Cognitive impairment after stroke in young adults

Mijntje M.I. Schellekens

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Cognitive impairment after stroke in young adults

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Part I

Introduction

Chapter 1

General introduction and outline

Introduction

Stroke is defined as an acute neurological deficit caused by a sudden occlusion (ischemic stroke or transient ischemic attack, TIA) or rupture of a cerebral artery (intracerebral hemorrhage, ICH). An estimated 10% of all strokes occur in young adults, aged between 18 and 50 years, with an increasing global incidence.[1, 2] Each year, over 2 million young adults experience a stroke worldwide.[1] Traditionally, TIA was a time-based definition, with neurological deficits resolving within 24 hours. However, advances in neuroimaging have led to a shift towards a tissue-based definition, which defines TIA by the visualization of acute infarction in the brain by neuroimaging.

Most young adults suffering from a stroke are active participants of society, with demanding social lives, young families and busy (developing) careers. Post-stroke outcome does not only depend on motor function, but also on cognitive performance. Despite the significant impact that cognitive impairments have on functional outcome after stroke, they remain understudied in patients a with stroke at a young age.

Prevalence and longitudinal course of cognitive impairment after stroke in young adults

Few short- [3-5] and long-term[6, 7] studies showed worse cognitive performance in patients with young stroke compared to healthy controls on a wide range of cognitive domains. Even in one third of young patients who fully recovered from focal neurological symptoms, impairment in one or more cognitive domains was present after a TIA.[8] However, large studies, including patients with evidence of cerebral infarction, covering all cognitive domains are lacking. Even less is known on the incidence of cognitive recovery or decline after stroke at a young age. Information about post-stroke cognitive impairment and early identification of those who will recover is essential for young stroke patients, as they will have to cope with the consequences for the rest of their lives.

Underlying mechanisms of post-stroke deficits

The variability of cognitive impairment among young stroke patients is not completely understood. Age, education level, vascular risk factors, stroke severity, stroke location, and lesion volume are related to post-stroke cognitive impairment,[9, 10] but do not explain the whole range of cognitive performance and recovery after stroke at a young age. Recent studies using lesion-symptom mapping (LSM) have provided evidence for the role of strategic infarct location in post-stroke

cognitive impairment.[9, 11-13] However, in young patients such a comprehensive map of lesion locations and their associations with post-stroke cognitive performance is lacking. Multivariate lesion analysis of structural imaging data is a relatively new LSM method,[14-16] that identifies the entire lesion-behavior association pattern simultaneously, rather than assessing the brain-behavior relation at each voxel separately.

Additionally, a potential mechanism of post-stroke cognitive deficits could be the presence of structural changes beyond the infarcted area.[17] Advanced MRI techniques are a promising tool in investigating these mechanisms of post-stroke deficits. Diffusion-weighted imaging (DWI) is an MRI technique sensitive to the diffusion of water molecules within the brain.[18] Diffusion Tensor Imaging (DTI) is a model that combines several DWI measurements in multiple directions.[19] This model allows for the characterization of both the magnitude (anisotropy) and direction of water diffusion. As a result, DTI provides detailed insights into the microstructure of the brain tissue, including the organization and integrity of white matter pathways.

If we better understand the mechanisms of post-stroke cognitive deficits and can identify individual patients at risk, we may be able to develop effective and personalized treatments.

Impact of cognitive impairment on return to work after stroke in young adults

The consequences after stroke, including cognitive impairment, fatigue and mood disorders, affect the ability to fully return to society and work. Unemployment has been associated with lower levels of subjective well-being and life satisfaction.[20] Previous studies on post-stroke cognition and return to work have often been limited by small sample sizes, and have predominantly focussed on patients over 50 years. Older patients, being closer to their retirement, may have, as a result, lower return to work rates compared to younger stroke survivors.[21] Furthermore, data on the ability of young stroke patients to retain their jobs after returning to work remain scarce. By gaining a better understanding of the factors influencing return to work and those associated with job retention, we can identify these factors in patients, treat them where possible, and provide better support for their return to work.

Aim of the thesis and study design

The aim of my thesis was to investigate the prevalence, longitudinal course, underlying mechanisms, and impact on return to work of cognitive impairment after ischemic stroke in young adults aged 18–50 years.

The studies presented in this thesis are based on the *'Observational Dutch Young Symptomatic StrokE studY'* (ODYSSEY).[22] The ODYSSEY study is a Dutch multicenter prospective cohort study investigating risk factors and prognosis of 1492 patients aged 18–49 years with a first-ever ischemic stroke or ICH. These patients were recruited from 17 centers across the Netherlands between 2013 and 2021. The primary outcomes of this study were all-cause mortality and risk of recurrent events. Secondary outcomes include the risk of post-stoke epilepsy and cognitive impairment. At baseline, all participants underwent a comprehensive clinical evaluation, including medical history, and imaging to confirm their stroke, which was usually done using MRI. Additionally, they underwent standardized structured questionnaires addressing demographics, education level, and cardiovascular risk factors. A subset of patients participated in an advanced MRI protocol. Within six months and again one year after the index event, patients underwent an extensive neuropsychological assessment. These assessments were complemented by questionnaires evaluating subjective cognitive complaints, mood, fatigue, and functional outcome. Finally, long-term follow-up was conducted annually via telephone or online surveys to monitor the occurrence of post-stroke epilepsy, recurrent vascular events and return to work. The key components of the ODYSSEY study used for this thesis are visualized in Figure 1.

Outline of this thesis

In **Part I**, I present a narrative overview of the literature on the prevalence and temporal course of cognitive impairment after stroke at a young age (**Chapter 2**). This review also includes data from studies presented in this thesis. In this review, we also discussed how a focal lesion affects structural and functional connectivity, and how this contributes to cognitive outcome. Additionally, we examined the evidence on cognitive rehabilitation interventions and neuromodulation for patients with post-stroke cognitive impairment.

In **Part II** of this thesis, I assessed the prevalence of objective cognitive impairment and subjective cognitive complaints in the subacute phase after ischemic stroke in a large cohort of young ischemic stroke patients (**Chapter 3**). Additionally, I investigated the longitudinal course, including its predictors, of cognitive performance during the first year after ischemic stroke (**Chapter 4**).

In **Part III**, I explored the underlying mechanisms of cognitive impairment from an imaging perspective. To evaluate if lesion locations were associated with post-

stroke cognitive performance, I performed a multivariate LSM study (**Chapter 5**). Additionally, I conducted a study to examine how an ischemic stroke lesion affects the integrity of surrounding white matter in the brain, and whether this integrity is associated with cognitive performance (**Chapter 6**).

In **Part IV,** I examined the impact of cognitive impairment on return to work, a key rehabilitation goal for patients. I investigated whether cognitive performance in the subacute phase after ischemic stroke was associated with unemployment and the inability to maintain employment among patients who returned to work (**Chapter 7**).

In **Part V**, the thesis is concluded by a summary (**Chapter 8**) and general discussion, in which I place the results of this work into perspective and offer directions for future research (**Chapter 9**).

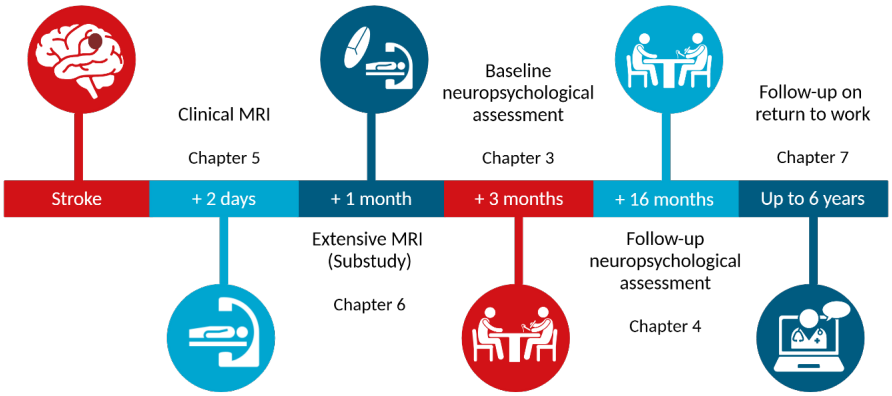

Figure 1 Outline of this thesis

Chapter 2

Understanding cognitive performance after stroke at young age

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Under review

Abstract

Around half of young stroke survivors experience cognitive impairment, and approximately a quarter have aphasia. While most patients show minimal cognitive recovery beyond the first few months after stroke, the variability in long-term cognitive outcomes remains poorly understood. In this review, we will outline the temporal course of cognitive performance and aphasia in young adults after stroke. We will review the literature on how stroke lesions contribute to brain damage, both at the lesion site and through disruption of (remote) structural and functional networks, ultimately affecting cognitive and language performance. Additionally, we will discuss the concept of brain resilience and review current evidence on cognitive rehabilitation interventions and neuromodulation as potential treatment options.

What is young stroke?

A stroke is an umbrella term for either a sudden occlusion ("ischemic" stroke; about 80% of all cases) or a sudden rupture ("hemorrhagic" stroke) of an artery supplying the brain. In this review, we will focus on ischemic stroke. It is most often caused by exposure to vascular risk factors including hypertension, smoking, diabetes and obesity, ultimately resulting in arterio(lo)sclerosis or cardio-embolic sources of stroke. A stroke is characterized by sudden neurological signs and symptoms including hemiparesis, visual loss, aphasia, but also by less visible symptoms including fatigue and cognitive impairment. Each year, over 2 million young adults (18–50 years) experience a stroke globally[1], which leaves them with functional impairments, often for the rest of their lives. Because of this high incidence, stroke poses an enormous challenge, both for societies as well as for the individual and relatives affected.

There is striking variability in the cognitive trajectories after stroke in young adults, with most patients showing (partial) recovery or remaining stable after stroke. However, some patients exhibit further cognitive deterioration after a stroke, even at a young age. Understanding the neurobiological underpinnings of this decline may provide direction to (intervention) studies with the aim to promote post-stroke cognitive recovery.

In this review, we will outline the temporal course of post-stroke cognitive and language performance, focusing on patients who experienced an ischemic stroke at a young age. We will review literature on lesion-induced focal effects and brain-wide functional and structural changes to provide a conceptual framework on how changes across connected brain regions after stroke impact cognitive performance and language, and we will discuss possible cognitive and device-aided rehabilitation.

Cognitive and language trajectory after stroke

Prevalence of cognitive impairment and aphasia

The proportion and severity of aphasia and cognitive impairment (outside the language domain) in ischemic and hemorrhagic young stroke patients was investigated in a recent systematic review and meta-analysis [23]. Of note, many studies focusing on cognitive impairment exclude individuals with aphasia. Generally, cognitive impairment and aphasia were determined based on standardized neuro-psychological assessments. The pooled prevalence of cognitive impairment (based

on 10 studies, total N = 1,495) was 44%, with a similar prevalence of 48% observed in the (sub)acute and chronic phases (>6 months post-stroke)[23]. For aphasia (based on 13 studies, total N = 9,530), the pooled prevalence was overall 22% [23]. Here a difference was found between the (sub)acute (23%) and chronic (13%) phase [23]. Overall cognitive performance after stroke was worse compared to a stroke-free, age-appropriate control group. The most severely affected domains were processing speed, visuo-construction, attention and executive functioning, immediate memory, language, and working memory. A recent study examining young stroke patients in the subacute phase (median three months post-stroke; N = 598) found similar results, with cognitive impairment most commonly observed in attention and working memory (23%), processing speed (23%), and visuo-construction (37%)[24]. In contrast to other studies, this study also reported a high prevalence of episodic memory deficits (21%)[24]. These findings confirm that young-stroke individuals can present with cognitive impairment following a stroke, despite the "beneficial" younger age. Moreover, these findings provide some indication that the prevalence and severity of impairment is similar to those found in the general stroke literature, which largely includes individuals of older age[25].

Cognitive recovery and decline

Research on post-stroke cognitive trajectory in young patients is limited, with variability in recovery patterns[26, 27]. Most cognitive recovery in this population occurs within the first few months post-stroke, with little recovery thereafter[26]. Notably, studies examining recovery within the first days or weeks are lacking. Cognitive recovery outcomes vary across domains. More than 50% of patients showed no change in cognitive performance between the subacute phase (three months post-stroke) and one year. However, approximately 20% improved after the first three months, while around 10% of the patients declined relative to their subacute performance. Among cognitively impaired patients at baseline, recovery was observed in 20-40% in processing speed, visuo-construction, and executive functioning.[27]

Clinical predictors for cognitive recovery or decline after stroke in younger adults have not been clearly identified in previous studies. The strongest predictor for cognitive performance in the chronic phase is cognitive performance in the acute or subacute phase[27, 28]. For language in particular, age at stroke onset is an important predictor of recovery, with those aged < 55 years at stroke onset showing the best improvement[29]. Additionally, there may be an association between post-stroke depression, post-stroke fatigue, and cognitive deficits[27]. However, predictions based solely on clinical factors remain limited in accuracy.

Lesion-induced brain network disconnection

In this section, we discuss how a focal lesion can influence post-stroke cognition through impact on structural and functional connectivity (Figure 1). We also explore the processes that promote secondary degeneration and mechanisms of brain resilience, including brain reserve, cognitive reserve and compensatory abilities (Figure 1).

Lesion size and location

Ischemic lesions can induce clinical symptoms either by disrupting local functional specialized brain regions or by interrupting connection between distributed brain regions. One recent study, specifically in young stroke (aged ≤45 years), identified lesions exceeding 3 cm^3 and those located in frontal, temporal and basal ganglia as important risk factors for post-stroke cognitive impairment.[30] Advances in lesion-symptom mapping (LSM) have improved our ability to precisely characterize the relationship between lesion location and cognitive impairment through voxel-wise analyses of lesion-behavior associations.[31] In a large multicohort lesion-symptom mapping study, infarcts in the left frontotemporal lobes, left thalamus, and right parietal lobe showed strong associations with post-stroke cognitive impairment,[9] corroborating with another study which showed global cognitive deficits were primarily associated with infarcts affecting left angular gyrus and left basal ganglia regions.[12] However, as these two studies were performed in older populations (mean age > 65 years of age), their findings may not fully generalize to younger stroke populations due to aging-related differences in brain, cognitive reserve and neural plasticity (see below). Future studies are essential to validate these findings in young age groups.

Structural and functional connectivity in post-stroke cognition

Lesion-symptom analyses provide fundamental insights into the relationship between lesion location and post-stroke cognitive impairments. However, several limitations should be considered: lesions in different locations may yield similar cognitive deficits[32] and symptoms may arise from remote disruption beyond the lesion site (diaschisis[33]) or from altered functional connectivity among structurally connected intact brain regions. Furthermore, higher-order cognitive functions emerge from dynamic interactions among distributed neural networks, not isolated brain regions.[34, 35] Consequently, a shift from a lesion-localization approach to a connectivity-based perspective, which considers how stroke lesions disrupt inter-regional connections and complex brain networks beyond their anatomical boundaries, may offer deeper insights into the underlying mechanisms of cognitive deficits observed in young stroke patients.

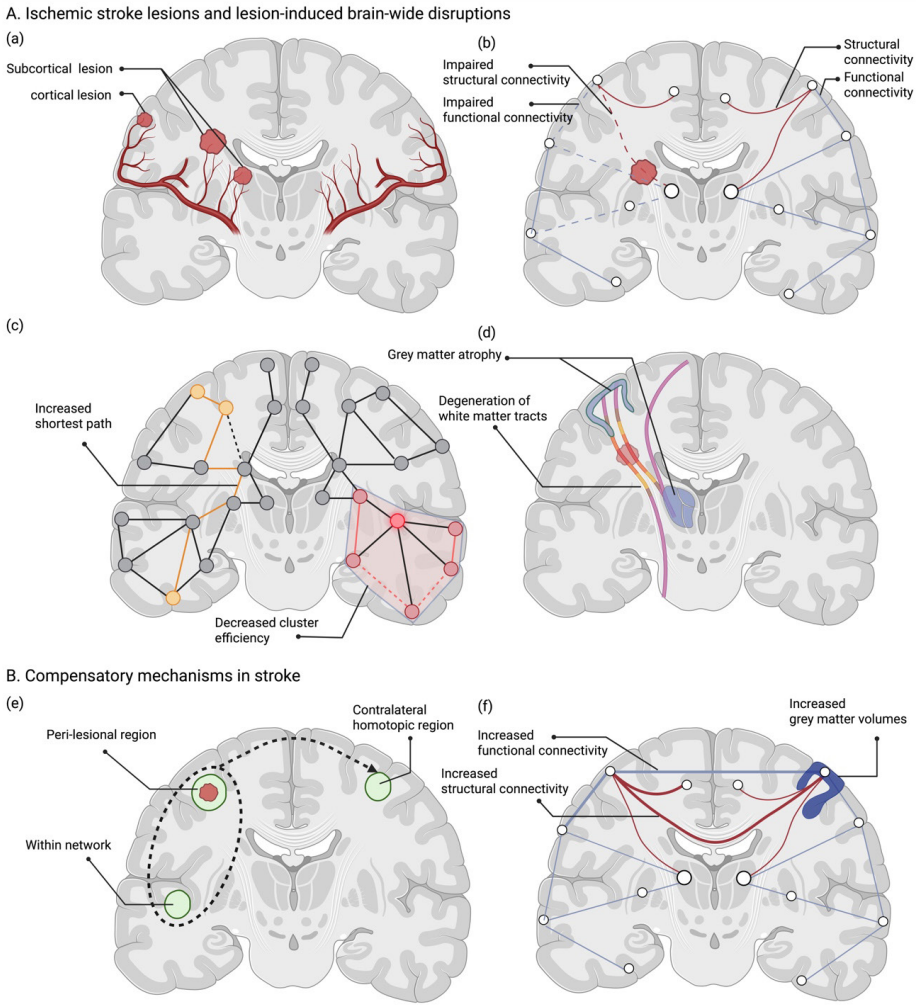

Figure 1 A. Impact of focal ischemic lesions and lesion-induced alterations in structural and functional connectivity on cognitive outcomes. (a). Ischemic lesions located in certain functional specialized brain regions contribute to cognitive deficits. (b) Ischemic lesions disrupt both structural (red) and functional (blue) brain connectivity, contributing to cognitive impairment. Structural connectivity is typically assessed using diffusion MRI-derived metrics such as mean diffusivity (MD) and fractional anisotropy (FA) along white matter tracts. Functional connectivity is based on the temporal correlation of blood-oxygen-level-dependent (BOLD) signals and might or might not have a structural underpinning. Dotted lines represent impaired connectivity. (c) Ischemic lesions disrupt the topological organization and properties of brain networks. The brain can be conceptualized as a network comprising nodes (brain regions) connected by edges (structural or functional connections between regions). Optimal brain function depends on a balanced topological organization that facilitates both global integration and local segregation, properties that can be measured using graph theory metrics. The characteristic path length is defined as the average of all shortest path lengths (the minimum number of edges that must be traversed to go from one node to the other, light yellow) between all pairs of nodes in the network, while global efficiency is calculated as the average inverse of these shortest path lengths. Both metrics assess

how effectively information can be integrated across the entire network. At the local level, the clustering coefficient quantifies the fraction of a node's neighbor's that are also connected to each other (pink), while local efficiency is defined as the inverse of the average shortest path length among all neighbor's of a given node. Clustering coefficient and local efficiency reflect the tendency of nodes to form tightly interconnected local groups. (d) Remote effects of the initial stroke. Stroke-related lesions can initiate secondary neurodegeneration along affected white matter tracts, resulting in progressive white matter damage (color gradient from red to purple) and grey matter atrophy (light blue) in brain regions that are structurally connected but distant from the primary infarct site.

Figure 1 B. Compensatory mechanisms that adapt to stroke-induced functional loss and pathological damage. (e). Functional remapping (green) in perilesional tissue, remote areas within the network, and contralateral homologous regions. (f). Brain-wide functional and structural changes, including increased structural and functional connectivity, depicted as bold solid lines (red for structural, blue for functional), as well as increased grey matter volume (green cortex). Created with BioRender.com.

Structural connectivity, predominantly mediated by white-matter pathways, provides the anatomical foundation for neural communication. Infarcts in white matter contribute to cognitive impairments by disrupting connections between specific brain regions. Diffusion-weighted imaging enables the assessment of connectivity and microstructural integrity of white matter tracts by measuring the directional diffusion of water molecules within brain tissue[36]. Previous studies, primarily conducted in older stroke populations, have shown that alterations in diffusion-derived parameters within specific pathways are linked to domain-specific cognitive dysfunction. For instance, damage to superior longitudinal fasciculus is strongly tied to executive function, while the integrity of the cingulum is linked to cognitive flexibility[37, 38]. One recent investigation, specifically examining younger stroke patients (under 50 years), reported that impaired processing speed was associated with widespread damage involving several major white-matter tracts (e.g., corona radiata, corpus callosum and Inferior occipital-frontal fascicle), whereas executive dysfunction was limited to damage in tracts such as the corona radiata and inferior cerebellar peduncle[39].

