 13 tasks ($p < 0.05$). However, in the BMT group, performance showed a nonsignificant trend towards a decline in two cognitive tasks. Gain scores did not differ significantly among the three treatment groups in any of the cognitive tasks (see table 4).

Women had significantly higher gain scores in visual learning than men ($U = 38$, $Z = -2.02$, $p = 0.043$). Age correlated significantly with the gain score of word production ($r = -0.27$, $p = 0.043$), verbal recognition ($r = -0.31$, $p = 0.019$), verbal recall ($r = -0.32$, $p = 0.014$), visual learning ($r = -0.39$, $p = 0.047$) and short term memory ($r = -0.26$, $p = 0.049$), with younger patients benefitting more from treatment. Presence of collaterals did not influence the gain scores of all tests.

Performance level at TP1, mood at TP1 and motor speed at TP1 were significantly correlated with gain scores in a negative way, such that greater improvement was observed in patients with low performance at TP1 (interference control: $r = -0.30$, $p = 0.025$; processing speed: $r = -0.47$, $p < 0.001$; verbal fluency: $r = -0.38$, $p = 0.003$; short term memory: $r = -0.37$, $p = 0.004$; verbal memory: $r = -0.45$, $p < 0.001$, visual learning: $r = -0.68$, $p < 0.001$; visual recognition: $r = -0.97$, $p < 0.001$; visual Rey immediate recall: $r = -0.60$, $p =$

| | Asymptomatic n = 36 | Symptomatic n = 22 | Group difference Z (p-value) |
|------------------------------|------------------------|-----------------------|---------------------------------|
| ARWMC | 4.37 (4.34) | 4.95 (3.03) | -1.01 (0.311) |
| Fazekas scale | 0.80 (0.79) | 1.14 (0.73) | -1.72 (0.085) |
| Relative grey matter volume | 1.01 (0.14) | 0.99 (0.14) | -0.34 (0.733) |
| Relative white matter volume | 1.00 (0.16) | 0.99 (0.13) | -0.07 (0.946) |

ARWMC = age-related white matter changes
Data are mean (standard deviation)

0.001; visual Rey late recall: $r = -0.38$, $p = 0.042$; anxiety: $r = -.40$, $p = 0.003$; depression: $r = -0.45$, $p = 0.001$, motor speed nondominant hand: $r = -.41$, $p = 0.002$). Hence, patients with low cognitive performance, low anxiety and depression or slow motor speed at TP1 benefitted most from endarterectomy.

The side of stenosis and the presenting symptoms (asymptomatic versus symptomatic) did not relate to performance at TP1, TP2 or gain scores. Time between treatment and follow-up was not associated with gain scores on any cognitive task. However, education level correlated with inter-

ference control, verbal fluency and word production at TP1 and TP2 (all: $r > 0.34$, $p < 0.05$).

Discussion

The present study showed that, independent of the treatment type, significant improvement of executive functions, visual memory and motor speed can occur following treatment of carotid artery disease. Following BMT, improvement occurred in fewer cognitive tasks than after CEA or CAS. However there was no significant effect of treatment group with regard to cognitive performance level at 1-year

Table 2: Patients' characteristics.

| | BMT n = 28 | CAS n = 10 | CEA n = 20 | Total n = 58 | Group differences H(2)/(p-value) |
|---|---------------|---------------|---------------|-----------------|-------------------------------------|
| Demographics | | | | | |
| Age, mean (SD) | 71.3 (8.1) | 65.4 (9.3) | 68.7 (7.9) | 69.4 (8.4) | 3.4 (0.18) |
| Male, n (%) | 21 (75.0) | 9 (90.0) | 13 (65.0) | 43 (74.1) | 2.2 (0.34) |
| Asymptomatic, n (%) | 20 (71.4) | 4 (40.0) | 12 (57.1) | 36 (62.1) | 3.1 (0.21) |
| Stenosis side, n (%) | | | | | |
| Right | 11 (39.3) | 6 (60.0) | 9 (45.0) | 26 (44.8) | 1.9 (0.39) |
| Left | 9 (32.1) | 3 (30.0) | 8 (40.0) | 20 (34.5) | |
| Both | 8 (28.6) | 1 (10.0) | 3 (10.0) | 12 (20.7) | |
| Vascular risk factors, n (%) | | | | | |
| Hypertension | 22 (83.3) | 5 (50.0) | 15 (75.0) | 42 (72.4) | 3.1 (0.22) |
| Diabetes | 7 (25.0) | 2 (20.0) | 7 (35.0) | 16 (27.6) | 0.9 (0.63) |
| Hypercholesterolaemia | 23 (82.1) | 5 (50.0) | 15 (75.0) | 43 (74.1) | 3.9 (0.14) |
| Coronary artery disease | 10 (35.7) | 6 (60.0) | 6 (30.0) | 23 (37.9) | 2.6 (0.27) |
| Thrombophilia | 0 | 0 | 1 (5.0) | 1 (1.7) | 1.9 (0.39) |
| Atrial fibrillation | 2 (7.1) | 0 | 2 (10.0) | 4 (6.9) | 1.0 (0.60) |
| Current smoking | 5 (17.9) | 2 (20.0) | 5 (25.0) | 12 (20.7) | 0.4 (0.84) |
| Number of risk factors | 2 (0-5) | 2 (1-4) | 2 (0-5) | 2 (0-5) | 1.7 (0.44) |
| Lesion analysis by structural MRI | | | | | |
| NIHSS score | 0 (0-4) | 0 (0-0) | 0 (0-0) | 0 (0-4) | 3.8 (0.15) |
| Grey matter volume | 1.02 (0.15) | 1.04 (0.07) | 0.96 (0.14) | 1.00 (0.14) | 3.9 (0.14) |
| White matter volume | 1.01 (0.17) | 1.02 (0.14) | 0.97 (0.12) | 1.00 (0.14) | 0.7 (0.70) |
| Faszekas scale | 1 (0-3) | 1 (0-3) | 1 (0-2) | 1 (0-3) | 1.4 (0.50) |
| ARWMC | 5.51 (4.34) | 4.70 (3.55) | 3.37 (3.45) | 4.59 (3.88) | 3.9 (0.19) |
| ARWMC = age-related white matter changes; BMT = best medical treatment; CAS = carotid artery stenting; CEA = carotid endarterectomy; MRI = magnetic resonance imaging; NIHSS = National Institute of Health Stroke Scale Data are mean (standard deviation), n (%) or median (range) | | | | | |

Table 3: Cognitive performance before (TP1) and after treatment (TP2; 1-year follow-up).

| | TP1 | TP2 | Z | r |
|--|------|------|-----------------------|------|
| Interference control [†] | 76.5 | 69.0 | -2.93** [†] | 0.39 |
| Processing speed | 19.0 | 21.0 | -1.82 | 0.24 |
| Verbal fluency | 18.0 | 21.0 | -2.69** | 0.35 |
| Word production | 23.0 | 26.0 | -2.27* | 0.29 |
| Verbal learning | 37.0 | 36.5 | -0.46 | 0.06 |
| Verbal recognition | 11.5 | 12.0 | -2.10* | 0.27 |
| Verbal recall | 10.0 | 10.0 | -1.20 | 0.15 |
| Short term memory | 5.5 | 6.0 | -4.20*** [†] | 0.55 |
| Visual learning | 17.5 | 17.0 | -0.29 | 0.05 |
| Visual recognition | 10.0 | 10.0 | -2.27* | 0.43 |
| Visual recall | 7.0 | 7.5 | -0.34 | 0.07 |
| Visual Rey immediate recall | 20.0 | 24.8 | -2.51* | 0.46 |
| Visual Rey late recall | 20.0 | 24.8 | -3.07** [†] | 0.57 |
| TP1 = cognitive assessment before treatment, TP2 = cognitive assessment at 1-year follow-up Data are median raw scores [†] In all tasks higher scores indicate higher performance, except in interference control where higher scores mean slower performance * p < 0.05, ** p < 0.01, *** p < 0.001 [†] p remains significant after Bonferroni correction | | | | |

follow-up. These results suggest that the effects of treatment type on cognition are small.

To the best of our knowledge, the present prospective study was the first to compare the long-term effects of different invasive revascularisation methods (CEA, CAS) and BMT on patients' cognitive performance. Results of several studies describing cognitive changes after treatment are consistent with our findings and suggest a trend towards better verbal memory, attention and cognitive speed after CAS [31–33] or CEA [34], in particular in symptomatic patients [35, 36]. A possible explanation for improved cognitive performance after treatment of carotid artery disease is the amelioration of haemodynamic pathology and reduction of embolism. Perfusion restoration due to CEA, CAS or BMT could improve cognitive dysfunction caused by a state of chronic hypoperfusion before treatment [37]. A study combining perfusion variables and cognitive scores suggested that improvement of blood flow in the middle cerebral artery is associated with greater cognitive improvement in attention and executive functioning [38].

However, other studies suggest stable cognitive performance after intervention [6, 7, 11] or even a decline of cognition following CEA [4]. Over the past two decades, pharmacological management of cardiovascular disease and the efficacy of therapy have improved. Therefore, when comparing studies about the treatment effects of carotid artery disease, results of older studies must be interpreted with caution.