Complementing the structural framework, functional connectivity captures the temporal coherence of neural activity across distributed brain regions. This connectivity enables dynamic, real-time synergy and reorganization, thereby supporting flexible responses to complex cognitive tasks[40]. Brain regions that subserve similar functions are grouped into brain networks (i.e., sets of highly interconnected regions), which collectively underpin human behavior. Among multiple brain networks identified, three networks are particularly relevant for cognitive function: the default mode network (DMN), executive control network (ECN), and salience network (SN)[41]. Each of these networks supports distinct cognitive domains, which have been extensively detailed elsewhere[41]. Briefly, the DMN is primarily active during self-referential processing in the resting-state and

typically shows reduced activity during externally oriented cognitive tasks [42]. The ECN plays a central role in executive functioning, attentional control, and working memory, while the SN is responsible for integrating internal and external stimuli to guide behavior [41, 43]. A recent meta-analysis of post-stroke resting-state functional MRI (rs-fMRI) studies, conducted across all age groups (although nearly all included studies focused on older adults aged over 50), suggested that focal ischemic lesions can induce changes in functional connectivity both within and between these brain networks (DMN, ECN, SN) [44]. Furthermore, the extent of connectivity disruption within networks such as the DMN and SN correlates with the severity of post-stroke cognitive impairment [45, 46]. Similarly, patients with post-stroke aphasia exhibit disruptions within language-specific networks, as well as between these networks and other networks, such as ECN and DMN, with the severity of these disruptions correlating with language impairment severity [47, 48].

Disruption of functional and structural brain networks after a stroke

As the conceptualization of the brain as a complex network advances, graph theory provides a mathematical framework to quantify and characterize network organization based on structural and functional connectivity. This approach models the brain by defining nodes (e.g., brain regions) and edges (e.g., functional or structural connections between brain regions), enabling systematic analysis of network topology. Ischemic lesions can disrupt these nodes and edges and thereby impair both globally integration and locally segregation of this brain network, presenting as measurable alterations in its topological (i.e., the network organization) properties. For instance, studies in older stroke patients have reported changes in network integration measures (e.g., decreased global efficiency, increased characteristic path length) and segregation measures (such as reduced local efficiency and reduced clustering) [49-51]. These findings reflect a shift toward a less integrated and less segregated network architecture post-stroke, where neural signals require additional steps to traverse the brain network and specialized information processing capacity is diminished, collectively reducing communication efficiency. Such changes have been related to cognitive deficits in multiple domains including attention and language in these studies of older stroke populations[49-51]. A similar change pattern was identified in a young stroke population[52], however, its association with cognitive deficits remains to be elucidated.

Remote effects of the initial stroke

Infarcts may initiate secondary structural disruptions (i.e., axonal degeneration, followed by trans-neuronal atrophy) along the white matter tracts, affecting regions adjacent to and distant from the infarct site. One longitudinal study in older stroke

patients (mean age: 66 years) has shown that stroke contributes to progressive white matter degeneration in both hemispheres over three years, predicting long-term deficits across multiple cognitive domains[53]. In young stroke, a recent diffusion-MRI study suggested microstructural damage specifically within white matter tracts passing through and extending beyond the lesion site within six months post-stroke, which correlated with deficits in processing speed and executive function[39]. Notably, these diffusion abnormalities gradually diminished with increasing distance from the lesion site, supporting the concept of secondary neurodegeneration process along the affected tracts. Another study showed reduced white matter integrity remote from the initial infarct lesion, associated with cognitive impairment even 11 years post-stroke[17]. This evidence collectively underscores the effects of secondary microstructural changes on post-stroke cognitive impairment in both the subacute and long-term stages.

Furthermore, this secondary neurodegenerative process extends beyond white matter to grey matter, manifesting as grey-matter atrophy in regions structurally connected but distant from the initial lesion site. Evidence supporting this phenomenon has emerged from studies in older adults. For instance, a previous study reported that chronic small subcortical infarcts were associated with regional cortical thinning in connected cortical areas [54]. Other studies reported associations with post-stroke cognitive performance and remote post-stroke alterations such as iron accumulation in certain regions of the thalamus, that are strongly connected with the initial stroke location, but not directly affected[55, 56]. From the network perspective, this is an interesting observation as the thalamus is considered a central hub of several networks, and thus, post-stroke changes as described above in the thalamus can cause global brain network disruption and disconnection from other remote regions[57]. While such detailed evidence is limited in young stroke patients, similar mechanisms may be possible. This is illustrated by a previous study in younger individuals that showed that cortical infarcts are associated with reduced microstructural integrity of the ipsilateral hippocampus, potentially explaining episodic memory deficits observed during neuropsychological examination[58]. Interestingly, the magnitude of secondary neurodegeneration may differ across age groups. One study investigating brain age, a global indicator of biological brain status using grey matter imaging, suggested smaller effects of infarct-induced brain aging process in individuals younger than 50 years compared to older adults[59].

Brain resilience and compensatory mechanism related to cognitive outcomes

Lesion-induced damage alone does not fully account for the heterogeneity observed in clinical deficits in young stroke patients. Notably, some patients retain functional

independence or present a favorable cognitive trajectory despite extensive lesion loads. This heterogeneity may be explained by the concept of brain resilience, which represents the capacity of patients to tolerate a degree of brain damage before clinical symptoms emerge. This resilience can be conceptualized as a combination of several mechanisms, including brain reserve, cognitive reserve and compensatory abilities[60].

Brain reserve represents the brain's capacity to withstand lesion-induced damage, playing a crucial role in moderating cognitive outcomes following stroke. This reserve primarily depends on an individual's pre-stroke brain health and age. For example, older patients with brain atrophy are more likely to experience post-stroke cognitive impairment[61, 62]. Another study proposed the "effective reserve index" combining age, white matter hyperintensity (WMH) volume and total brain volume[63]. In this study of stroke patients (mean age 66.4 years), a higher effective reserve index, characterized by younger age, lower WMH volume, and greater total brain volume, was associated with better 90-day outcomes on the modified Rankin Scale[63]. Although these findings may not translate directly to young stroke populations, who typically exhibit less overt aging-related atrophy or WMH, they nonetheless offer valuable insights. These young patients may still possess subtle microstructural damage due to vascular risk factors[64]. Such damage, detectable by advanced neuroimaging techniques, could contribute to variability in brain reserve, thereby influencing cognitive outcomes following stroke.

Unlike brain reserve, which emphasizes the degree of structural attributes (e.g., total brain volume), cognitive reserve is grounded in the cognitive skills and abilities acquired before the onset of brain damage[65, 66]. These cognitive assets actively cope with stroke-related brain damage and mitigate functional deficits[65, 66]. Cognitive reserve is influenced by factors such as education, intellectual engagement, or social activities, collectively known as cognitive reserve proxies. A recent review reported a small to medium ($z' = 0.25$), yet significant beneficial effect of education on post-stroke cognitive outcome in young stroke survivors, albeit that age was an important confounding factor to be taken into account[67]. More recently, one study demonstrated that cognitive reserve indeed predicted post-stroke rehabilitation outcomes, with cognitive reserve proxies like education, bilingualism, and active participation in cognitive activities having beneficial effects[68]. Assessing cognitive reserve, preferably using multi-index measures, such as the Cognitive Reserve Index Questionnaire, as a potential moderating variable in cognitive rehabilitation outcome studies[69], taking age into account, can therefore be considered[70, 71].

Compensatory ability refers to the brain's capacity to adapt to functional loss and pathological damage. This adaptive process is underpinned by neural plasticity,

manifesting as functional remapping and brain-wide network connectivity changes. Functional remapping is well documented in the recovery of post-stroke aphasia, involving perilesional tissue, remote areas within the language network, and contralateral homologous regions[72]. For instance, functional MRI studies showed increased activation in perilesional regions, as well as in spared portions of the language network (e.g., temporoparietal regions for frontal lesions or frontal regions for temporoparietal lesions) during language tasks[73, 74]. Regarding contralateral hemisphere homologous regions, increased activation of right-hemisphere areas mirroring their damaged left-hemisphere counterparts was also reported by several studies (for details and an example, see figure 2)[74, 75]. However, this activation may vary depending on lesion size, lesion location, and stroke phase, and its clinical benefits remain debated[73, 74, 76, 77]. Beyond functional remapping, the re-connection and re-organization across distributed neural networks constitute another critical component of compensatory ability. In particular, previous studies have reported improved connectivity within key networks, particularly the DMN and the frontotemporal EN, which correlates with cognitive improvement during the sub-acute phase after stroke[78, 79]. Interestingly, patients exhibiting diffuse, non-specific increases in connectivity tended to have poorer cognitive recovery, underscoring the importance of targeted and effective brain network re-connection[79]. Furthermore, such neural re-connection extends beyond a single functional brain network, rather involving both inter-network and inter-hemispheric connectivity. A recent task-based functional MRI study reported that post-stroke aphasia patients exhibit increased connectivity[80]. This was found both in the multiple-demand network and the language network, and correlated with subsequent language recovery[80]. Similar findings emerged for inter-hemispheric connectivity: patients showing continued cognitive improvement displayed an initial increase in cross-hemispheric connections, followed by a subsequent decrease[81].

Compared to functional changes, evidence for structural changes underpinning the brain's compensatory capacity remains relatively limited. However, several case reports have shown that re-normalization of specific white matter tracts (e.g., the corpus callosum and the inferior longitudinal fasciculus) is associated with language recovery in young stroke patients with aphasia[82, 83]. Additionally, a recent volumetric-based morphometry study reported increased grey matter volume in both the lesioned and contra-lesional hemispheres, which correlated with improved cognitive functions, especially language[84]. Notably, these increases in grey-matter volume appeared in contra-lesional homologous regions[85, 86].

Overall, brain reserve, determined by inherent structural and functional characteristics, and cognitive reserve, established by premorbid cognitive abilities, explain an individual's resilience to withstand post-stroke cognitive impairment. Conversely, the degree of recovery from cognitive deficits is predominantly influenced by post-stroke neural plasticity driving functional and structural reorganization. In young stroke patients, baseline brain reserve, cognitive reserve, and neural plasticity are typically more robust compared to elderly patients. However, the extent to which these age-related differences influence the magnitude and trajectory of post-stroke cognitive impairment requires further investigation.

Box 1. Neuroplasticity of language in young stroke: A single-case study

A single-case of a right-handed woman with chronic aphasia from a large ischemic stroke at the age of 21 provided insights into stroke-induced neuroplasticity supporting language[75]. The stroke affected the left temporal lobe (Fig 2A) and underlying structural connectivity, with damage to most of the left arcuate fasciculus and of other left ventral tracts.

Functionally, the patient was studied using magnetoencephalography (MEG), which provides a direct measure of neuronal activity, otherwise not affected by vascular damage[87]. Capitalizing on MEG's temporal resolution, the patient's brain activity *during* picture naming was examined, whereby a distinction could be made between cases when the patient successfully named the pictures (about 47% of the time) versus cases when the patient had an anomia, that is, she could identify the object to be named but could not find the word for it (about 41% time). Brain activity was linked to specific time points relative to the appearance of each picture.

Within the first 150 ms upon seeing a picture (Figure 2B), brain activity in a neurologically healthy, demographically matched participant was predominantly left lateralized in the occipital cortex, including the cuneus, and in anterior and mid portions of the left temporal lobe. In the patient, by contrast, this early activity was already strongly right lateralized in the occipital cortex, mirroring those seen in the control participant, despite her intact left occipital areas.

Around 400 ms upon seeing a picture, a period corresponding to word retrieval processes before articulation[88], a spatial distinction was found for the patient between successful and unsuccessful naming (Figure 2C): Brain activity increased for successful relative to unsuccessful naming in the right mid-posterior portions of the temporal lobe, but decreased in the right inferior frontal gyrus. This spatial dissociation is especially interesting considering that the timing of recruitment of these areas was similar.

Naming in this young-stroke patient was largely supported by activity in the contralesional, right hemisphere, starting from visual and object-recognition processes, indicating neuroplasticity. Yet, despite this neuroplasticity, the involvement of the right, non-language dominant hemisphere was not enough to fully overcome the language impairment. In line with previous literature[89], these findings suggest that the severity of the stroke with accompanying lesion size and location remain the critical predictors of language recovery, regardless of the patient's neuroplastic potential.

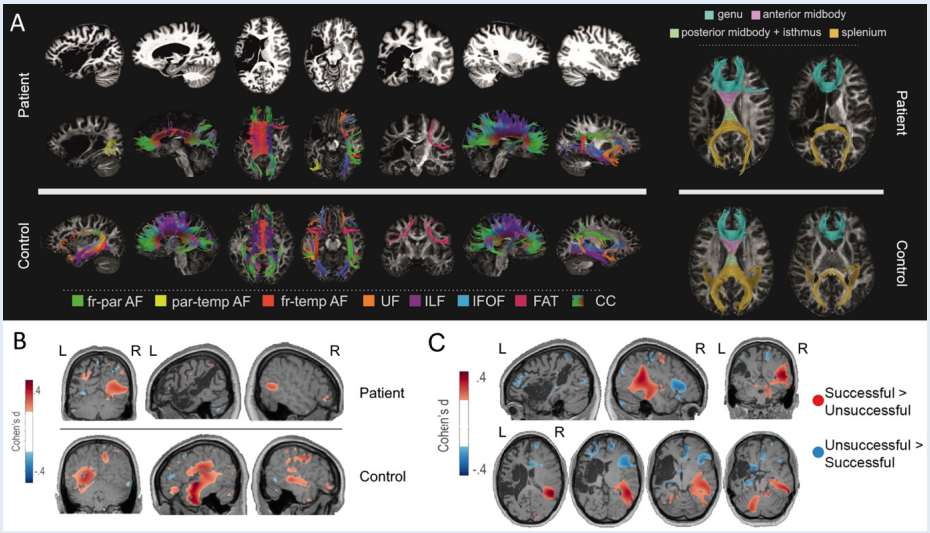

Figure 2. A. Structural MRI (T1 weighted) depicting the extent of the infarct in sagittal, coronal and axial plane (top row, left). The middle and bottom left rows show the language-relevant tracts for the patient (middle) and for the demographically matched control (bottom). The right panel shows the corpus callosum (CC), with its subdivisions, for the patient (top) and for the demographically matched control (bottom). AF, arcuate fasciculus; FAT, frontal aslant tract; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; UF, uncinate fasciculus. Images are depicted in neurological convention (i.e., left hemisphere on the left-hand side). **B.** Sources of visual evoked brain activity between 150-180 ms post-picture onset, shown with their measure of effect size (Cohen's d) for the patient (top, mostly right lateralized) and for the control (bottom, most left lateralized). Positive values indicate stronger activity relative to rest. **C.** Sources of naming-related responses in the patient between 330 and 440 ms post-picture onset, shown with their measure of effect size (Cohen's d). Positive values indicate stronger activity for successful naming relative to unsuccessful naming; negative values indicate stronger activity for unsuccessful naming relative to successful naming. L, left; R, right. Reproduced with permission from the authors following minor modifications to combine separate figures (from doi:10.6084/m9.figshare.19228119, doi: 10.6084/m9.figshare.19228161, doi: 10.6084/m9.figshare.19228194, available under CC-BY 4.0 licence. No changes were made to the figures' contents).

Rehabilitation of post-stroke cognitive impairment and aphasia

Cognitive rehabilitation intervention

Persistent cognitive impairment occurs in a large proportion of young stroke patients. In people who have had a stroke at a young age, cognitive impairment is a strong predictor of long-term inability to work [21, 90], with a 2-3 times higher risk of long-term unemployment than the general population[91]. Despite this, cognitively impaired young stroke patients are more likely to be discharged without rehabilitation than older adults, and only 15% of them receive any form of cognitive screening [92]. Also, young stroke patients indicated that rehabilitation programs are not age-adapted, stressed the need for attention to vocational functioning, and expressed frustration over the invisibility of their cognitive symptoms[93]. This illustrates the need for age-tailored cognitive rehabilitation programs in this patient population. Cognitive rehabilitation may take the form of restorative cognitive retraining, that is, behavioral interventions aimed to restore the impaired cognitive function, or compensatory strategy training, that is, teaching individuals with stroke to compensate for cognitive impairments in daily activities.

Cognitive (re)training

Cognitive (re)training often takes the form of computerized exercises that patients perform with a high intensity (i.e. multiple times a week over weeks to even months). These exercises (often referred to as 'brain training') may target either a single cognitive domain (memory, executive function, speed of processing) or adopt a multi-domain approach. Most of such interventions use an adaptive approach, gradually increasing difficulty during training to maximally induce neural-network plasticity[94]. Only a few single-domain cognitive training studies have been performed in samples that also included young stroke patients. Although improved performances on the trained tasks after six weeks of training were found, no transfer was found to neuropsychological tests that were not practiced during training[95]. A randomized controlled trial on a 12-week adaptive computerized executive function training in stroke patients aged 30-80 years showed a similar improvement in the intervention group compared to controls, again with no differences in transfer to untrained tasks[96]. Single-domain cognitive retraining has been found to be effective in visuospatial deficits after right-hemisphere stroke (e.g., visual scanning training for neglect) and for cognitive-linguistic therapy after left-hemisphere stroke[97].

With respect to multi-domain cognitive training, a global cognitive improvement was found compared to a control group after an 8-week computerized cognitive

training focusing on attention, executive function, memory and spatial cognition in a stroke sample (N = 35) with an average age of 43.1 years[98]. A recent RCT on a 4-week adaptive computerized training targeting attention, executive function, processing speed and visuospatial ability showed improvement on all cognitive outcomes compared to an active control group, although sustainability of effects are uncertain[99]. Even though these multi-domain cognitive training studies seem promising from a proof-of-principle perspective, 'brain training' has been criticized as generalization or transfer to measures of daily functioning is absent or limited[100] and studies suffer from methodological limitations such as small samples and the lack of appropriate control groups[101].

Compensatory strategy training

Compensatory strategy training has been found to be more effective than drill-and-practice brain training to improve cognitive function at everyday activity level in individuals with acquired brain injury, including stroke. This form of training usually takes the form of multiple sessions with a therapist or neuropsychologist, in which specific strategies or algorithms are taught that can be applied by the patient in everyday settings and the person's home environment, and that have transfer to everyday activities and functional outcomes (i.e. far transfer) as its primary goal. While promising, there is a lack of high-quality RCTs on compensatory strategy training in young stroke[101, 102].

Gamification

Recent developments in cognitive rehabilitation focus on home-based interventions supported by digital tools. In the field of speech and language therapy, a plethora of apps has been developed to augment face-to-face therapy (for an overview see [103]) that may especially be feasible in young stroke patients, who are generally used to using smartphones and apps in daily life. A more recent development is the topic of gamification or serious games. Providing cognitive exercises or compensatory training as a more attractive game-like tool or app may improve treatment adherence and reduce dropout[104]. Still, to date most serious games targeting cognitive function have adopted a restorative approach, while research on game-supported compensatory strategies is currently ongoing[105].

In sum, there is a need for cognitive rehabilitation interventions that are targeted at the young stroke population with cognitive impairment, although more research is needed to substantiate the true clinical effects, their duration and dose/intensity. Furthermore, predicting treatment outcome in individuals with young stroke remains challenging, but individual factors, such as baseline cognition and

measures of learning and training gain, as well as proxies for cognitive reserve (e.g. education level and premorbid intelligence) and age should be taken into account.

Neuromodulation

Neuromodulation is a potential adjunct in the rehabilitation of post-stroke cognitive impairment in young stroke as it may promote neuroplasticity. For example, repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique in which neuronal networks are stimulated by a pulsed magnetic field. A possible mechanism for the effectiveness of rTMS is that rTMS could modulate the neural excitability of the cortical brain regions and hereby modifying brain plasticity by stimulation of intrinsic plasticity mechanisms, such as synaptic potentiation[106]. This can potentially stimulate the structural and functional connectivity across the brain regions, altered by the stroke lesions, and hereby restructuring the connectivity and modulating network recovery.

rTMS has changed the treatment options for difficult to treat depression due to its good combination with both psychological and pharmacological treatment options[107]. There are several small studies showing that rTMS was associated with improved global cognitive functioning, visual and spatial attention, verbal comprehension and expressive naming[108]. However, the overall effect size was small and heterogeneous, and these studies were conducted in patients over the age of 50 years. Therefore, there currently is no evidence to recommend rTMS for treatment of post-stroke cognitive/affective impairment in young adults. However, further studies are needed to investigate whether rTMS is effective in improving cognitive functioning in young ischemic stroke patients.

Concluding remarks and future perspectives

A stroke at a young age is a devastating disease that suddenly changes not only the life of the patient affected, but also of their entire family; often for the rest of their lives. Cognitive impairment and aphasia are among the most disabling post-stroke sequelae. Half of the patients suffer from these post-stroke consequences resulting in loss of independence and quality of life. The remarkable variability in post-stroke cognition and its recovery, ranging from virtual no impairment to profound dementia with otherwise identical stroke characteristics, fuels research on its neurobiological underpinning. We are beginning to understand that post-stroke cognitive impairment and recovery is the resultant of on the one hand the location and the extent of the stroke lesion and the brain's resilience on the other

hand. Another important insight in our understanding of post-stroke cognition and its recovery comes from recent evidence showing that these effects extend to brain regions remote from the site of stroke that can be as far as the contralateral hemisphere. Future research is aimed at identifying mechanisms of these (remote) disconnections, as this may be a stepping stone to the development of rational therapies.

Meaningful treatment of post-stroke cognitive impairment is one of the next frontiers in clinical stroke research. rTMS may be one of these promising treatment modalities as it has the potential to restore the stroke-induced alterations in structural and functional connectivity across the brain regions, that are key in the pathophysiology of post-stroke cognition. The next step is to translate these observations from often small-sized observational cohort studies to large randomized clinical trials, which will allow for the generalizability to clinical practice, when efficacy is proven, by incorporating this into international clinical stroke guidelines.

Currently, there is a central role for rehabilitation in clinical practice to improve post-stroke prognosis. Especially when it comes to improving post-stroke cognition, there are several strategies as outlined in this review, however they are only rarely evidence based.

Obtaining high quality evidence, preferably from randomized controlled trial on interventions that are clinically meaningful, scalable and generalizable is among the most important challenges for future stroke research.

Part II

Prevalence and longitudinal course of cognitive impairment

Chapter 3

Subacute cognitive impairment after first-ever transient ischemic attack or ischemic stroke in young adults: the ODYSSEY study

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Abstract

Introduction

We aimed to investigate the prevalence of cognitive impairment in the subacute phase after transient ischemic attack (TIA) and ischemic stroke (IS), factors associated with a vascular cognitive disorder, and the prevalence of subjective cognitive complaints and their relation with objective cognitive performance.

Patients and methods

In this multicenter prospective cohort study, we recruited patients with first-ever TIA and IS, aged 18–49 years, between 2013 and 2021 for cognitive assessment up to 6 months after index event. We calculated composite Z-scores for seven cognitive domains. We defined cognitive impairment as a composite Z-score <-1.5. We defined major vascular cognitive disorder as a Z-score <-2.0 in one or more cognitive domains.

Results

Fifty-three TIA and 545 IS patients completed cognitive assessment with mean time to assessment of 89.7 (SD 40.7) days. The median NIHSS at admission was 3 (interquartile range, 1–5). Cognitive impairment was common in five domains (up to 37%), with similar proportion in TIA and IS patients. Patients with major vascular cognitive disorder had a lower education level, higher NIHSS scores and more frequent lesions in the left frontotemporal lobe than without vascular cognitive disorder (p<0.05 FDR-corrected). Subjective memory and executive cognitive complaints were present in about two-thirds of the patients, but were weakly associated with objective cognitive performance (β:-0.32 and β:-0.21, respectively).

Discussion and conclusion

In the subacute phase after TIA or stroke in young adults, cognitive impairment and subjective cognitive complaints are prevalent, but they are weakly associated with each other.

Introduction

Stroke in young adults affects at least 1.5 million people worldwide each year, with increasing incidence of stroke globally.[1, 2] Many young patients with a stroke experience lifelong disabling consequences, including cognitive impairment.[6] Post-stroke cognitive impairment (PSCI) is an important clinical outcome in young patients as it affects their social life, quality of life and return to work, independent of physical recovery.[21] However, data on PSCI in young patients are scarce.

Few short term (acute phase up to 12 months)[3-5] and long term (up to several years)[6, 7] studies showed worse cognitive performance in patients with young stroke compared to healthy controls on a wide range of cognitive domains. Even in one third of patients after a transient ischemic attack (TIA) aged 45–65 years, impairment in one or more cognitive domains was present within 3 months after their TIA.[8] However, earlier studies in the subacute phase had a small sample size,[3-5] did not cover all cognitive domains,[5] included events with and without radiological evidence,[4, 8] or only included infratentorial infarcts.[4] In addition, subjective cognitive complaints are prevalent in young adults measured in a small group of patients in the subacute phase and up to years after stroke, but its relation with objective cognitive impairment is uncertain.[109-111]

The goal of the present study therefore was (1) to investigate the cognitive performance prospectively covering all cognitive domains in the subacute phase (till 6 months) after a first-ever ischemic stroke (IS) or TIA with radiological evidence in a large cohort of young patients, (2) to explore clinical and radiological factors potentially associated with a cognitive disorder, and (3) to assess the prevalence of subjective cognitive complaints in the subacute phase and whether they predict objective cognitive performance.

Patients and methods

Patients and study design

This study is part of the '*O*bservational *D*utch *Y*oung *S*ymptomatic *S*trok*E* stud*Y*' (ODYSSEY), a multicenter prospective cohort study on the risk factors and prognosis of patients with a stroke in young adults.[22] The present study comprises patients with first-ever TIA or IS with radiological evidence of cerebral ischemia, aged 18–49 years, included between May 2013 and February 2021. We defined acute stroke as a rapidly evolving focal neurological deficit, without positive phenomena, with a

vascular cause, lasting for more than 24 h. We defined TIA similarly with a duration of clinical symptoms less than 24 h with radiological evidence of cerebral ischemia (tissue-based definition). Exclusion criteria were a history of stroke, TIA, retinal infarction, and cerebral venous sinus thrombosis. Detailed information on the data collection is described elsewhere.[22] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study. We obtained written informed consent from all participants. If the patient was unable to provide informed consent, consent was provided by the patient's legally acceptable representative.

Cognitive assessment

Neuropsychological tests were administrated up to 6 months after the index event. Cognitive assessment included tests used in other large scale epidemiologic studies covering the most relevant cognitive domains.[112, 113] The following cognitive domains were examined: *Episodic memory* (3-trial version of the Rey Auditory Verbal Learning Test), *Processing speed* (the written version of the Symbol-Digit Modalities Test, the abbreviated Stroop Color Word Test, parts I and II), *Visuoconstruction* (Rey-Osterrieth Complex Figure (ROCF)-copy trial), *Executive functioning* (Fluency test, Stroop interference score, Brixton Spatial Anticipation Test), *Visual neglect* (Star Cancellation of the Behavioral Inattention Test), *Language deficits* (Short Token Test), *Attention and working memory* (Digit Span subtest from the Wechsler adult Intelligence Scale – Fourth Edition). Global cognitive functioning was examined with the Mini Mental State Examination. If a specific test was not performed due to technical problems, physical disability, cognitive impairment that prevented the patient from understanding the instruction, or refusal of the patient, only the reliably and valid administered tests were included. Supplementary Table 2 provides the reasons for non-completion for each test. We calculated composite scores to account for speed-accuracy trade-off on the Stroop test (accuracy(%)/reaction time). We computed Stroop interference by dividing the composite Stroop part III score by the mean of the composite scores of parts I and II. To prevent potential bias in scoring the ROCF, two researchers independently rated 10% of the complex figures, with high inter-rater reliability using the Pearson's correlation coefficients (r_s= 0.95).[114]

For most tests, we used the normative data from the Advanced Neuropsychological Diagnostics Infrastructure (ANDI) that includes data from up to 26,000 healthy individuals from all ages, enabling fine-grained adjustment for age, sex and/or education level, where appropriate.[115] For the written version of the Symbol-Digit Modalities Test, we used the normative data from the test manual (n=1,307),[116] adjusted for age and education level. For the abbreviated Stroop Color Word Test, we used age- and education-matched control data from our earlier young-stroke

study (n=146).[6] We used healthy controls from another stroke study for the Star Cancellation test (n=63).[117]

We converted raw test scores to Z-scores per test for each participant based on the normative data from the ANDI dataset, or based on the mean and the SD of control data, adjusted for age and education level (age- and education-adjusted normative mean: Z=0; SD=1). In four patients, education level was missing, we used simple imputation with the median (education category 5, i.e. middle school / secondary vocational training) for these missing values. We corrected Z-scores >3 or <-3 to 3 and -3 respectively, to correct for outliers. Next, averaging Z-scores of cognitive tests that reflected the same cognitive domain resulted in a composite Z-score per cognitive domain. If one test of a particular domain was missing, the domain score was based on the remaining tests of that domain. We defined cognitive impairment on a test as a Z-score of <-1.5 (i.e., reflecting a performance level of more than 1.5 SD below the age- and education-adjusted normative mean) on that particular test. We defined cognitive impairment on a domain as a composite Z-score of <-1.5 and a below average performance as a composite Z-score between -1.0 and -1.5.[118]

To compare patients on various clinical and radiological parameters, we used the diagnostic criteria for vascular cognitive disorder (VCD) of the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG). We defined mild VCD as a composite Z-score of between -1.5 and -2.0 in one or more cognitive domains (representing 4.4% of the normal population).[119] We defined major VCD as a composite Z-score of <-2.0, in one more cognitive domains (representing 2.3% of the normal population). These criteria are more conservative and have a higher specificity than the VASCOG cut-off criteria, which define mild VCD as a Z-score in one or more cognitive domains between -1.0 and -2.0.[120] This interval, however, represents 13.6% of the normal population, resulting in a poor specificity and the risk of a too high proportion of false positive diagnoses.

Subjective cognitive assessment

We used a 15-item semi-structured interview on subjective cognitive complaints, which has been applied in previous research,[110] to assess the presence of subjective cognitive complaints in the past month. Subjective cognitive complaints were considered present when a participant scored a '2' (moderate) or higher on a scale of 0 to 3 on at least 1 item or scored a '1' (present) on 1 item with dichotomous answers. Next, we calculated the total scores of subjective memory complaints (2 questions with a 4-point scale and 8 questions witch dichotomous answers) and subjective executive complaints (3 questions with a 4-point scale).

Other measurements

We scored level of education with a Dutch scoring system, using 7 categories (1=less than primary school; 7=university degree),[121] comparable with the UNESCO international classification of education levels.[122] Symptoms of depression and fatigue were assessed using the Mini International Neuropsychiatric Interview (MINI),[123] and the subscale Subjective Fatigue of the revises Checklist on Individual Strength (CIS-20R).[124] We evaluated functional outcome at the time of the cognitive assessment using the Barthel Index[125] and modified Rankins Scale (mRS).[126] We defined good functional outcome as a mRS score of 0–1 and a Barthel Index of ≥85. Furthermore, we assessed the etiology of stroke(based on modified Trial of ORG 10172 in Acute Stroke Treatment; TOAST)[127] and severity at discharge (National Institutes of Health Stroke Scale; NIHSS)[128] retrospectively using a validated approach,[129, 130] because this scale was not used in all medical files. Lesion locations and vascular territories were visually scored on the available imaging modalities. We determined whether there was recurrent stroke before the cognitive assessment based on patient records or a telephone interview.

Statistical analyses

We performed all statistical analyses with RStudio 3.6.2 and IBM SPSS Statistics 25. We compared baseline characteristics of patients with cognitive assessment and patients without cognitive assessment using a Pearson's χ^2 test, Mann-Whitney *U* test, or Student's *t*-test when appropriate.

We used one-sample *t*-test with one-tailed *p*-values for the composite Z-scores of each cognitive domain in TIA and IS patients separately to determine if they were lower than the age, education and/or sex-adjusted control. We investigated differences in composite Z-scores between TIA and IS with Student's *t*-test. We used a one-way analysis of covariance (ANCOVA) to determine whether there were significant differences in composite Z-scores between each stroke subtype adjusting for fatigue severity and symptoms of depression.

We used a Pearson's χ^2 test (or Fisher's exact test when an expected cell count was less than 5) to investigate differences in TIA and IS patients in the proportion of participants with a below average performance or cognitive impairment.

We compared patients without VCD, with mild VCD and major VCD using a one-way analysis of variance (ANOVA), Pearson's χ^2 test or Kruskal-Wallis test when appropriate. If there was a significant difference between the groups, we used the Pearson's χ^2 test or the Mann-Whitney *U* test to perform pairwise comparisons as

post-hoc analysis. Furthermore, we compared patients without VCD, with mild VCD and major VCD on infarcts involving the left frontotemporal lobe, left thalamus, or right parietal lobe, since lesions in these locations are strongly associated with post-stroke cognitive impairment.[9]

We determined the prevalence of subjective memory complaints and subjective executive complaints. Subsequently, the distribution of the total scores of subjective memory and executive complaints is reported as a measure of severity of subjective complaints. The association between subjective cognitive complaints and objective performance was calculated in two ways. First, we determined the association between total scores of subjective memory complaints and the domain score of attention and working memory, and between subjective executive failure and the domain score of executive functioning using linear regression, while adjusting for depression and fatigue. Next, we determined the association between the total scores of subjective cognitive complaints and the number of cognitively impaired tasks, using linear regression.

To explore the effect of differences in time from index event to the neuropsychological assessment on the composite Z-score in each domain we used Pearson correlation analysis. Next, we performed a median split in 'time from index event to cognitive assessment' and compared the groups with 1) the composite Z-scores in each domain using a Student's t-test and 2) the proportion of patients with cognitive impairment on a domain using Pearson's $\chi 2$ test.

To correct for multiple comparisons, we applied a Benjamini-Hochberg procedure, with false discovery rate Q set at 0.05.[131] We reported 2-tailed *p*-values, unless the use of a one-tailed *p*-value is specifically stated.

To investigate whether a recurrent event influenced the results, we performed post-hoc analyses in which we conducted all above described analyses after excluding patients with a recurrent stroke before the first cognitive assessment.

Results

This study consisted of 53 TIA and 545 IS patients (Figure 1). Baseline characteristics of the study population are described in Table 1 and neuropsychological test scores are presented in Table 2, both stratified by the type of event. Mean age of patients at stroke onset was 41.7 (SD 7.7) years, 48.2% were women, and the median NIHSS at

admission was 3 (interquartile range, 1–5). Mean time from index event to cognitive assessment was 89.7 (SD 40.7) days. Baseline characteristics of patients with (n=598) or without cognitive assessment (n=685) are presented in Supplementary Table 1.

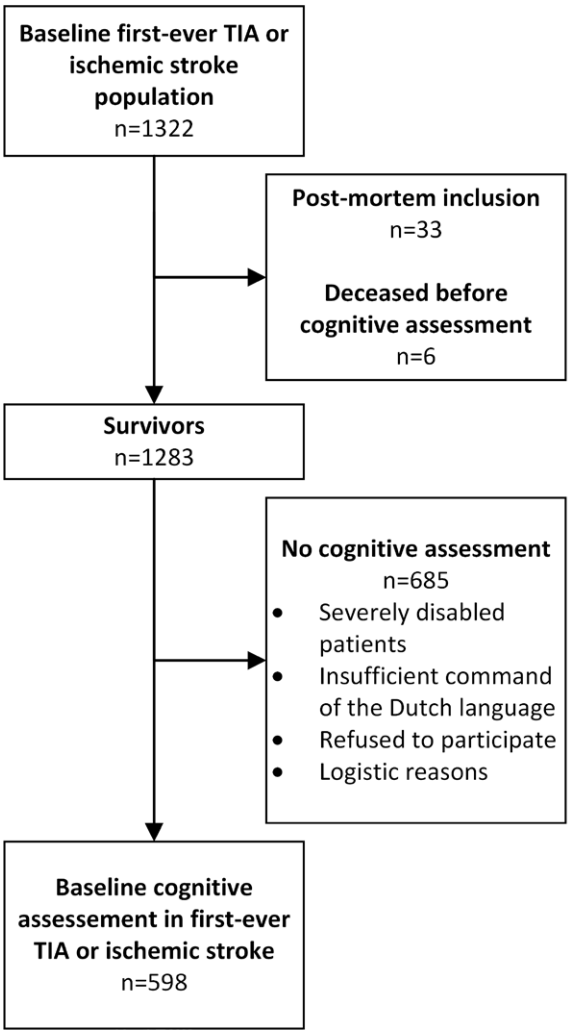


Figure 1 Flowchart of the study population

Table 1 Baseline characteristics

	All participants (n=598)	TIA (n=53)	Ischemic stroke (n=545)
Mean age at index event, years (SD)	41.7 (7.7)	39.3 (9.1)	41.9 (7.5)
Men, N (%)	310 (51.8)	25 (47.2)	285 (52.3)
Mean time to assessment, days (SD)	89.7 (40.7)	92.3 (43.4)	89.5 (40.4)
Lesion location, right/left, N (%)			
Anterior	349 (58.4)	40 (75.5)	309 (56.7)
MCA	185(30.9)/149(24.9)	17(32.1)/22(41.5)	168(30.8)/127(23.3)
ACA	1 (0.2)/6 (1.0)	0 (0)/0 (0)	1 (0.2)/6 (1.1)
MCA and ACA	5 (0.8)/3(0.5)	1 (1.9)/0 (0)	4 (0.7)/3 (0.6)
Posterior	184 (30.8)	9 (17.0)	175 (32.1)
PCA	25 (4.2)/39 (6.5)	1 (1.9)/4 (7.5)	24 (4.4)/35 (6.4)
Vertebrobasilar	120 (20.1)	4 (7.5)	116 (21.3)
Watershed	3 (0.5)/4 (0.7)	0 (0)/ 0 (0)	3 (0.6)/4 (0.7)
Multiple	58 (9.7)	4 (7.5)	54 (9.9)
Median education level (IQR)	5 (5–6)	5 (5–6)	5 (5–6)
Median NIHSS score at admission (IQR)	3 (1–5)	0 (0–1)	3 (1–5)
Median NIHSS score at discharge (IQR)	1 (0–2)	0 (0–0)	1 (0–2)
Mean Barthel Index at assessment (SD)	98.3 (7.0)	99.7 (1.2)	98.1 (7.4)
Good outcome (BI≥85), N (%)	550 (96.3)	51 (100)	499 (96.0)
Median mRS at assessment (IQR)	1 (1–2)	1 (0–1)	1 (1–2)
Good outcome (mRS 0–1), N (%)	377 (65.6)	43 (82.7)	334 (63.9)
Median MMSE (IQR)	28 (26–29)	28 (27–29)	28 (26–29)
MINI-symptoms of depression present, N (%)	54 (9.3)	3 (5.7)	51 (9.7)
Mean CIS-20R-fatigue severity (SD)	32.9 (11.9)	32.8 (12.8)	32.9 (11.8)
Mild fatigue 27–35, N (%)	135 (27.7)	12 (26.1)	123 (27.8)
Severe fatigue ≥36, N (%)	205 (42.0)	19 (41.3)	186 (42.1)
TOAST, N (%)			
Atherothrombotic	25 (4.2)	0 (0.0)	25 (4.6)
Likely atherothrombotic	70 (11.7)	4 (7.5)	66 (12.1)
Small vessel	85 (14.2)	3 (5.7)	82 (15.0)
Cardioembolic	97 (16.2)	17 (32.1)	78 (14.7)
Rare causes	125 (20.9)	9 (17.0)	116 (21.3)
Multiple causes	37 (6.2)	4 (7.5)	33 (6.1)
Cryptogenic	159 (26.6)	16 (30.2)	143 (26.2)

IQR: interquartile range. MCA: Middle Cerebral Artery; ACA Anterior Cerebral Artery; PCA: Posterior Cerebral Artery; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; MMSE: Mini-Mental State Examination; MINI: Mini International Neuropsychiatric Interview; CIS-20R: Checklist Individual Strength; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.
Education category 5, i.e. middle school / secondary vocational training.
Missing data: NIHSS at admission 3 (0.5%); NIHSS at discharge 3 (0.5%); Barthel index 27 (4.5%); mRS 23 (3.8%); MMSE 32 (5.4%); MINI-symptoms of depression 20 (3.3%); CIS-20R-fatigue 110 (18.4%).

Table 2 Raw neuropsychological test scores and percentage of patients with cognitive impairment on a test

Cognitive domain & test	All participants (n=598)	Percent cognitive impaired[a]	TIA (n=53)	Percent cognitive impaired[a]	Ischemic stroke (n=545)	Percent cognitive impaired[a]
Episodic memory						
RAVLT trial 1–3	21.3 (6.2)	25.0	21.3 (4.5)	28.3	21.3 (6.3)	24.6
RAVLT delayed recall	6.7 (2.9)	20.6	6.7 (2.6)	10.0	6.7 (3.0)	20.7
Processing speed						
SDMT	49.9 (12.0)	27.3	55.0 (9.9)	15.4	49.4 (12.1)	28.5
Stroop part I [b]	4.2 (1.0)	23.1	4.5 (0.9)	7.8	4.1 (1.0)	24.6
Stroop part II [b]	3.3 (0.8)	23.4	3.6 (0.7)	9.8	3.3 (0.8)	24.7
Visuoconstruction						
ROCF copy	29.9 (4.7)	37.0	31.7 (3.7)	28.3	29.7 (4.8)	37.9
Executive functioning						
Verbal fluency	19.4 (5.0)	13.5	20.6 (4.4)	9.4	19.2 (5.0)	13.9
Stroop interference [b]	0.57 (0.1)	7.0	0.59 (0.1)	0.0	0.57 (0.1)	7.3
Brixton test	12.7 (6.1)	8.4	11.0 (4.7)	1.9	12.9 (6.2)	9.1
Visual neglect						
Star Cancellation	53.6 (1.3)	6.8	53.9 (0.3)	0.0	53.6 (1.4)	7.5
Language deficits						
Short token test	19.5 (1.9)	18.7	19.6 (2.2)	17.0	19.5 (1.9)	18.8
Attention and working memory						
Digit span test	24.6 (5.1)	22.8	25.3 (4.8)	23.1	24.5 (5.1)	22.8

RAVLT: Rey Auditory Verbal Learning Test; SDMT: Symbol-Digit Modalities Test; ROCF: Rey-Osterrieth Complex Figure.

Data were expressed as mean (SD). Test not valid/performed: RAVLT trial 1–3: n=9 (1.5%); RAVLT delayed recall n=19 (3.2%); SDMT n=37 (6.2%); Stroop part I n=26 (4.3%); Stroop part II n=25 (4.2%); ROCF copy n=31 (5.2%); Verbal fluency n=13 (2.2%); Stroop interference n=29 (4.8%); Brixton test n=17 (2.8%); Star Cancellation n=14 (2.3%); Short token test n=30 (5.0%); Digit span test n=28 (4.7%).