Comparison of CEA and CAS showed that CEA was associated with longer periods of ipsilateral carotid flow arrest compared with balloon inflations used during CAS [39]. On the other hand, CAS showed a higher frequency of microembolism [40] and higher rates of new ischaemic lesions [41]. The present data suggest that treatment method does not influence cognitive outcome. We conclude that transient blood flow arrest, despite the increased likelihood of new ischaemic lesions, is not detrimental to long-term cognitive function.

Variable study results are likely due to methodological differences such as absence of a control group, timing of cognitive testing with regard to recent symptoms and interventions, use of general anaesthesia during intervention, age of patients or differences in the follow-up time between treat-

ment and assessment. Higher age of patients (>68 years) is suggested to be associated with a greater, more persistent decline of cognitive functions after CEA than after CAS [42]. Short intervals between pre-treatment and post-treatment cognitive assessment may not be sufficient to detect cognitive changes, in particular when effects of general anaesthesia and neurological or psychological factors are considered [5]. Furthermore, the motivation to undergo cognitive assessment immediately after treatment is expected to be lower than at a follow-up assessment. Hence, cognitive scores collected in the first few days after treatment may not reliably reflect cognitive performance level. Indeed, studies with short test-retest time intervals (days to months) generally found a decline or no change in cognitive performance after treatment [5, 43, 44]. In our study, mean time between treatment and assessment was about one year and we did not find an influence of time on cognitive change after treatment.

When interpreting the present study results, it has to be considered that new but clinically silent ischaemic lesions after CEA or CAS could lead to additional cognitive impairment [45]. However, a recent study found no association between the numbers of new lesions on diffusion weighted imaging and cognitive performance after 6 weeks or 3 months of follow-up [33]. The clinical significance of new ischaemic lesions on early diffusion weighted imaging can be questioned because of the partial reversibility of lesions. In addition, most lesions may be too small to cause cognitive impairment.

Our study participants were generally free of severe cognitive impairments. The homogeneity of the treatment groups, in particular the homogeneity of the symptomatic and asymptomatic patients with carotid artery disease, was confirmed by MRI (table 1). Still, patients with lower cognitive performance and worse emotional state before treatment benefited most from treatment, independent of treatment type. These results highlight the functional plasticity of the adult brain, even among patients with circumscribed morphological brain lesions due to carotid artery disease.

The lack of a perfusion measure is a limitation of the present study. Furthermore, time between treatment and follow-up was rather long and, hence, cognitive changes occurring immediately after treatment might not have been

Table 4: Gain scores across the treatment groups.

| | BMT | CAS | CEA | H(2)(p-value) |
|-----------------------------|---------|--------|--------|---------------|
| Interference control | -0.093* | -0.071 | -0.017 | 0.40 (0.82) |
| Processing speed | 0.042 | -0.072 | 0.167* | 2.74 (0.25) |
| Verbal fluency | 0.088 | 0.053 | 0.163 | 1.10 (0.58) |
| Word production | 0.000 | 0.000 | 0.033 | 0.30 (0.86) |
| Verbal learning | -0.009 | 0.079 | -0.028 | 2.29 (0.32) |
| Verbal recognition | 0.000 | 0.035* | 0.000 | 0.66 (0.72) |
| Verbal recall | 0.000 | 0.056 | 0.097 | 1.72 (0.42) |
| Short term memory | 0.083* | 0.083* | 0.000* | 0.33 (0.85) |
| Visual learning | -0.027 | 0.000 | 0.177 | 2.03 (0.36) |
| Visual recognition | 0.000 | 0.000 | 0.000 | 1.41 (0.49) |
| Visual recall | 0.000 | 0.000 | 0.222 | 0.69 (0.71) |
| Visual Rey immediate recall | 0.039 | 0.191* | 0.160 | 0.78 (0.68) |
| Visual Rey late recall | 0.152* | 0.269* | 0.148 | 1.16 (0.56) |

BMT = best medical treatment; CAS = carotid artery stenting; CEA = carotid endarterectomy
 Data are median gain scores
 * Indicates a significant improvement between first and second assessment (p <0.05)

detected. Following minor stroke or TIA, patients classified as asymptomatic are not always truly asymptomatic; they are still likely to show mild neurological symptoms. A control group would strengthen the study results, as possible practice effects and spontaneous improvement could be controlled for. However, a parallel version of the tasks was used whenever possible.

In conclusion, treatment of carotid artery stenosis improves long-term cognitive performance, independent of treatment type. With the progressive ageing of the population, the burden of cognitive impairment becomes increasingly important. It is therefore crucial to recognise cognitive improvement after treatment of carotid artery disease when estimating the risks and benefits of different reperfusion methods such as CEA, CAS or BMT.

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