[a] Percent cognitive impaired: the percentage of the patients with a Z-score of <-1.5 on the test.

[b] Speed-accuracy composite score.

Higher scores indicate better performance on all measures, except for the Brixton test (number of errors).

Cognitive outcome after TIA or ischemic stroke

TIA and IS patients had a mean composite Z-score below the normative mean on respectively 5 and 6 domains (Figure 2). IS patients had worse cognitive performance than TIA patients on processing speed (p=0.001), visuoconstruction (p=0.002), executive functioning (p=0.004), and visual neglect (p=0.02). After additional adjustment for fatigue severity and symptoms of depression, IS patients had worse cognitive performance than TIA patients on processing speed (p=0.008)

and visuoconstruction (p=0.007). Time from index event to neuropsychological assessment was not significantly associated with cognitive performance in any of the domains. In addition, there were no differences in composite Z-scores on any of the cognitive domains using a median split in "time from index event to cognitive assessment" (i.e., neuropsychological assessment within 83 days versus after 83 days).

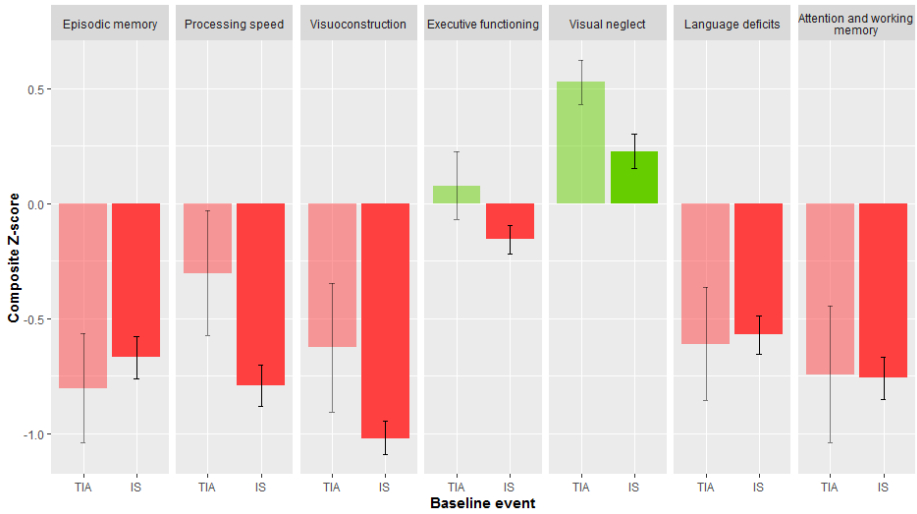


Figure 2 Cognitive performance after first-ever TIA or ischemic stroke. Cognitive performance after TIA or ischemic stroke in young adults. Mean composite Z-score (95% confidence interval) per cognitive domain. Z-scores were based on the raw scores of our patients compared with a control group or normative data. IS: ischemic stroke. Missing values in different domains: 0.2%-5.7%.

Below-average performance and cognitive impairment after TIA or ischemic stroke

The percentage of patients with cognitive impairment on each test is presented in Table 2. The total number of cognitively impaired tests in a patient is described in Supplementary Table 3. Among TIA and IS patients, there was a high proportion of patients with below-average performance and cognitive impairment (Figure 3). Cognitive impairment in episodic memory (21.4%), processing speed (23.3%), visuoconstruction (37.0%), language deficits (18.7%), and attention and working memory (22.8%) were most common. There were no significant differences between TIA and IS patients in the proportion of patients with below-average performance or cognitive impairment. There were no significant differences between patients who completed the cognitive assessment within 83 days after the event versus more than 83 days after the event with respect to the proportion of patients with a cognitive impairment.

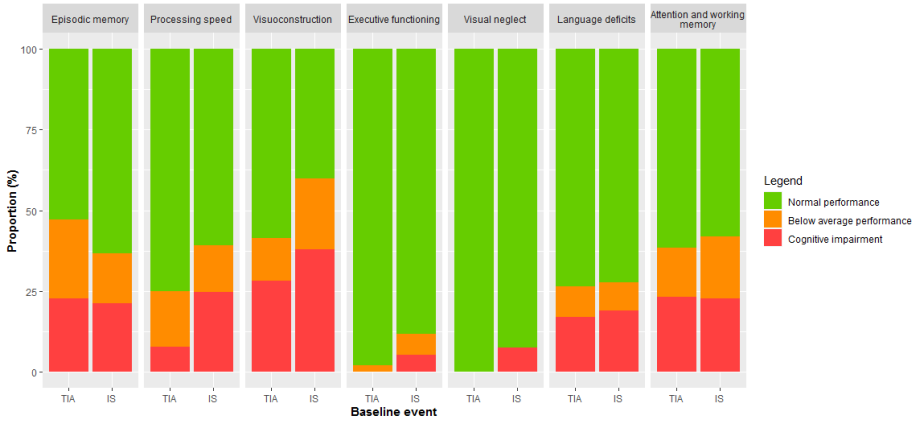


Figure 3 Below average performance and cognitive impairment stratified by event. The proportion of patients (%) with TIA and ischemic stroke at young age with below average performance (composite Z-score between -1.5 and -1.0) or a cognitive impairment (composite Z-score <-1.5). IS: ischemic stroke.

Mild and major vascular cognitive disorder

30.2% of TIA patients had mild VCD and 28.3% had major VCD. In IS patients, the prevalence of mild and major VCD was 33.8% and 34.3% respectively. Differences in baseline and imaging characteristics between patients without VCD, mild VCD and major VCD are described in Table 3. Patients with major VCD had a lower education level, had more frequent lesions in the left frontotemporal lobe, a higher NIHSS score at admission and at discharge than patients without VCD (all $p<0.05$ FDR-corrected).

Table 3 Patients with mild and major vascular cognitive disorder and no cognitive disorder

Characteristics	Without VCD (n=196)	Mild VCD (n=200)	Major VCD (n=202)
Mean age at index event, years (SD)	42.6 (6.9)	42.3 (7.0)	44.5 (8.8)
Mean time to assessment, days (SD)	93.4 (42.0)	89.6 (42.3)	86.3 (37.5)
Median education level (IQR)[a]	5 (5–6)	5 (5–6)	5 (5–6)
Ischemic stroke, N (%)	174 (88.8)	184 (92.0)	187 (92.6)
Territorial lesion, N (%)	144 (73.5)	150 (75.0)	151 (74.8)
Lesion location, N (%)			
Left frontotemporal lobe[c]	36 (18.4)	38 (19.0)	58 (28.7)
Left thalamus	18 (9.2)	20 (10.0)	15 (7.4)
Right parietal lobe	19 (9.7)	29 (14.5)	29 (14.4)
Median NIHSS score at admission (IQR)[b]	2 (1–5)	2 (1–5)	3 (1–6)
Median NIHSS score at discharge (IQR)[a]	0 (0–2)	1 (0–2)	1 (0–3)

Table 3 Continued

Characteristics	Without VCD (n=196)	Mild VCD (n=200)	Major VCD (n=202)
Thrombolysis, N (%)	52 (26.6)	52 (26.1)	47 (23.2)
Thrombectomy, N (%)	13 (6.6)	9 (4.5)	16 (7.9)
BI good outcome (≥85), N (%)	185 (96.9)	187 (97.9)	178 (94.2)
mRS good outcome (0–1), N (%)	135 (70.7)	128 (66.0)	114 (60.0)
MINI-symptoms of depression present, N (%)	10 (5.2)	23 (11.8)	21 (11.1)
Mean CIS-20R-fatigue severity, (SD)	31.4 (11.7)	33.1 (11.8)	33.5 (12.2)
Mild fatigue 27-35, N (%)	45 (26.5)	45 (27.4)	45 (29.2)
Severe fatigue ≥ 36, N (%)	66 (38.8)	70 (42.7)	69 (44.8)
TOAST, N (%)			
Atherothrombotic	7 (3.6)	6 (3.0)	12 (5.9)
Likely atherothrombotic	21 (10.7)	26 (13.0)	23 (11.4)
Small vessel	25 (12.8)	28 (14.0)	32 (15.8)
Cardioembolic	38 (19.4)	31 (15.5)	28 (13.9)
Rare causes	41 (20.9)	36 (18.0)	48 (23.8)
Multiple causes	13 (6.6)	15 (7.5)	9 (4.5)
Cryptogenic	51 (26.0)	58 (29.0)	50 (24.8)

IQR: interquartile range. VCD: vascular cognitive disorder; NIHSS: National Institutes of Health Stroke Scale; BI: Barthel Index; mRS: modified Rankin Scale; MINI: Mini International Neuropsychiatric Interview; CIS-20R: Checklist Individual Strength.

Education category 5, i.e. middle school / secondary vocational training.

Missing data: NIHSS at admission 3 (0.5%); NIHSS at discharge 3 (0.5%); thrombolysis 2 (0.3%); thrombectomy 2 (0.3%); Barthel index 27 (4.5%); mRS 23 (3.8%); MINI-symptoms of depression 20 (3.3%); CIS-20R-fatigue 110 (18.4%).

[a] Indicating significant difference between without VCD and mild VCD, and without VCD and major VCD after Benjamini-Hochberg correction.

[b] Indicating significant difference between without VCD and major VCD after Benjamini-Hochberg correction.

[c] Indicating significant difference between without VCD and major VCD, and mild VCD and major VCD after Benjamini-Hochberg correction.

Subjective cognitive complaints

Subjective memory complaints were present in 60.4% of the TIA patients and 71.5% of the IS patients. Subjective executive complaints were present in 45.3% of the TIA and 63.5% of the IS patients. Supplementary Figure 1 shows the distribution of total scores of subjective memory and executive complaints. Higher scores of subjective memory complaints were associated with lower cognitive performance on the cognitive domain attention and working memory in the overall study population (β:-0.32, $p<0.001$) and for the IS patients (β:-0.34, $p<0.001$), but not for TIA patients.

However, the effect sizes were small with an $R^2_{adjusted}$ of 0.10 and 0.11, respectively. Higher scores of the subjective executive complaints were associated with lower cognitive performance on the cognitive domain executive functioning in the overall study population (β:-0.21, $p<0.001$) and for the IS patients (β:-0.20, $p<0.001$), but not for TIA patients. Again, the effect sizes were small with an $R^2_{adjusted}$ of 0.04 in both the analyses. Supplementary Figure 2 shows the association between the total scores of subjective cognitive complaints and the number of cognitively impaired tasks. The effect size of this relation is small, with an R^2 of 0.06 ($p<0.05$).

Recurrent stroke

After excluding patients who had a recurrent TIA (n=4) or IS (n=24) before the cognitive assessment, we no longer found a significant difference in cognitive performance between TIA and IS on processing speed, after adjustment for fatigue severity and symptoms of depression. In addition, we found a lower proportion of patients with symptoms of depression in the group without VCD compared to the group with mild VCD ($p=0.015$). Excluding patients with a recurrent stroke did not influence the other results.

Discussion

In this large prospective study in young patients with TIA or IS, we found that (1) a high proportion of both TIA and IS patients showed worse cognitive performance on a wide range of cognitive domains in the subacute phase (up to 6 months after index event) compared to healthy controls, (2) higher NIHSS score at admission and discharge, stroke lesion in the left frontal lobe and lower education level were more common in patients with a major VCD than in patients without VCD, and (3) subjective cognitive complaints were prevalent, but were weakly associated with objective cognitive performance.

This study has multiple strengths. First, this is a multicenter prospective study with large sample size consisting of first-ever TIA and IS patients at a young age. Second, both TIA and IS were supported by radiological evidence, which reduces the risk of stroke mimics. Third, we used extensive neuropsychological testing (though a weakness is that this may prevent people from participating because of the extensiveness of the examination), as well as comprehensive questionnaires on mood and subjective cognitive complaints, with limited missing data. Finally, we used the normative data from the ANDI database, containing scores on neuropsychological tests from a large group of healthy controls.

However, several limitations need to be addressed. First, cognitive data of patients who were unable (for example severe aphasia) or refused to participate were lacking. This selection bias could affect the results, as patients without cognitive assessment had higher NIHSS scores at admission and discharge, but we expect that this bias, if any, would most likely lead to underestimation of the actual deficits. A shorter domain-specific assessment such as the Oxford Cognitive Screen,[132] less confounded by aphasia, may be used in future research to get an estimate of the cognitive status of individuals unable to complete a full comprehensive neuropsychological assessment. Second, due to logistic reasons, not all the neuropsychological tests were performed at the exact same time point after stroke. Time between the stroke and neuropsychological assessment might affect the cognitive performance, as recovery may have occurred in some patients. Nevertheless, all cognitive tests were performed within 6 months after the event and time from index event to assessment was unrelated to the test performance nor was it different between without, mild and major cognitive disorder. Third, premorbid cognitive performance of our patients is unknown. However, all patients are under the age of 50 and we expect that other neurodegenerative disorders will be negligible. Fourth, the lack of a strong association between subjective cognitive complaints and objective cognitive performance could have been due to the instrument used to measure it, as the semi-structured interview on subjective cognitive complaints is a generic instrument. A stroke-specific instrument, such as the Checklist of Cognitive an Emotional Consequences after stroke (CLCE-24), may be more preferable for future studies.[111] Finally, our patients with stroke at young age scored well on the Star Cancellation test, leading to better performance on visual neglect compared to controls. For this test, we used a control group as reference, who were on average older than ours. [117] However, the main advantage of using this control group is to obtain a continuous outcome measure.

We showed that cognitive impairment was common in young patients after IS and TIA with an equal proportion of patients with a below average performance and cognitive impairment. This suggest that TIA patients exhibit cognitive impairment similar to IS patients, even after full recovery from focal neurological symptoms. In our study, all TIA patients had recent cerebral ischemia on MRI. This could cause temporary or permanent disruption of the brain network, resulting in cognitive impairment. In addition, anxiety, depression and fatigue may also contribute to cognitive impairment.

Consistent with other studies with similar severity of stroke in terms of NIHSS and mRS, deficits in memory, language deficits, attention, and especially processing

speed were most common.[3, 5-8] Our patients performed relatively well on executive functioning. This domain is partly evaluated based on the performance of the Stroop parts I and II, which was scored relatively low in a high proportion of participants, resulting in relatively unimpaired Stroop interference scores. In addition, another explanation for this result is the use and the timing of different subtests and operationalization of the executive domain in studies,[5, 6] which may result in different outcomes. For instance, both our Stroop interference score (which adjusts for baseline processing speed by computing a ratio score) and the Brixton test (which is not timed and does not require a motor response) are not confounded by the patients' processing speed deficits, making them a more process-pure measure of executive function.

The results of this study provide evidence for high prevalence of mild or major VCD in the subacute phase. Up to two-third of our patients had mild or major VCD, even after using strict criteria for VCD with a higher specificity. Factors that are related to major VCD, are lower education level, higher NIHSS scores at admission and at discharge and lesions in the left frontotemporal lobe. Previous studies have found that left hemisphere stroke is more frequent associated with cognitive impairment.[6] This may be explained by the involvement of language area as the most cognitive tests are heavily language-based. Note that in this study, we only scored lesion locations visually. Lesion symptom mapping might be more specific to support this hypothesis. In addition, disrupted brain network involved in cognitive process due to strategic infarct locations and lower remote white matter integrity could lead to the development of PSCI.[9, 17] These findings suggest that if one of these factors is present, clinicians should be aware that PSCI might be present.

Subjective memory and executive complaints were present in about two-third of the participants. The high prevalence of subjective cognitive complaints may be due to the cut-off values (i.e. one positive answer already results in classification as 'subjective cognitive failures present'. This makes it a very sensitive method for assessing subjective cognitive complaints, but not very specific.

The subjective cognitive complaints scores were only weakly associated with objective cognitive performance. This suggests that in addition to objective cognitive impairment other factors, including distress-related psychological factors, coping and personality traits,[133, 134] may also be linked to subjective cognitive complaints. Interventions such as psycho-education, physical therapy and cognitive rehabilitation and cognitive rehabilitation might be a valuable addition to stroke rehabilitation reducing subjective cognitive complaints.[133] This

highlights the importance of the evaluation of objective and subjective cognitive performance in the first few months after the stroke, since these information may helpful to provide adequate patient-centered stroke care.

Conclusion

In conclusion, we showed that cognitive impairment on a wide range of cognitive domains and subjective cognitive complaints were prevalent in young patients after TIA and IS. However, they are only weakly associated with each other. Both neuropsychological assessment in the (sub)acute phase and subjective cognitive assessment may be considered in young stroke and TIA patients to obtain detailed information regarding the cognitive deficits. Future research projects should focus on the temporal dynamics of cognitive impairment after stroke and factors associated with cognitive impairment (including the role of strategic infarct locations), but also with cognitive recovery. This information might be important for patients and caregivers, as well as for the treating rehabilitation team.

Supplementary data

Supplementary Table 1 Baseline characteristics of the study population en patients without cognitive assessment

	Patients with cognitive assessment (n=598)	Patients without cognitive assessment (n=685)	p-value
Mean age at index event, years (SD)	41.7 (7.7)	41.8 (7.3)	0.83
Men, N (%)	310 (51.8)	364 (53.1)	0.64
Type index event, N (%)			0.08
TIA	57 (9.5)	47 (6.9)	
Ischemic stroke	541 (90.5)	638 (93.1)	
Median NIHSS score at admission (IQR)	3 (1–5)	3 (1–7)	<0.05
Median NIHSS score at discharge (IQR)	1 (0–2)	1 (0–3)	<0.05
TOAST, N (%)			0.65
Atherothrombotic	25 (4.2)	27 (3.9)	
Likely atherothrombotic	70 (11.7)	96 (14.0)	
Small vessel	85 (14.2)	81 (11.8)	
Cardioembolic	97 (16.2)	124 (18.1)	
Rare causes	125 (20.9)	149 (21.8)	
Multiple causes	37 (6.2)	42 (6.1)	
Cryptogenic	159 (26.6)	166 (24.2)	
Vascular risk factors, N (%)			
Hypertension	224 (37.5)	269 (39.3)	0.51
Diabetes mellitus	55 (9.2)	75 (10.9)	0.30
Dyslipidemia	392 (65.6)	458 (66.9)	0.62
Obesity	78 (13.0)	108 (15.8)	0.17
Morbid obesity	32 (5.4)	48 (7.0)	0.22
Smoking	283 (47.3)	356 (52.0)	0.10
Alcohol	34 (5.7)	54 (7.9)	0.12

IQR: interquartile range. NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of ORG 10172 in Acute Stroke Treatment. Missing data in patients without cognitive assessment: NIHSS at admission 1 (0.1%); NIHSS at discharge 8 (1.2%).

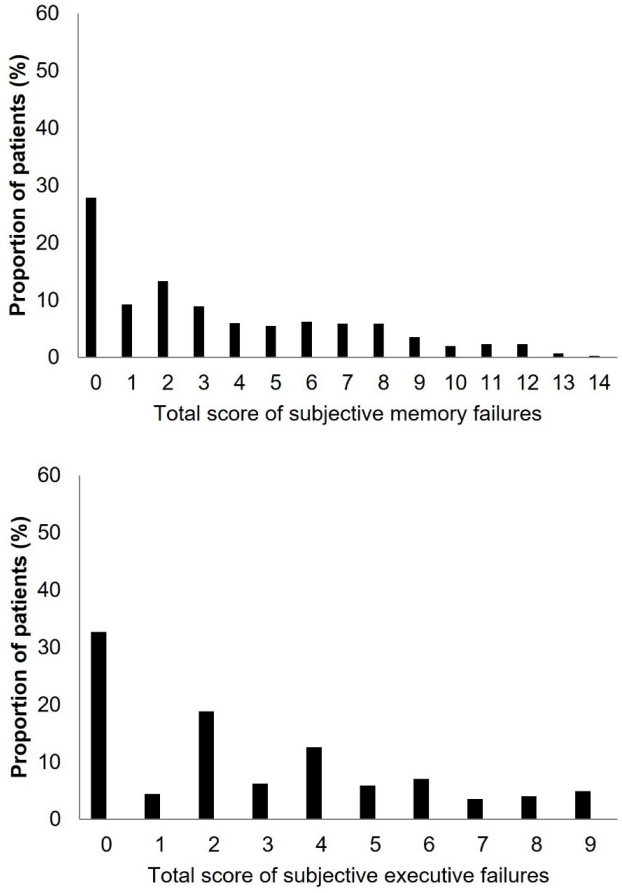
Supplementary Table 2 Reasons for non-completion for each test

Cognitive test	Total non-completion	Technical problems	Physical disability	Severe cognitive impairment[a]	Refusal
RAVLT trial 1-3	9	5	0	1	2
RAVLT delayed recall	19	11	0	2	6
SDMT	37	4	30	0	3
Stroop part I	26	14	6	4	2
Stroop part II	25	13	6	4	2
ROCF copy	31	1	28	1	1
Verbal fluency	13	6	0	3	4
Stroop interference	29	15	6	6	2
Brixton test	17	8	1	5	3
Star Cancellation	14	2	7	0	5
Short token test	30	16	2	4	8
Digit span test	28	9	0	4	15

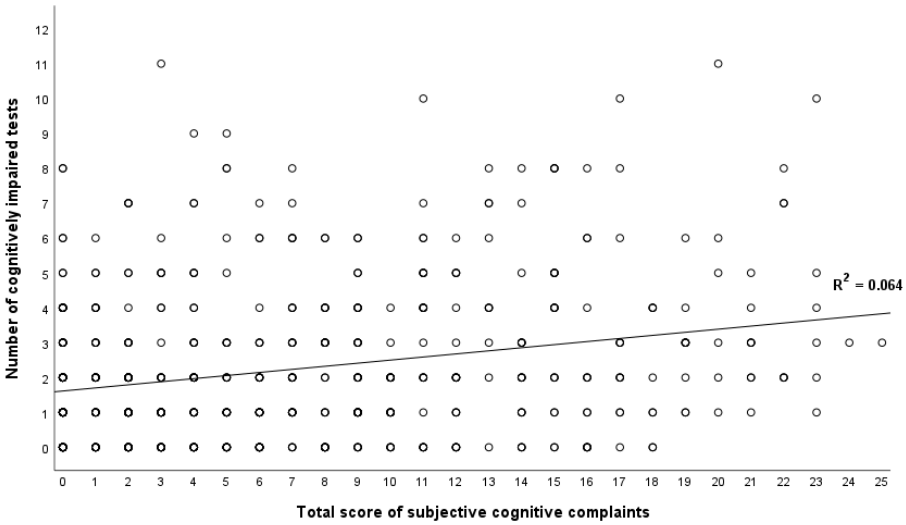
Data were expressed as numbers. RAVLT: Rey Auditory Verbal Learning Test; SDMT: Symbol-Digit Modalities Test; ROCF: Rey-Osterrieth Complex Figure. a) Severe cognitive impairment that prevented the patient from understanding the instruction.

Supplementary Table 3 Total number of cognitively impaired tests in a patient

Total tests cognitively impaired	Total patients
0	132
1	145
2	116
3	67
4	52
5	30
6	23
7	13
8	13
9	2
10	3
11	2



Supplementary Figure 1 Severity of subjective cognitive failures



Supplementary Figure 2 Relation between subjective cognitively complaints score and number of cognitive impaired tests

Chapter 4

Cognitive trajectory in the first year after first-ever ischemic stroke in young adults: the ODYSSEY study

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J Neurol Neurosurg Psychiatry. 2024 May 14;95(6):571-579.

Abstract

Background

Limited data exists on cognitive recovery in young stroke patients. We aimed to investigate the longitudinal course of cognitive performance during the first year after stroke at young age and identify predictors for cognitive recovery.

Methods

We conducted a multicenter prospective cohort study between 2013 and 2021, enrolling patients aged 18–49 years with first-ever ischemic stroke. Cognitive assessments were performed within 6 months and after 1 year following the index event, covering seven cognitive domains. Composite Z-scores using normative data determined cognitive impairment (Z-score<1.5). A Reliable Change Index (RCI) assessed cognitive recovery (RCI>1.96) or decline (RCI<-1.96).

Results

393 patients (median age 44.3 years, IQR 38.4–47.2) completed cognitive assessments with a median time interval of 403 days (IQR 364–474) between assessments. Based on RCI, a similar proportion of patients showed improvement and decline in each cognitive domain, while the majority exhibited no cognitive change. Among cognitively impaired patients at baseline, improvements were observed in processing speed (23.1%), visuoconstruction (40.1%) and executive functioning (20.0%). Younger age was associated with better cognitive recovery in visuoconstruction, and larger lesion volume was related to cognitive recovery in processing speed. No other predictors for cognitive recovery were identified.

Conclusions

Cognitive impairment remains prevalent in young stroke even 1 year after the event. Most patients showed no cognitive change, however, recovery may have occurred in the early weeks after stroke, which was not assessed in our study. Among initially cognitively impaired patients, cognitive recovery is observed in processing speed, visuoconstruction and executive functioning. It is still not possible to predict cognitive recovery in individual patients.

Introduction

At least 1.5 million young adults (18–50 years) are affected by stroke every year, with an increasing global incidence.[1] Post-stroke outcome does not only depend on motor function, but also on cognitive performance after stroke. A meta-analysis revealed that nearly half of young adults experience cognitive impairment after stroke, both in the (sub)acute and chronic phase (often after excluding patients with aphasia).[135] These findings align with our recent study, which reported that up to 37% of young stroke patients experience impairment in five cognitive domains in the subacute phase (on average 3 months after ischemic stroke): episodic memory; processing speed; visuoconstruction; executive functioning and attention and working memory.[136] However, previous studies on cognitive performance at different post-stroke intervals were predominantly cross-sectional rather than longitudinal.[135] Surprisingly, limited research has been done on the incidence and risk factors associated with cognitive recovery or decline after stroke at a young age. Information about post-stroke cognitive impairment and to identify those who will recover is essential for young stroke patients, as they will have to cope with the consequences for the rest of their lives, which can have an effect on family planning or a career.[137] Several studies have examined potential predictors for cognitive recovery after ischemic stroke in older patients. These predictors included younger age, female sex, higher level of education, stroke location and severity, vascular risk factors, emotional status, lesion volume and white matter hyperintensity severity, although results varied across studies.[28, 138-142] It remains unclear whether similar patterns and risk factors for cognitive performance apply to the younger stroke population. We therefore aimed to investigate the longitudinal trajectory of cognitive performance across multiple cognitive domains during the first year (i.e. subacute and chronic phase) after first-ever ischemic stroke, as well as explore factors associated with cognitive recovery in a cohort of young stroke patients.

Patients and methods

Patients and study design

This study is part of the *'Observational Dutch Young Symptomatic StrokE studY'*, a multicenter prospective cohort study examining risk factors and prognosis of stroke at young age.[22, 136] The present study included patients aged 18–49 years with a first-ever ischemic stroke with radiological evidence of cerebral ischemia. Patients were included between May 2013 and February 2021. Exclusion criteria were a history of stroke, retinal infarction and cerebral venous sinus thrombosis. Detailed information

regarding data collection has been provided elsewhere.[22] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study (NL41531.091.12). We obtained written informed consent from all participants. If the patient was unable to provide informed consent, consent was provided by the patient's legal representative.

Cognitive assessment at baseline and follow-up

Patients underwent an extensive neuropsychological assessment at baseline (within 6 months after stroke) and follow-up (1 year after stroke). The seven most relevant cognitive domains were assessed using multiple tests: *episodic memory* (3-trial version of the Rey Auditory Verbal Learning Test), *processing speed* (the written version of the Symbol-Digit Modalities Test, the abbreviated Stroop Color Word Test, parts I and II), *visuoconstruction* (Rey-Osterrieth Complex Figure -copy trial), *executive functioning* (Fluency test, Stroop interference score, Brixton Spatial Anticipation Test), *visual neglect* (Star Cancellation of the Behavioral Inattention Test), *language deficits* (Short Token test), *attention and working memory* (Digit Span subtest from the Wechsler Adult Intelligence Scale- Fourth Edition). Global cognitive functioning was examined with the Mini-Mental State Examination. Further details regarding the collection of cognitive data can be found elsewhere.[136]

Normative data from the Advanced Neuropsychological Diagnostics Infrastructure (ANDI), which includes data of 26,000 healthy individuals across all age groups were employed for most tests. This allowed fine-grained adjustment based on age, sex and education level.[115] Prior to inputting the data of the abbreviated Stroop Color Word Test into ANDI, we multiplied the raw scores by two, to account for using half of the card. For the written version of the Symbol-Digit Modalities Test, we used the normative data from the test's manual (n=1,307),[116] adjusted for age and education level, as this test is not available in the ANDI data set. For the Star Cancellation Test, which by definition is a negatively skewed outcome variable, we used a cutoff value (<44) instead of Z-scores, to indicate visuospatial neglect.[143]

Based on the regression-based normative data from ANDI, adjusted for age and education level, raw test scores were converted to Z-scores per test for each participant. To correct for outliers, we adjusted Z-scores >3 or <-3 to 3 and -3, respectively.[136] We used simple imputation with the median (education category five, ie, middle school/secondary vocational training) for the missing data on education level in two patients. Subsequently, the composite Z-score for each cognitive domain was computed by averaging the Z-scores of cognitive tests that are reflective of the same cognitive domain. If one test within a particular domain was missing, the domain score was based on the remaining tests within that domain.

For each test, cognitive impairment was defined as a Z-score of <-1.5 (ie, reflecting performance more than 1.5 SD below the age-adjusted and education-adjusted normative mean). Cognitive impairment on a domain was defined as a composite Z-score of <-1.5 and below average performance was defined as a composite Z-score between -1.0 and -1.5.[118, 136] To calculate mean test scores and proportions within the cognitive performance categories based on composite Z-score, only patients who fulfilled the domain score in both assessments were included.

Reliable Change Index

The raw test scores were converted to a Reliable Change Index (RCI) with the Chelune formula, which accounts for measurement errors and practice effects.[144] More detailed information on the Chelune formula can be found in the Supplementary Data. Data from control groups was found in the literature.[28, 145-150] For the Star Cancellation Test, an RCI could not be computed, due to the nonparametric nature of the test's outcome. After calculating the RCI for each individual cognitive test, we averaged RCIs of cognitive tests that assessed the same cognitive domain into domain RCI scores. If one test of a specific domain was missing, the domain RCI was based on the remaining tests within that domain. Next, we calculated the total RCI by averaging the RCIs per domain, reflecting an individual's change across all cognitive domains. Reliably cognitive recovery was defined as an RCI greater than 1.96, while reliable decline was defined as an RCI less than -1.96. An RCI between -1.96 and 1.96 indicated an unchanged cognitive performance.[144]

Other measurements

Level of education was scored with a Dutch scoring system comprising seven categories[121] that align with the UNESCO international classification of education levels.[122] We assessed symptoms of depression and fatigue using the Mini International Neuropsychiatric Interview [123] and the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R)[124], respectively. We used the Barthel Index[125] and modified Rankin Scale (mRS)[126] to assess functional outcome at the time of the baseline cognitive assessment. We defined good functional outcome as an mRS score of 0–1 and a Barthel Index of ≥85. Additionally, we evaluated the etiology of stroke (based on modified Trial of ORG 10172 in Acute Stroke Treatment)[151, 152] and severity at admission and discharge (National Institutes of Health Stroke Scale; NIHSS)[128], if necessary retrospectively, using a validated approach,[129, 130] because this scale was not consistently applied in all medical files. Lesion locations were visually identified, and semi-automatic segmentation was performed on diffusion-weighted imaging (DWI) (MRI < 14 days after stroke) or FLAIR images (MRI > 14 days after stroke) using ITK-SNAP. All lesion segmentations were visually inspected, and lesion volumes were

calculated. We determined whether there was recurrent stroke before or between the cognitive assessments based on patient records.

Statistical analysis

We compared the baseline characteristics of patients who completed both the baseline and follow-up cognitive assessment with those who completed only a baseline cognitive assessment, using the independent t-test, Mann-Whitney U test or Pearson's χ^2 test (or Fisher's exact test when an expected cell count was less than five) when appropriate.

To investigate differences in proportions of cognitively impaired patients between baseline and follow-up, we used the McNemar test. A difference in proportion of recovered and declined patients per cognitive domain based on RCI was examined with Pearson's χ^2 test. We determined the association of post-stroke fatigue (based on CIS-20R) at baseline and the RCI per cognitive domain using linear regression.

Potential predictive factors for recovery and cognitive performance at follow-up, selected based on the literature, including sex, age, NIHSS at admission and discharge, education level, lesion location, lesion volume, acute treatment, discharge destination, post-stroke fatigue, post-stroke depression,[28, 138-142] were tested. Additionally, the interval between stroke and first assessment was specifically assessed as a predictive factor for recovery and cognitive performance at baseline was specifically assessed as a predictive factor for cognitive performance at follow-up. Potential predictors for recovery were tested univariately in cognitively impaired patients at baseline using independent t-test, Mann-Whitney-U-test or Pearson's χ^2test (or Fisher's exact test when an expected cell count was less than five). In univariate tests, there was, if any, only one potential predictor significant for each domain. Therefore, multivariable analyses were not applicable.

To analyze the potential predictors for cognitive performance at follow-up, we used linear regression. First, we assessed strong correlations among numeric potential predictors, setting a threshold at 0.7, and found that none exceeded this limit. Subsequently, we tested potential variables through univariable analysis, and if they were found to be significant, we included them in our multivariable linear regression. If the variable was categorical, we selected a reference category.

To investigate the influence of recurrent stroke on the results, we performed post-hoc analyses, in which we conducted all above-described analyses after excluding patients with a recurrent stroke between baseline and follow-up assessment.

All statistical analyses were performed using RStudio 2022.02.01.

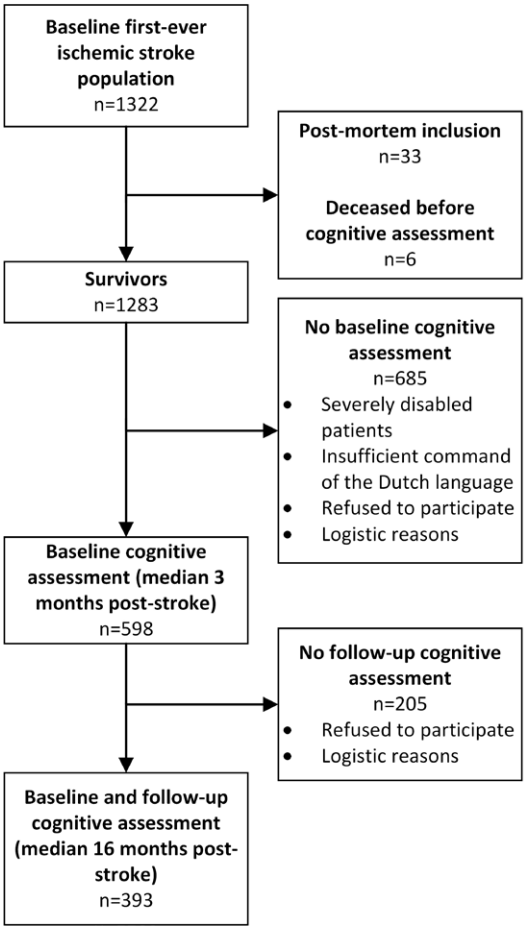

Figure 1 Flowchart of the study population

Results

In total, 1322 patients had an ischemic stroke at young age, of whom 598 completed a baseline neuropsychological assessment and 393 participated in both, a baseline and follow-up neuropsychological assessment (Figure 1). Baseline characteristics of the study population are presented in Table 1. Median age of patients at stroke onset was 44.3 years (IQR 38.4–47.2), 49.6% (n=195) were women. Median NIHSS at admission was 2 (IQR 1–5). Median time from index event to the first cognitive assessment was 80 days (IQR 54–114) and median time between the first and

second cognitive assessment was 403 days (IQR 364–474). Baseline characteristics of patients with a baseline cognitive assessment only (n=205) are presented in Supplementary Table 1. Participants who dropped out after the baseline assessment had a lower education level (p=0.037), a higher NIHSS at admission (p=0.010), more often had an unfavorable Barthel Index (p=0.027) and a longer time to baseline neuropsychological assessment (p=0.026) compared with the participants who completed both assessments.

Table 1 Baseline characteristics

	Baseline and follow-up assessment completed (n=393)
Median age at index event, years (IQR)	44.3 (38.4–47.2)
Men, N (%)	198 (50.4)
Median time to baseline assessment, days (IQR)	80 (54–114)
Median time to follow-up assessment, days (IQR)	493 (435–562)
Median interval baseline and follow-up, days (IQR)	403 (364–474)
Lesion location, N (%)	
Right supratentorial	142 (36.1)
Left supratentorial	138 (35.1)
Bilateral supratentorial	21 (5.3)
Infratentorial	65 (16.5)
Unilateral supratentorial and infratentorial	13 (3.3)
Bilateral supratentorial and infratentorial	14 (3.6)
Lesion volume on MRI, mL (SD)	11.0 (34.8)
Median education level (IQR)	5 (5–6)
Median NIHSS score at admission (IQR)	2 (1–5)
Median NIHSS score at discharge (IQR)	1 (0–2)
Median Barthel Index at baseline (IQR)	100 (100–100)
Good outcome (BI≥85), N (%)	367 (97.9)
Median mRS at baseline (IQR)	1 (1–2)
Good outcome (mRS 0–1), N (%)	257 (67.6)
Median MMSE at baseline (IQR)	28 (26–29)
MINI symptoms of depression present at baseline, N (%)	37 (9.7)
Mean CIS-20R - fatigue severity at baseline (SD)	33.0 (11.8)
Mild fatigue 27–35, N (%)	88 (26.3)
Severe fatigue ≥ 36, N (%)	144 (43.0)
TOAST, N (%)	
Atherothrombotic	12 (3.1)
Likely atherothrombotic	40 (10.2)

Table 1 Continued

	Baseline and follow-up assessment completed (n=393)
Small vessel disease	55 (14.0)
Cardioembolic	70 (17.8)
Rare causes	85 (21.6)
Multiple causes	28 (7.1)
Cryptogenic	103 (26.2)

Education category 5, that is, middle school/secondary vocational training. Missing data: lesion volume 34 (8.7%) ; NIHSS at admission 3 (0.8%); NIHSS at discharge 3 (0.8%); Barthel Index 18 (4.6%); mRS 13 (3.3%); MMSE 16 (4.1%); MINI - symptoms of depression 13 (3.3%); CIS-20R-fatigue 58 (14.8%). BI: Barthel Index; CIS-20R: Checklist Individual Strength; MINI: Mini International Neuropsychiatric Interview; MMSE: Mini-Mental State Examination; mRS: modified Rankins Scale; NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

Individual neuropsychological test scores and the percentage of patients with cognitive impairment for each test are presented in Table 2.

Table 2 Raw neuropsychological test scores and percentage of patients with cognitive impairment on a test

Cognitive domain and test	Baseline (n=393)	Percent cognitively impaired [a]	Follow-up (n=393)	Percent cognitively impaired [a]
Episodic memory				
RAVLT trial 1–3	21.7 (6.1)	23.8	23.6 (6.4)	13.6
RAVLT delayed recall	6.8 (2.9)	19.3	7.6 (3.1)	14.2
Processing speed				
SDMT	51.3 (11.3)	22.0	52.1 (11.4)	19.8
Stroop part I	25.5 (9.2)	30.1	25.7 (8.8)	31.1
Stroop part II	31.6 (10.6)	24.3	31.0 (9.6)	21.2
Visuoconstruction				
ROCF copy	30.3 (4.2)	34.0	30.9 (4.2)	30.7
Executive functioning				
Verbal fluency	19.8 (5.0)	11.8	16.6 (3.9)	27.0
Stroop interference	50.6 (22.0)	17.3	48.5 (22.9)	12.8
Brixton test	12.3 (6.0)	7.3	10.7 (5.2)	4.3
Visual neglect				
Star Cancellation [b]	53.7 (1.3)	0.5	53.7 (1.3)	0.5
Language deficits				
Short token test	19.6 (2.0)	17.0	19.9 (1.6)	9.1

Table 1 Continued

Cognitive domain and test	Baseline (n=393)	Percent cognitively impaired [a]	Follow-up (n=393)	Percent cognitively impaired [a]
Attention and working memory				
Digit span test	24.9 (5.0)	4.8	25.2 (5.3)	4.3

Data were expressed as mean (SD). Test not valid/performed: RAVLT trial 1–3 n=11 (2.8%); RAVLT delayed recall n = 14 (3.6%); SDMT n=29 (7.4%); Stroop part I n=11 (2.8%); Stroop part II n=11 (2.8%); ROCF copy n=19 (4.8%); Verbal fluency n=11 (2.8%); Stroop interference n=12 (3.1%); Brixton test n=22 (5.6%); Star Cancellation n=8 (2.0%); Short token test n=29 (7.4%); Digit span test n=17 (4.3%). Higher scores indicate a better performance on all measures, except for the Brixton test (number of errors).

[a] Percent cognitively impaired: the percentage of the patients with age, education and sex-adjusted Z-score of <-1.5 on the test.

[b] A score <44 indicates cognitive impairment.

RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey-Osterrieth Complex Figure; SDMT: Symbol-Digit Modalities Test.

Below-average performance and cognitive impairment

Proportions of patients with below average performance and cognitive impairment based on composite Z-scores per domain are shown in Figure 2. A smaller proportion of patients was classified as cognitively impaired at follow-up compared with baseline on episodic memory (11.7% vs 19.1%; p=0.001), processing speed (23.0% vs 27.6%; p=0.021) and language deficits (9.1% vs 17.0%; p<0.001).

Change in performance category

For all cognitive domains, most patients neither improved nor declined in performance category between baseline and follow-up (Figure 3). We found the highest proportion of patients that improved in performance category for episodic memory (21.9%), processing speed (16.6%), visuoconstruction (26.8%) and language deficits (17.6%). In the other domains, less than 10% of patients improved. Focusing on patients who were cognitively impaired at baseline, most patients improved to below average or normal performance at follow-up in episodic memory (65.8%), executive functioning (56.0%) and language deficits (67.7%). In other cognitive domains, improvement in one-third to half of patients was observed.

Cognitive recovery per cognitive domain

The total RCI and RCI per cognitive domain per patient are presented in Figure 4. Overall, there was no cognitive change in most patients (98.7%) based on total RCI. Among the cognitive domains, the highest percentage of patients showed improvement in processing speed (7.2%) and visuoconstruction (18.1%). However, equal proportions of patients also experienced decline in these cognitive domains, with 8.2% declining in processing speed and 11.5% in visuoconstruction. For all

domains, we observed equal proportions of patients with cognitive recovery and decline based on RCI. In patients who were cognitively impaired at baseline, recovery was observed in 25/108 (23.1%) in processing speed, 51/127 (40.1%) in visuoconstruction and 5/25 (20.0%) in executive functioning, while in other domains improvement was less than 4%.

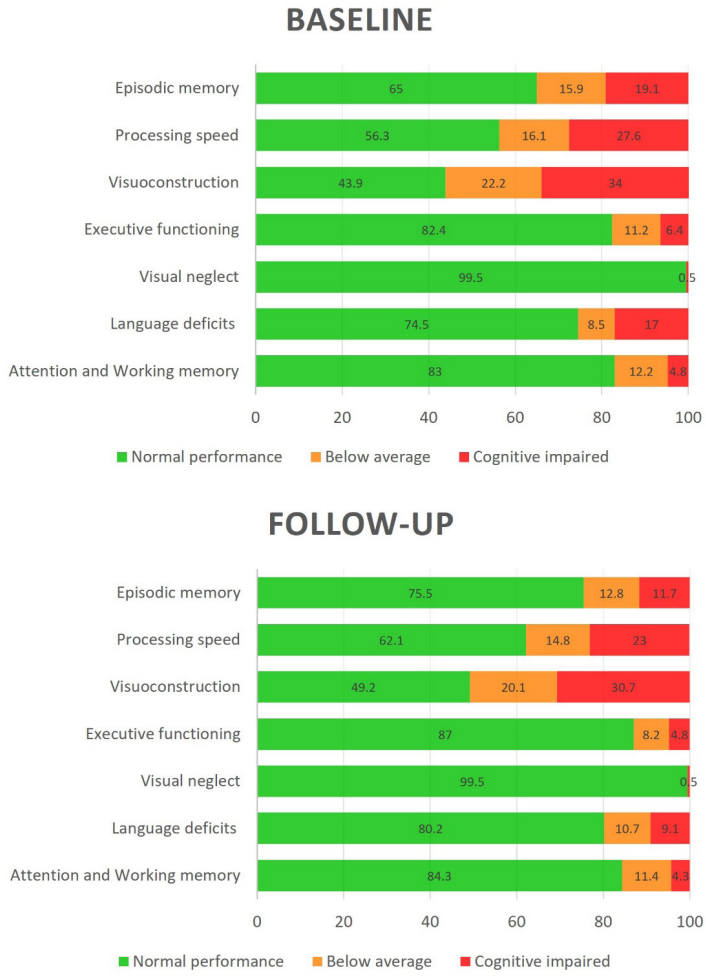

Figure 2 Domain-specific below average performance and cognitive impaired at baseline and follow-up. The proportion of patients (%) with young ischemic stroke with domain-specific below average performance (composite Z-score between -1.5 and -1.0) or a cognitive impairment (composite Z-score <-1.5) at baseline and follow-up. For visual neglect a raw score <44 indicates impairment. Only patients with a domain score at baseline and follow-up were included. Missing values: episodic memory 10 (2.5%); processing speed 2 (0.5%); visuoconstruction 19 (4.8%); executive functioning 1 (0.3%); language deficits 29 (7.4%); attention and working memory 17 (4.3%).

Higher scores of post-stroke fatigue at baseline were associated with a lower RCI in executive functioning (β=-0.012; p=0.004). However, the effect size was small with an $R^2_{adjusted}$ of 0.021. There were no significant associations between post-stroke fatigue and RCI of the other cognitive domains.

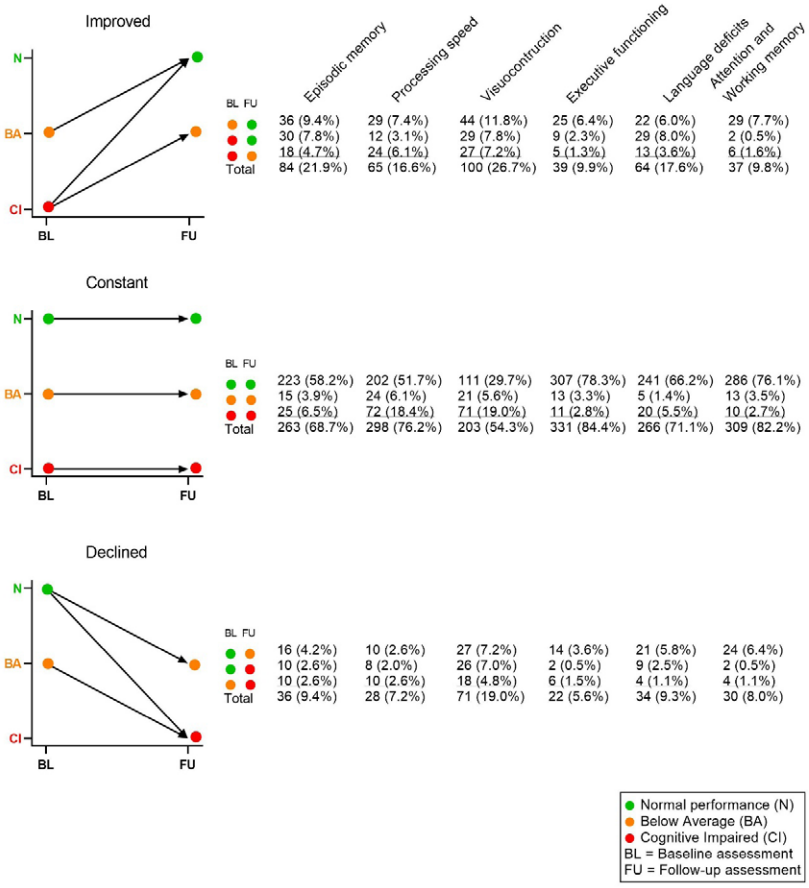

Figure 3 Change in performance categories between baseline and follow-up. Patients with improved, constant or declined performance based on composite Z-score between baseline and follow-up assessment for each cognitive domain. Only patients with a domain score at baseline and follow-up were included. Missing values: episodic memory 10 (2.5%); processing speed 2 (0.5%); visuoconstruction 19 (4.8%); executive functioning 1 (0.3%); language deficits 29 (7.4%); attention and working memory 17 (4.3%).

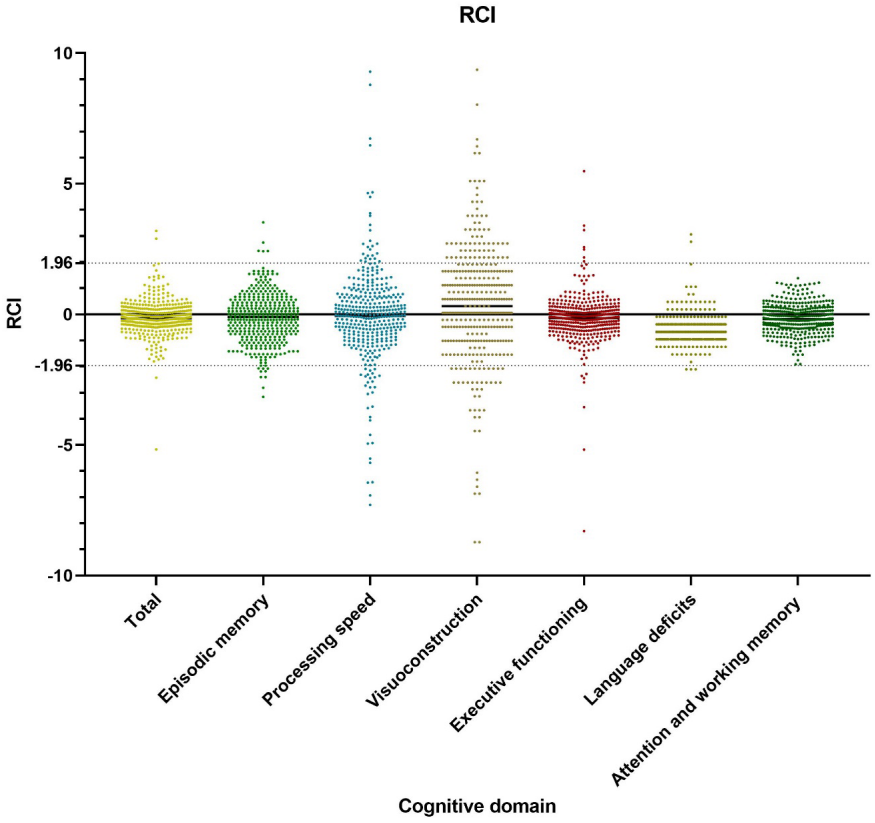

Figure 4 Reliable Change Index overall and per cognitive domain. RCI > 1.96 indicates cognitive recovery, RCI < -1.96 indicates cognitive decline. Not displayed values (out of range): RCI total 1 (10.8), RCI processing speed 3 (-17.8 , -11.0 , 30.6). Missing values: episodic memory 10 (2.5%); processing speed 2 (0.5%); visuoconstruction 19 (4.8%); executive functioning 1 (0.3%); language deficits 29 (7.4%); attention and working memory 17 (4.3%).

Predictive factors for cognitive recovery in cognitively impaired patients at baseline

Patients who were cognitively impaired in processing speed at baseline and who recovered (based on RCI) had a larger lesion volume (26.8mL (SD 37.7) vs 10.1mL (SD 17.8), p=0.006) compared with patients who did not recover. In visuoconstruction, patients who were cognitively impaired at baseline and who recovered, were younger than patients who did not recover, with a median age of 40.2 years versus 44.6 years (p=0.045), respectively. No other predictive factors were found to be significant in any of the tested cognitive domains.

Predictive factors for cognitive performance at follow-up

Domain specific predictive factors for cognitive performance at follow-up are presented in Supplementary Table 2. In all domains, the Z-score at baseline of a domain was significantly associated with the Z-score of that particular domain at follow-up. The effect sizes were medium to large (β varied between 0.39 and 0.83). In episodic memory, a high education level (compared with low) and in visuoconstruction middle and high education level (both compared with low) were significantly associated with lower Z-scores at follow-up (β varied between -0.19 and -0.29).

Recurrent stroke

After excluding patients with a recurrent stroke before the follow-up assessment (n=23), younger age was no longer a predictive factor for recovery of visuo-construction in cognitively impaired patients at baseline. The results of all other analyses remained similar.

Discussion

In this prospective cohort study of young ischemic stroke patients, we found that in most patients their cognitive performance did not change based on RCI in the first year after their index stroke. However, in cognitively impaired patients at baseline, we observed recovery based on RCI in one to two-fifths of the patients in processing speed, visuoconstruction and executive functioning. One to two-thirds of patients who were cognitively impaired at baseline were no longer categorized as cognitively impaired at follow-up in all domains (i.e., they were classified as below average or normal). We could not identify predictive factors for cognitive recovery in patients who were cognitively impaired at baseline.

We found that even 1 year after relatively mild strokes (median NIHSS 2) multi-domain cognitive impairment is still prevalent in young stroke patients. This is in line with previous cross-sectional young stroke studies with longer follow-up periods (up to several years).[6, 7, 135] Studies on cognitive recovery in young stroke patients are scarce. A study in a relatively small sample of young stroke patients (n=87), with a median NIHSS of 2, found lower prevalence rates of cognitive impairment after 3 months, compared with the acute phase (within 3 weeks), in processing speed, attention, executive functioning, but not in fluency.[5] We found lower prevalence rates in the chronic phase compared with the subacute phase in episodic memory, processing speed and language deficits, but not in the other tested domains. This

could be explained by differences in cognitive domains studied and tests used for assessing different domains. Besides that, it is possible that certain cognitive domains recover faster, resulting in differences in prevalence rates at different phases after stroke. A relatively small sample study (n=38) in stroke patients, aged 18–65, showed significant improvement in visuospatial function in the subacute phase (7 months) compared with the acute phase (1 week) and in working memory in the chronic phase (10 years), compared with the acute and subacute phase.[153] Another study (n=153) in stroke patients, aged 18–65, showed that the majority of recovery in all seven tested cognitive domains took place within the first 6 months after stroke, but little recovery occurred after 6 months, as 90% of the patients remained either cognitively unimpaired or cognitively impaired between 6 months and 2 years.[26] While these studies, with a smaller sample size, looked at group-level changes and did not use the RCI, most recovery seemed to occur in the first months after stroke. Therefore, it could be that we found relatively little recovery because our baseline assessment took place on average 3 months after stroke, and not in the acute phase. Also, recovery detected through RCI is a fairly strict method, which may have led to fewer patients with recovery than studies that used other methods to measure change in cognition. The latter could also explain why we were unable to find strong predictive factors for cognitive recovery. Since relatively few patients recovered, our study sample may not have had enough power to identify predictors for recovery. However, using the RCI to detect recovery is more reliable than using delta scores for change, since it reduces the chance of overestimating a true recovery.[144] Post-stroke fatigue may play a role in the cognitive recovery after stroke. However, we only identified a significant association between post-stroke fatigue and cognitive recovery in executive functioning, but this does not explain the cognitive recovery in this domain as the effect size was very small. Although we did not find a uniform predictor, we found that in visuoconstruction younger patients who were cognitively impaired at baseline were more likely to recover. In processing speed patients with a larger stroke lesion who were cognitively impaired at baseline were more likely to recover. The latter finding could be explained by the fact that lesion volumes were mainly derived from DWI images, and a DWI lesion does not necessarily result in permanent brain damage. Second, the role of the exact location of the lesion and other structural brain changes, such as brain atrophy and pre-existent vascular damages, might influence cognitive recovery.[62]

The best predictor for cognitive performance at follow-up in our study was the cognitive performance at baseline. This finding is not surprising, considering the limited cognitive change over time. The finding that higher education levels were associated with lower cognitive performance in episodic memory and

visuoconstruction at follow-up, as compared with lower educational levels, could be attributed to the prior adjustment of Z-scores for education differences. This unexpected finding, however, needs to be replicated and further investigated in more detail in future studies. We found a similar proportion of patients who declined compared with those who have recovered. This decline was not expected and cannot be explained by the presence of recurrent strokes. Other factors such as secondary neurodegeneration, ongoing chronic neuroinflammation, or ongoing damage to neural networks may be involved in determining the clinical status 1 year after the initial stroke index. However, future studies are needed to validate these findings and to understand the underlying pathophysiological mechanisms of this decline.

Strong elements of this study are the large sample size of patients at young age with first-ever, radiologically confirmed, ischemic stroke and its prospective and longitudinal multicenter character, in which general and university hospitals participated. Second, we used extensive neurocognitive testing instead of short cognitive screening tests, with limited missing data. Third, we used RCI analyses to assess cognitive recovery, which allowed us to adjust for learning effects. Finally, we used regression-based normative data based on large groups of healthy controls, resulting in clinically relevant classifications of test performances.

However, several limitations need to be addressed. First, cognitive data of patients who were unable or refused to participate were lacking (for example because of severe stroke). This resulted in a population with relatively mild strokes (median NIHSS 2). This might affect the generalizability of our results to the whole young stroke population. Since patients without cognitive assessment had higher NIHSS scores,[136] we expect that this bias, if any, would most likely lead to underestimation of the actual deficits. Second, cognitive data of patients who were unable or refused to participate in the follow-up assessment were lacking. These patients had more severe stroke, as indicated by higher NIHSS scores at admission, compared with patients with complete assessment. Third, due to logistic reasons not all neuropsychological tests were performed at the same time after stroke. The baseline assessment was assessed up to 6 months after stroke (with a median of 80 days after the index stroke), which might have affected the results, as recovery may have occurred in the first weeks after stroke. Furthermore, the wide temporal range of the baseline assessments may potentially influence the outcomes, as cognition may not remain stable during the first months after stoke. Fourth, we did not collect data on other interventions patients received, such as cognitive rehabilitation, which could have mediated cognitive recovery. Fifth, there could be a ceiling effect of multiple tests we used, making them less sensitive.

Clinicians could use the results of this study to inform patients and their caregivers about what to expect regarding their cognitive performance after stroke. Future research should address the role of change in cognitive performance on functional outcomes, such as resuming work. In addition, it would be interesting to identify reliable predictors for the development and recovery of cognitive impairment. Strategic infarct locations, lower white matter integrity, or brain reserve might play a role in this process. Future studies should focus on these topics, since this can clarify the mechanisms of post-stroke cognitive recovery or decline, which also might be important in the neurorehabilitation process.

In conclusion, cognitive impairment after mostly mild stroke in young adults is still common 1 year after stroke and in most patients, there was no cognitive change after the first months after stroke. Cognitive recovery could have taken place in the acute phase after stroke, which we were unable to investigate because of the lack of neuropsychological data for this timeframe in our study. These findings are relevant for young stroke patients, as they have to cope with these consequences for the rest of their lives. Predicting cognitive recovery for the individual patient remains difficult.

Supplementary data

Chelune formula

Raw test scores were converted to a Reliable Change Index (RCI) with the Chelune formula that takes measurement errors and practice effects into account (equation 1).

(1) $$RCI = \frac{(X_2 - X_1) - (\overline{X}_{C2} - \overline{X}_{C1})}{SE_{diff}}$$

X_1 and X_2 denote individual test scores measured at baseline and follow-up, respectively. and denote mean test scores from the control group, at baseline and follow-up, respectively.

SE_{diff} denotes the standard error of the difference score, calculated by equation 2:

(2) $$SE_{diff} = \sqrt{2s_1^2(1 - r_{12})}$$

r_{12} denotes test-retest reliability in the control group and s_1 denotes the standard deviation of the baseline score in the control group.

Supplementary Table 1 Baseline characteristics of the study population and patients who only completed a baseline assessment.

	Baseline and follow-up assessment completed (n=393)	Only baseline assessment completed (n=205)	p-value
Median age at index event, years (IQR)	44.3 (38.4-47.2)	44.5 (38.4-47.6)	0.787
Men, N (%)	198 (50.4)	113 (55.1)	0.271
Median time to assessment BL, days (IQR)	80 (54-114)	89 (60-126)	0.026*
Median education level (IQR)	5 (5-6)	5 (5-6)	0.034*
Median NIHSS score at admission (IQR)	2 (1-5)	3 (1-5)	0.010*
Median NIHSS score at discharge (IQR)	1 (0-2)	1 (0-2)	0.070
Barthel Index good outcome (BI≥85), N (%)	367 (97.9)	185 (93.9)	0.014*
mRS good outcome (mRS 0-1), N (%)	257 (67.6)	121 (61.7%)	0.158
MINI- symptoms of depression present, N (%)	37 (9.7)	18 (9.0)	0.788
Mean CIS-20R-fatigue severity (SD)	33.0 (11.8)	32.6 (12.2)	0.676
TOAST, N (%)			0.134
Atherothrombotic	12 (3.1)	13 (6.3)	
Likely atherothrombotic	40 (10.2)	30 (14.6)	
Small vessel disease	55 (14.0)	30 (14.6)	
Cardioembolic	70 (17.8)	27 (13.2)	
Rare causes	85 (21.6)	39 (19.0)	
Multiple causes	28 (7.1)	9 (4.4)	
Cryptogenic	103 (26.2)	57 (27.8)	
Vascular risk factors, N (%)			
Hypertension	145 (36.9)	79 (38.5)	0.694
Diabetes mellitus	32 (8.1)	23 (11.2)	0.277
Dyslipidemia	249 (63.4)	143 (69.8)	0.118
Obesity	51 (13.0)	27 (13.2)	0.947
Morbid obesity	24 (6.1)	8 (3.9)	0.256
Alcohol	22 (5.6)	12 (5.9)	0.898
Cognitive impaired at baseline, N (%)			
Episodic memory	76 (19.5)	49 (24.4)	0.173
Processing speed	108 (27.6)	68 (33.8)	0.118
Visuoconstruction	129 (34.1)	81 (42.2)	0.059
Executive functioning	26 (6.6)	19 (9.3)	0.236
Visual neglect	1 (0.5)	2 (0.5)	1.000
Language deficits	40 (20.8)	66 (17.5)	0.335
Attention and working memory	19 (5.0)	12 (6.2)	0.547

Education category 5, i.e. middle school / secondary vocational training. * indicates significant p-values (p<0.05). Missing data in patients with only baseline assessment completed**:** Barthel Index 8 (3.9%); mRS 9 (4.4%); MMSE 5 (2.4%); MINI - symptoms of depression 6 (1.5%); CIS-20R-fatigue 47 (22.9%); Cognitive impaired: episodic memory 4 (2.0%); processing speed 4 (2.0%); visuoconstruction 13 (6.3%); executive functioning 1 (0.5%); visual neglect 5 (2.4%); language deficits 13 (6.3%); attention and working memory 11 (5.4%). CIS-20R: Checklist Individual Strength; MINI: Mini International Neuropsychiatric Interview; NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

Supplementary Table 2 Multivariable linear regression analysis of cognitive domain specific predictors for the Z-scores at follow-up

Predictor	Episodic memory		Processing speed	
	Beta Coefficient (β)	**p-value**	**Beta Coefficient (β)**	**p-value**
Z-score at baseline (same domain as outcome)	0.653	**<0.001***	0.827	**<0.001***
Age at event, year	-	-	0.002	0.916
Gender [a]	-	-	-	-
Education [b]				
Middle (5)	-0.010	0.960	-0.139	0.607
High (6-7)	-0.290	**0.009***	-0.135	0.205
NIHSS at admission	-0.025	0.054	-0.002	0.916
NIHSS at discharge	0.017	0.693	0.010	0.916
CIS-20R - fatigue severity at baseline	-0.005	0.275	-	-
MINI symptoms of depression at baseline [c]	-	-	-	-
Lesion location [d]				
Right supratentorial	0.106	0.426	0.012	0.916
Bilateral supratentorial	-0.015	0.960	0.049	0.916
Infratentorial	0.172	0.275	-0.015	0.916
Unilateral supratentorial and infratentorial	0.011	0.960	-0.063	0.916
Bilateral supratentorial and infratentorial	0.426	0.180	-0.103	0.916
Discharge to [e]				
Clinical rehabilitation	-0.253	0.219	-0.146	0.647
Outpatient rehabilitation	-0.076	0.693	-0.059	0.916
Nursing home	NA	NA	NA	NA
Different	-0.540	0.140	-0.124	0.916
Lesion Volume on MRI, mL	-	-	<-0.001	0.916
Adjusted R-squared	0.478		0.754	

Education category 5 , i.e. middle school/ secondary vocational training. Variables that were not statistically significant in univariable analysis were excluded from the multivariable regression model and are represented as '-' in the table. Variables that were not statistically significant in any univariable analysis were omitted from the table.

[a] Reference category Gender: Male.

[b] Reference category Education level: Low(1-4).

Visuoconstruction		Executive functioning		Language deficits		Attention and working memory	
Beta Coefficient (β)	**p-value**	**Beta Coefficient (β)**	**p-value**	**Beta Coefficient (β)**	**p-value**	**Beta Coefficient (β)**	**p-value**
0.471	**<0.001***	0.591	**<0.001***	0.391	**<0.001***	0.775	**<0.001***
-	-	-	-	0.016	**0.003***	-	-
-	-	-	-	-	-	-0.075	0.367
-0.291	**0.039***	-0.070	0.632	-	-	-0.087	0.401
-0.186	**0.047***	-0.140	0.142	-	-	-0.069	0.401
-	-	-0.007	0.430	-0.016	0.065	-	-
-	-	<-0.001	0.997	-0.009	0.631	-	-
-	-	-0.005	0.156	-	-	-	-
-	-	-0.160	0.251	-	-	-	-
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-
-	-	-0.015	0.978	-	-	0.003	0.962
-	-	0.029	0.898	-	-	0.075	0.401
-	-	NA	NA	-	-	-1.372	**0.016***
-	-	-0.305	0.251	-	-	-0.146	0.401
-	-	-	-	-	-	-	-
0.216		0.487		0.274		0.595	

[c] Reference category MINI symptoms of depression: No.
[d] Reference category Lesion location: Left supratentorial.
[e] Reference category Discharge to: Home.
Numbers with * and bold indicates significant p-values after FDR-correction.
CIS-20R: Checklist Individual Strength; MINI: Mini International Neuropsychiatric Interview; NIHSS: National Institutes of Health Stroke scale.

Part III

Underlying mechanisms of cognitive impairment: imaging insights

Chapter 5

Lesion locations are associated with cognitive impairment after ischemic stroke in young adults

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Under review

Abstract

Background and Objectives

Stroke location is an important determinant of post-stroke cognitive impairment. However, in young adults, a comprehensive map of lesion patterns and their relations to post-stroke cognitive impairment is lacking. The objective of this study is to identify stroke lesion locations associated with poorer cognitive performance in young stroke patients.

Methods

We conducted a multicenter prospective cohort study between 2013 and 2021, enrolling patients aged 18–49 years with first-ever ischemic stroke and a visible stroke lesion on MRI. Cognitive assessments were performed within six months after the index event, covering seven cognitive domains. We categorized patients as having no/mild or major vascular cognitive disorder (VCD), defined as a Z-score <-2.0 in one or more domains. We assessed aphasia by the NIHSS language subscale. We performed multivariate lesion-symptom mapping to identify lesion locations associated with major VCD, poorer cognitive performance in each domain, and aphasia.

Results

Among 522 patients (median age 44.3 years [IQR 37.7–41.5]; 257 [49.2%] women), 168 (32.2%) had major VCD. Lesions in both hemispheres and cerebellar regions were associated with presence of a major VCD, and lower performance in episodic memory, processing speed, executive functioning, language, and attention and working memory. Aphasia had the strongest relationship with left fronto-temporo-parietal regions, while the left angular gyrus was the region most associated with major VCD.

Discussion

We show that lesion locations associated with poorer cognitive performance in young stroke patients are widely distributed across various brain regions, including in the cerebellum. This showcases the complexity in the relationships between affected brain regions and cognitive symptoms, explaining the variability in post-stroke cognitive outcome.

Introduction

Each year, more than two million young adults (18–50 years) suffer an ischemic stroke worldwide.[154, 155] Stroke location is, in addition to age, education level, vascular risk factors, stroke severity and lesion volume, an important determinant of post-stroke outcome.[9, 10] Recent studies using lesion-symptom mapping, investigating the relationship between structural damage and behavioral deficits, have provided further evidence for the role of strategic infarct location in post-stroke cognitive impairment.[9, 11-13] However, these studies involved older patients, who often have a history of stroke in addition to the index event and age-related neurodegenerative pathology. Additionally, not all of these studies used extensive cognitive assessments and, consequently, a comprehensive lesion-symptom map is still lacking in young adults. The relationship between stroke location and post-stroke cognitive performance may differ from stroke patients >50 years as in young adults the influence of other neurovascular changes, such as cerebral small vessel disease or neurodegenerative disorders, is less likely, suggesting that the results are less affected in this group. Clinical MRI scans in the acute phase may be used to predict cognitive outcomes in the first months after stroke, which could be valuable for early information provision and rehabilitation planning.

Multivariate lesion analysis of structural imaging data is a lesion-symptom mapping (LSM) method[14-16] that identifies the entire lesion-symptom association pattern simultaneously, rather than assessing the brain-behavior relation at each voxel separately, as in traditional voxel-based lesion-symptom mapping.[31]

The objective of this study is to evaluate lesion locations associated with post-stroke cognitive impairment in young adults. For this purpose, we performed a multivariate LSM study in a large cohort of young stroke patients and investigated whether lesion locations are associated with poorer cognitive performance.

Methods

Patients and study design

This study is a part of the *'Observational Dutch Young Symptomatic StrokE studY' (ODYSSEY)*, a multicenter prospective cohort study examining risk factors and prognosis of stroke at young age.[22, 136] The present study included patients aged 18–49 years with a first-ever ischemic stroke with radiological evidence of cerebral ischemia on MRI. Patients were included between May 2013 and February 2021. Exclusion criteria were

a history of stroke, retinal infarction, and cerebral venous sinus thrombosis. Detailed information regarding data collection has been provided elsewhere.[22]

Standard Protocol Approvals, Registrations, and Patient Consents

This study involves human participants and was approved by the Medical Review Ethics Committee region Arnhem-Nijmegen (NL41531.091.12). We obtained written informed consent from all participants. If the patient was unable to provide informed consent, consent was provided by the patient's legal representative.

Cognitive assessment

Patients underwent an extensive neuropsychological assessment (at a median time point slightly less than three months after stroke). The seven most relevant cognitive domains were assessed: (i) Episodic memory, (ii) Processing speed, (iii) Visuoconstruction, (iv) Executive functioning, (v) Visual neglect, (vi) Attention and working memory, and (vii) Language. Using normative data, we converted raw test scores into Z-scores per test for each participant, using the individual's age, sex and/or education level. Further details regarding the collection and processing of cognitive data can be found in the Supplementary Methods section and elsewhere.[136, 156]

We used the criteria for vascular cognitive disorder (VCD) based on the criteria of the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG).[120] We defined major VCD as a composite Z-score of <-2.0, in one or more cognitive domains (representing 2.3% of the normal population). All remaining patients were classified as no/mild VCD.

Neuroimaging Data Acquisition

Structural MRI scans were performed in a clinical setting on 1.5T or 3T scanners. The imaging protocol included at least a clinical diffusion-weighted imaging (DWI) and a fluid attenuated inversion recovery (FLAIR) scan.

Neuroimaging Data Processing

Lesion segmentation

All stroke lesions were segmented semi-automatically using ITK-SNAP.[157] Lesions were segmented on DWI (n=468) when identified approximately within two weeks from the index event; on FLAIR (n=52) when identified approximately after two weeks, or, if unavailable, on T1 (n=1) or T2 (n=1) sequences. The lesions were reviewed and manually adjusted if necessary.

Spatial normalization

Using Advanced Normalization Tools (ANTs, v 2.1.0),[158] we registered brain images to the Montreal Neurological Institute (MNI) 152 ICBM 2009c Nonlinear Symmetric template. To improve the registration, the anatomical images were bias corrected, denoised and skull-stripped. The registration was performed by moving the template to the patients' image and then using the inverse transformation to bring the patients' image into standard space. If the registration was not possible with ANTs, we used elastix[159], a software program for intensity-based medical image registration, to directly register the skull-stripped images to the MNI 152 ICBM 2009c Nonlinear Symmetric space. We visually checked all registered images and lesions. In three patients, the registration of the lesion to the template was unsuccessful for both methods due to anatomical (n=1) or technical (n=2) reasons, leading to their exclusion from the analysis. We calculated normalized lesion volumes using FSLstats.[160]

Other measurements

We scored the level of education of the patients with a Dutch scoring system comprising seven categories[121] that approximately align with the UNESCO international classification of education levels.[122] We determined symptoms of depression using the Mini International Neuropsychiatric Interview (MINI)[123] and fatigue using the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R) at the time of the baseline cognitive assessment.[124] We used the Barthel Index[125] and modified Rankin Scale (mRS)[126] to assess functional outcome at the time of the baseline cognitive assessment. We quantified the severity of the stroke at admission and discharge (National Institutes of Health Stroke Scale; NIHSS)[128], if necessary retrospectively, using a validated approach.[129, 130] Additionally, we evaluated the etiology of stroke (based on the modified Trial of ORG 10172 in Acute Stroke Treatment; TOAST).[151, 152]

Statistical analysis

We compared baseline characteristics between patients with no/mild VCD versus major VCD, using independent t-test or Mann-Whitney U test for continuous variables and Pearson's Chi-squared test for categorial variables.

Multivariate lesion-symptom mapping

We performed multivariate LSM using the spare canonical correlation analysis (SCCAN) as implemented in the LESYMAP package (version: 0.0.0.9222) in R.[161] In brief, SCCAN maps the associations between brain regions and cognitive deficits by identifying sets of voxels that collectively explain variance in cognitive

performance scores (multivariate method). LESYMAP runs internal 4-fold cross-validation procedures to find the best sparseness. Sparseness refers to how much the algorithm is restricted or allowed in terms of the number of voxels it can include in the model. A larger sparseness allows the algorithm to retain more voxels with smaller weights. To find the best sparseness, 75% of the patients is used to identify voxel weights and 25% is used to predict the cognitive scores with those weights. Once the best sparseness value is found, a final SCCAN is run on all patients usings this optimal sparseness value. We excluded voxels with minimal lesion coverage <10% (fewer than five voxels), which is a standard approach. We performed separate multivariate LSMs for the presence of a major VCD, Z-score of each cognitive domain, and aphasia assessed by the NIHSS language subscale at discharge. If scores were missing at random, we performed mean imputation. To identify peak regions of interest (ROIs) with the strongest associations with the cognitive outcomes from the lesion-symptom map, a cluster tool in FSL was used. All lesion-symptom maps were spatially normalized to the MNI152 T1-weighted 1mm template provided by FSL. We based anatomical locations of the lesions on the Harvard-Oxford cortical and subcortical structural atlas,[162-165] and the JHU ICBM white-matter atlas,[166-168] available in FSL. We identified the structures to which the center of mass of each cluster predominantly belongs. If the center of mass was located in unclassified white matter, we additionally reported, when possible, another (sub)cortical structure or white matter tract to which the center of mass belongs. Intensity values for each cluster ranged from -1 to 1, with -1 and 1 indicating the most robust relationship between the region and the cognitive score. We report only regions with poorer cognitive performance. To facilitate interpretability, we inverted the intensity values of the cognitive domain scores, as lower Z-scores indicate poorer cognitive performance, to ensure that the intensity values were positive.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator after permission of regulatory bodies and medical ethics committees.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT, to improve the language of the manuscript. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Results

Of the 1,322 patients included in the ODYSSEY study with an ischemic stroke, 522 ischemic stroke patients were included in this analysis, see Supplementary Figure 1 for a flowchart of the study population. Baseline and imaging characteristics, stratified by major or no/mild VCD, are described in Table 1. Median age of patients at stroke onset was 44.3 years (IQR 37.7-41.5), 257 (49.2%) were woman, and median NIHSS score at admission was 2 (IQR 1-4). Median time from index event to MRI was 2 days (IQR 1-5) and median normalized lesion volume was 2.3 mL (IQR 0.7-13.3). Median time from index event to cognitive assessment was 83 days (IQR 56-119). Patients with a major VCD were more frequently women (p=0.043), had a lower education level (p<0.001), a higher NIHSS score at admission (p<0.001), and at discharge (p=0.002), a lower Barthel Index (p<0.001), a higher mRS score (p=0.005), more frequently depressive symptoms, and a larger lesion volume (p=0.003) compared to patients with no/mild VCD. Cognitive scores are presented in Table 2.

Table 1 Baseline characteristics

	Patients			
	All patients (n=522)	**No/mild VCD (n=354)**	**Major VCD (n=168)**	**p-value**
Median age, years (IQR)	44.3 (37.7-41.5)	44.3 (38.4-47.1)	44.2 (36.4-47.8)	0.732
Men, n (%)	265 (50.8)	191 (54.0)	74 (44.4)	0.043
Median time to cognitive assessment, days (IQR)	83 (56-119)	85 (55-121)	76 (57-113)	0.262
Median education level (IQR)	5 (5-5)	5 (5-6)	5 (5-5)	<0.001
Median NIHSS score at admission (IQR)	2 (1-4)	2 (1-4)	3 (1-5)	<0.001
Median NIHSS score at discharge (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.002
Median Barthel Index at baseline (IQR)	100 (100-100)	100 (100-100)	100 (100-100)	<0.001
Good outcome (BI≥85), n (%)	488 (97.2)	336 (97.7)	152 (96.2)	
Median mRS (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.005
Good outcome (mRS 0-1), n (%)	337 (66.7)	241 (69.7)	96 (60.4)	
Symptoms of depression present, n (%)	49 (9.6)	27 (7.7)	22 (13.9)	0.042
Mean CIS-20R - fatigue severity (SD)	32.9 (12.0)	32.0 (11.7)	35.2 (12.2)	0.011
No/mild fatigue <36, n (%)	251 (57.7)	183 (60.2)	68 (51.9)	
Severe fatigue ≥ 36, n (%)	184 (42.3)	121 (39.8)	63 (48.1)	
Median time to MRI, days (IQR)	2 (1-5)	3 (1-5)	2 (1-5)	0.620
Median normalized lesion volume, mL (IQR)	2.3 (0.7-13.3)	2.0 (0.6-9.4)	4.2 (0.8-24.5)	0.003

Table 1 Continued

	Patients			
	All patients (n=522)	**No/mild VCD (n=354)**	**Major VCD (n=168)**	**p-value**
TOAST, n (%)				0.379
Atherothrombotic	18 (3.4)	8 (2.3)	10 (6.0)	
Likely atherothrombotic	62 (11.8)	42 (11.8)	20 (11.9)	
Small vessel disease	80 (15.3)	53 (15.0)	27 (16.1)	
Cardioembolic	86 (16.5)	64 (18.1)	22 (13.1)	
Rare causes	102 (19.5)	68 (19.2)	34 (20.2)	
Multiple causes	31 (5.9)	21 (5.9)	10 (6.0)	
Cryptogenic	143 (27.4)	98 (27.7)	45 (26.7)	

VCD: Vascular Cognitive Disorder; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; BI: Barthel Index; mRS: modified Rankin Scale; MINI: Mini International Neuropsychiatric Interview; CIS-20R: Checklist Individual Strength; TOAST: Trial of ORG 10172 in Acute Stroke Treatment. Education category 5, i.e. middle school / secondary vocational training.
Missing data: NIHSS ad admission 2 (0.4%); NIHSS at discharge 3 (0.6%); Barthel Index 20 (3.8%); MINI symptoms of depression 14 (2.7%); CIS-20R-fatigue 87 (16.7%).

Table 2 Cognitive performance

	Patients (n=522)
Z-score cognitive domain, mean (SD)	
Episodic memory	-0.7 (1.0)
Processing speed	-0.8 (1.1)
Visuoconstruction	-1.0 (0.9)
Executive functioning	-0.3 (0.8)
Visual neglect	0.3 (0.8)
Attention and working memory	-0.4 (0.7)
Language	-0.6 (0.9)
Aphasia, n (%)	
No aphasia	470 (90.6)
Mild to moderate aphasia	36 (6.9)
Severe aphasia	12 (2.3)
Mutism or global aphasia	1 (0.2)

SD: Standard Deviation; VCD: Vascular Cognitive Disorder. Missing data: episodic memory 6 (1.1%); processing speed 3 (0.6%); visuoconstruction 25 (4.8%); visual neglect 11 (2.1%), language 25 (4.8%), attention and working memory 17 (3.3%); aphasia 3 (0.6%).

Lesion coverage

Lesion overlap maps are shown in Figure 1. Patients most often had a lesion in the territory of the right middle cerebral artery. The involvement of regions within the territories of the anterior and posterior cerebral artery, as well as portions of the brainstem and cerebellum, was too infrequent to allow for multivariate lesion-symptom mapping.

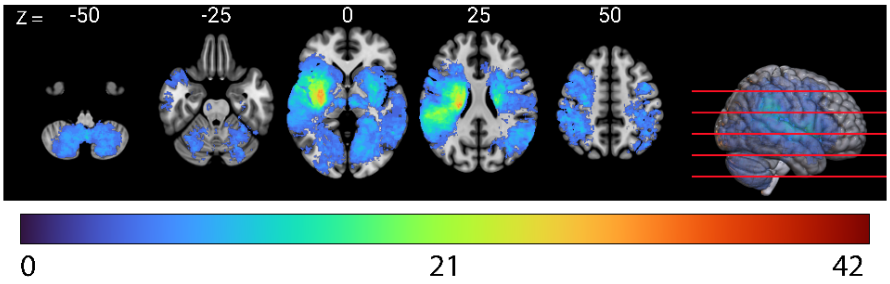


Figure 1 Lesion overlap maps of all patients (n=522). Axial slices with a minimum overlap of 5 lesions. The images are presented in radiological orientation.

Multivariate lesion-symptom mapping

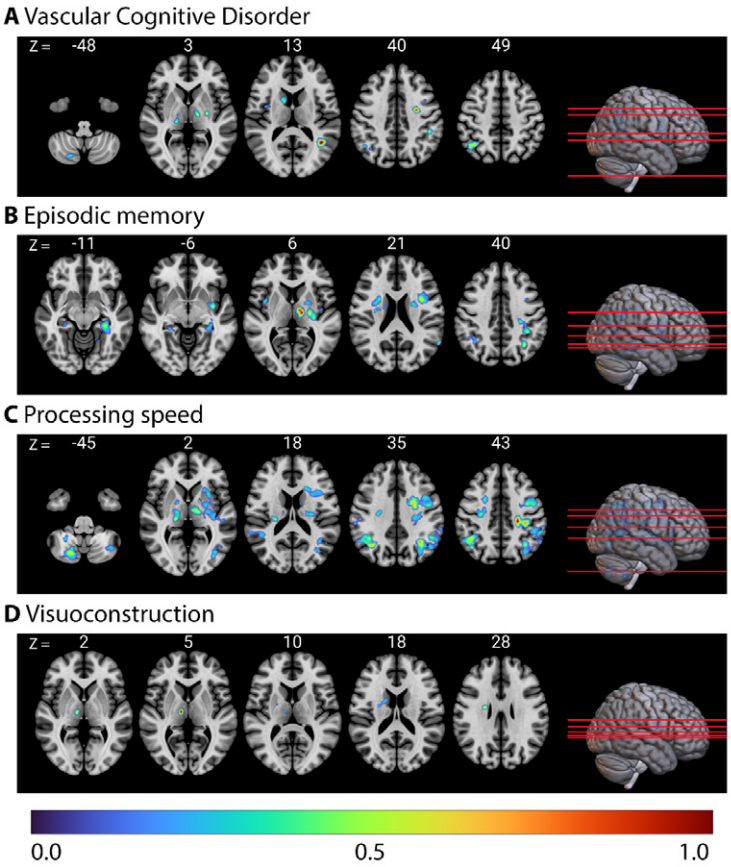
The LSM identified brain regions associated with poorer behavioral performance (Figure 2). Supplementary Table 1 presents all identified peak regions associated with poorer performance, along with the peak ROI coordinates (X, Y, Z) for each cluster.

The presence of a major VCD was associated with regions in both hemispheres, with the strongest relationship observed in left angular gyrus. An additional cluster was located in the right cerebellum ($r = 0.187$, $p < 0.001$, optimal sparseness = 0.110).

The regions associated with poorer performance in episodic memory were mainly localized in bilateral frontal and hippocampal regions, left thalamus, and left insular regions ($r = 0.168$, $p < 0.001$, optimal sparseness = -0.271). For processing speed, regions associated with poorer performance were predominantly found in bilateral frontoparietal regions, left insular regions, and bilateral cerebellar regions ($r = 0.222$, $p < 0.001$, optimal sparseness = 0.485). Deep right frontal white matter and the right thalamus were associated with poorer performance in visuoconstruction ($r = 0.092$, $p = 0.036$, optimal sparseness = 0.019). For executive functioning, regions associated with poorer performance were mainly identified in bilateral frontoparietal and insular regions, with stronger relationships observed in the left hemisphere, and additionally, bilateral cerebellar regions ($r = 0.277$,

p < 0.001, optimal sparseness = 0.637). Regions associated with visual neglect were right-lateralized, with the strongest relationships observed in small clusters in the right angular and precentral gyri. Additionally, there were regions located in the cerebellum (r = 0.167, p < 0.001, optimal sparseness = 0.027). Regions associated with poorer performance in attention and working memory were mainly located in bilateral parietal and insular regions, and left frontal regions, with an additional region the right cerebellum (r = 0.167, p < 0.001, optimal sparseness = 0.027).

For language, regions associated with poorer performance were mainly located in the left hemisphere, with the strongest relationship observed in a cluster in the left parietal white matter. An additional cluster was identified in the right cerebellum (r = 0.128, p = 0.003, optimal sparseness = 0.106). Finally, regions associated with aphasia, assessed with the NIHSS subscale, were predominantly left-lateralized (r = 0.626, p < 0.001, optimal sparseness = -0.456), and located in the fronto-temporo-parietal regions.



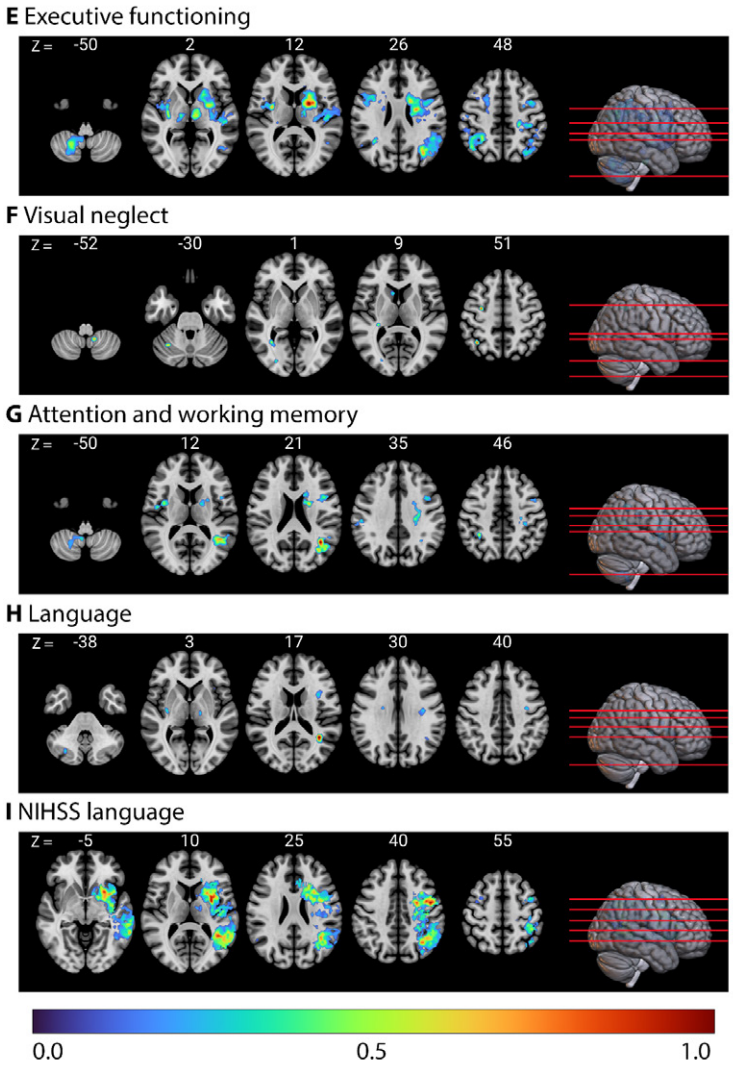


Figure 2 Lesion-symptom mapping results for the presence of a major vascular cognitive disorder, each cognitive domain, and aphasia. Axial slices in radiological orientation highlighting lesion locations associated with poorer cognitive performance. (**A**) Vascular Cognitive Disorder. (**B**) Episodic memory. (**C**) Processing speed. (**D**) Visuoconstruction. (**E**) Executive functioning. (**F**) Visual neglect. (**G**) Attention and working memory. (**H**) Language (**I**) NIHSS language subscale.

Discussion

In this study, we show that lesion locations in different brain regions, often in different vascular distributions, are associated with poorer performance on various cognitive domains in young ischemic stroke patients. Additionally, we found that stroke lesions in the cerebellum, often overlooked in the context of stroke and cognition, were also associated with poorer cognitive performance in multiple cognitive domains. This widespread distribution showcases the complexity in the relationships between affected brain regions and cognitive symptoms, explaining the variability observed in young ischemic stroke patients with post-stroke cognitive impairment.

For most of the tested cognitive domains, including episodic memory, processing speed, executive functioning, language, attention and working memory, as well as for the presence of a major VCD, we identified regions in both hemispheres associated with poorer cognitive performance. While the overall distributions of the lesion locations associated with poorer cognitive performance appears widespread, the regions identified per cognitive domain correspond with established findings in the lesion literature. For example, involvement of the hippocampus, the prefrontal cortex, and the thalamus in episodic memory is well-documented.[169] However, previous lesion-symptom mapping studies did not report bilateral brain regions associated with poorer cognitive performance across all these domains.[9, 13] In older participants with stable, focal stroke brain lesions in the chronic phase (three months or more after lesion onset), only left-hemispheric clusters were associated with worse performance in episodic memory and with language deficits.[7] One possibility for the difference with our study is that, performing imaging in the chronic phase, as that study did, may allow for more precise lesion segmentation, since diffusion restriction in the acute phase does not always indicate permanent tissue damage. This suggests that our findings could be less robust, as acute diffusion restriction does not reflect lasting structural damage. However, imaging from the chronic phase alone cannot fully account for the stronger left-lateralized associations with cognition. Another study, which included 12 cohorts of ischemic stroke patients and imaging in the acute phase, also found significant associations exclusively within the left hemisphere for verbal memory, language, and attention and executive functioning, using voxel-based lesion-symptom mapping.[9] It is possible that language deficits might have played a larger role in their findings, as only seven cohorts explicitly excluded patients with severe language impairment. This could potentially account for the observed lesion pattern typically associated with language. Consistent with our study, that study found regions in bilateral

hemispheres predicting impairment in processing speed and overall post-stroke cognitive impairment, comparable with major VCD.[9] However, we found more smaller regions and less involvement of the left frontotemporal lobe in patients with major VCD. This difference, with our findings showing smaller regions compared to the voxel-based method, might be attributed to differences in analytical approaches, as multivariate methods are generally more accurate than mass-univariate approaches.[170] Another study involving 172 first-time stroke patients, of whom 80% were older than 50 years, with imaging conducted one to two weeks post-stroke, demonstrated that lesion location explained more variance in motor and language deficits than in attention and memory impairments. In contrast to that study, we identified several small, distributed regions associated with poorer performance in attention and memory.[171] This may suggest that, in young stroke patients, these associations are less confounded by other age-related cerebral comorbidities. Nevertheless, we concur with the authors that cognitive functions such as attention and memory likely depend on distributed patterns of activation.

In our study, the right angular and the right precentral gyrus were associated with neglect, consistent with the literature.[172, 173] This supports the relevance of these regions, but the identification of additional regions in other studies highlights the anatomical complexity and potentially diverse locations of brain regions involved in hemispatial neglect.[9, 172, 174]

The NIHSS language subscale showed a strong brain-behavior relationship in our study. Specifically, left-sided fronto-temporo-parietal regions were associated with the presence of aphasia. This is in contrast with language deficits measured using cognitive tests, where we found a weak brain-behavior relationship and identified smaller clusters in various locations, including the cerebellum. The difference in the strength and the locations found in the different models might be due to the timing of the NIHSS, which was assessed in the acute phase along with the clinical MRI, whereas the cognitive tests were conducted three months later, as well as with the difference in coarseness between the measures.

Interestingly, infratentorial lesions were also associated with the cognitive impairment in several cognitive domains. The cerebellum has often been a neglected region in earlier studies in relation to cognitive function. However, there is increasing evidence supporting its role in cognitive function.[175] Lesions of the posterior cerebellar lobe supposedly produce dysmetria of thought and emotion, also known as the cerebellar cognitive affective syndrome.[175] Our results align with a meta-analysis conducted in healthy adults, highlighting the role of cerebellar

areas for language processing, especially in the right cerebellum.[176] In addition, we found cerebellar regions associated with poorer performance for processing speed, executive functioning, visual neglect, language, attention and working memory, and the presence of a major VCD. This highlights the involvement of the cerebellum in cognitive processes.

Our study has several strengths. First, this study includes a large prospective cohort of young adults who experienced a first-ever ischemic stroke, minimizing confounding factors like neurovascular and neurodegenerative changes, often seen in older adults. This provides a clearer view of stroke-induced cognitive changes. Second, we used extensive neuropsychological testing with minimal missing data. Finally, an important methodological strength is our use of multivariate LSM, which provides a more nuanced understanding of how specific brain regions contribute to cognitive outcomes.

However, some study limitations need to be addressed. First, cognitive data were lacking for patients who were unable to participate, for example due to severe aphasia. The underrepresentation of patients with a severe language impairment may have attenuated associations with language-related brain regions, potentially underestimating findings related to language deficits. Second, we did not collect data on other interventions patients received, such as cognitive rehabilitation, which could have influenced cognitive recovery and impacted our results. Third, the strengths of most brain-behavior relationships, except for the NIHSS language subscale, are weak with *r* values ranging from 0.092 to 0.277. These weak correlations may be attributed to the widespread distribution of the identified regions. Another possible explanation for the weak correlations could be the time gap between the initial MRI (performed median two days post-stroke) and the cognitive assessment (conducted at a median time point slightly less than three months post-stroke). This delay may result in a mismatch between the lesion location on MRI and cognitive functioning at three months, as early-stage diffusion restriction may not fully reflect its long-term impact, or recovery could alter the relationship over time.

The findings of this study could be used to determine whether the locations of the infarcts in the acute phase might potentially predict post-stroke cognitive impairment after three months in young ischemic stroke patients. The development of prediction models for post-stroke cognitive impairment, as earlier done for older patients,[9] might be useful to identify patients at risk for developing cognitive impairment at an early stage. This knowledge may support neurologists and other healthcare professionals to tailor individualized rehabilitation strategies that

consider the variability in lesion location and their impact on different cognitive functions. However, such a prediction model would ideally be developed specifically for young ischemic stroke patients. Additionally, our findings primarily highlight focal regions associated with poorer cognitive performance. Future studies should explore whether these regions interact within broader neural networks. Such research could help clarify whether cognitive impairments arise from focal lesions or network disruptions.

In conclusion, lesion locations associated with poorer cognitive performance in young stroke patients are widely distributed across various brain regions, with the specific cognitive deficits varying depending on the affected brain region. This widespread distribution showcases the complexity in the relationships between affected brain regions and cognitive symptoms, explaining the variability observed in young ischemic stroke patients with post-stroke cognitive impairment. Healthcare providers should be aware of this observation and integrate this knowledge into rehabilitation planning as well as when explaining the consequences of stroke to patients and their families. Future studies should focus on development of prediction models for post-stroke cognitive impairment in young stroke patients to improve personalized rehabilitation strategies.

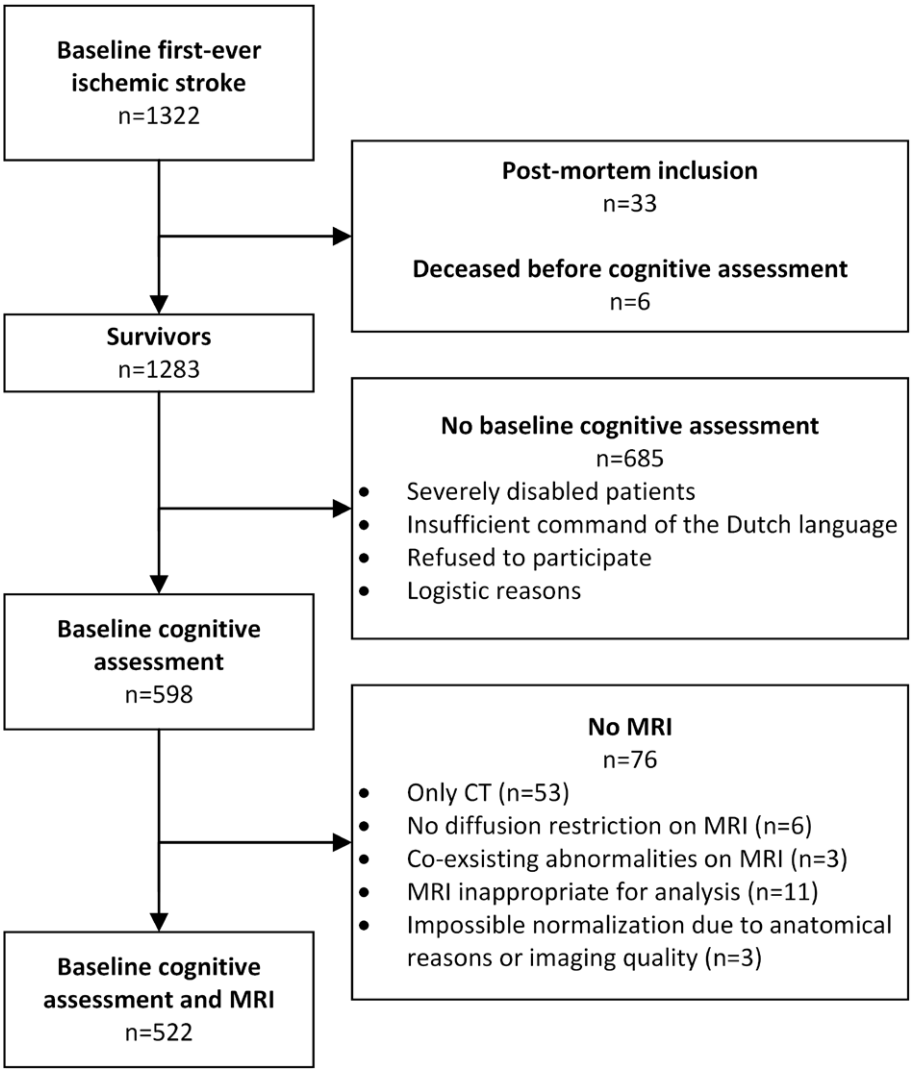
Supplementary data

Supplementary Methods

Cognitive assessment

We assessed seven cognitive domains using multiple tests: *(i) Episodic memory* (3-trial version of the Rey Auditory Verbal Learning Test), (ii) *Processing speed* (the written version of the Symbol-Digit Modalities Test, the abbreviated Stroop Color Word Test, parts I and II), (iii) *Visuoconstruction* (Rey-Osterrieth Complex Figure (ROCF)-copy trial), (iv) *Executive functioning* (Fluency test, Stroop interference score, Brixton Spatial Anticipation Test), (v) *Visual neglect* (Star Cancellation of the Behavioral Inattention Test), (vi) *Attention and working memory* (Digit Span subtest from the Wechsler adult Intelligence Scale – Fourth Edition), and (vii) *Language* (Short Token Test). Normative data from the Advanced Neuropsychological Diagnostics Infrastructure (ANDI), which includes data of 26,000 healthy individuals across all age groups were employed for most tests. This allowed fine-grained adjustment based on age, sex and education level. For the written version of the Symbol-Digit Modalities Test (Smit A, 2010), we used the normative data from the test's manual. We used healthy controls from another stroke study for the Star Cancellation test (Nys GM et al., 2006).

Supplementary Figure



Supplementary Figure 1 Flowchart of the study population.

Supplementary Table

Supplementary Table 1 Listing of the peak clusters for the presence of a major vascular cognitive disorder, each cognitive domain, and aphasia. Anatomical location is the location to which each center of mass of the cluster belongs to. Intensity values ranging from 0 to 1, with 1 being the most robust positive relationship between the region and the inverse Z-score of each cognitive outcome, the presence of a vascular cognitive and the score of the NIHSS language subscale. Location of the peak ROI (X, Y, Z) for each cluster.

VCD

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	L Angular gyrus	5410	0.996	-43	-54	13
2	R Lateral occipital cortex, superior division	3012	0.688	37	-58	49
3	L Cerebral white matter	2487	0.884	-29	-7	40
4	R Cerebral white matte	961	0.614	31	-2	18
5	R Thalamus	789	0.574	17	-25	1
6	R Cerebellum	785	0.325	19	-74	-48
7	R Caudate	773	0.623	13	6	15
8	L Thalamus	764	0.501	-14	-14	4
9	L Supramarginal gyrus, anterior division	686	0.751	-48	-39	42
10	L Middle frontal gyrus	492	0.361	-42	7	37
11	L Putamen	459	0.578	-27	-12	3

Episodic memory

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	L Putamen	6434	0.599	-25	-15	6
2	L Temporal fusiform cortex, posterior division	5707	0.495	-32	-33	-11
3	L Cerebral white matter, L Inferior frontal gyrus	4488	0.607	-36	5	21
4	R External capsule	3296	0.523	28	1	18
5	L Thalamus	2726	0.970	-14	-14	8
6	L Cerebral white matter, L Postcentral gyrus	2515	0.569	-36	-31	45
7	R Cerebral white matter, R Angular gyrus	1447	0.290	35	-55	32
8	L Lateral occipital cortex, superior division	1234	0.479	-39	-73	30
9	L Angular gyrus	1220	0.590	-35	-60	40
10	L Cerebral white matter	820	0.569	-28	-17	32
11	L Cerebral white matter	766	0.243	-29	-64	15
12	R Hippocampus	662	0.210	26	-39	-6

Episodic memory continued

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
13	R Angular gyrus	336	0.321	51	-58	32
14	L Angular gyrus	304	0.369	-62	-58	21
15	L Lingual gyrus	287	0.209	-23	-54	-13
16	L Angular gyrus	287	0.254	-50	-57	15

Processing speed

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	L Superior corona radiata	38002	0.979	-25	-27	44
2	L Angular gyrus	17859	0.718	-35	-57	35
3	R Cerebral white matter, R precentral gyrus	9371	0.522	24	-25	16
4	R Angular gyrus	9292	0.709	42	-53	41
5	R Cerebellum	3901	0.756	19	-74	-49
6	L Lateral occipital cortex, inferior division	2408	0.359	-41	-73	1
7	R Thalamus	1868	0.518	17	-24	2
8	R Angular gyrus	1506	0.384	46	-49	21
9	R Middle temporal gyrus, temporooccipital part	1152	0.364	60	-58	9
10	L Cerebellum	1030	0.319	-42	-66	-43
11	R Cerebellum	820	0.306	25	-53	-46
13	R Superior temporal gyrus, posterior division	718	0.177	50	-31	-2
14	R Supramarginal gyrus, anterior division	532	0.244	59	-31	36
15	L Hippocampus	463	0.241	-33	-29	-14
16	Brain-stem	421	0.284	5	-23	-31
17	R Pallidum	302	0.234	15	0	2
18	R Lateral occipital cortex, inferior division	286	0.195	49	-74	11

Visuoconstruction

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	R Superior fronto-occipital fasciculus	2072	0.630	23	-9	28
2	R Thalamus	813	0.943	10	-15	5

Executive functioning

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	L Putamen	54028	0.982	-22	0	11
2	L Angular gyrus	29139	0.700	-37	-71	26
3	R Cerebral white matter, R Central opercular cortex	24245	0.674	32	-5	12
4	R Superior parietal lobe	16925	0.576	29	-49	49
5	R Cerebellum	13480	0.503	20	-59	-50
6	L Cerebral white matter, L Postcentral gyrus	4029	0.619	-25	-29	44
7	R Thalamus	1759	0.410	13	-17	2
8	L Middle temporal gyrus, posterior division	1724	0.277	-63	-24	-10
9	Brain-stem	913	0.722	4	-23	-30
10	R Retrolenticular part of internal capsule	792	0.356	27	-27	19
11	R Postcentral gyrus	670	0.194	51	-18	48
12	R Cerebral white matter, R Hippocampus	564	0.168	28	-27	-16
13	L Lateral occipital cortex, inferior division	456	0.232	-49	-64	2
14	L Cerebellum	340	0.187	-26	-57	-23
15	R Lingual gyrus	340	0.167	19	-43	-7

Visual neglect

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	R Angular gyrus	887	0.970	37	-57	49
2	R Cerebellum	510	0.590	31	-62	-30
3	R Posterior thalamic radiation	486	0.527	32	-57	0
4	L Cerebellum	470	0.679	-13	-52	-52
5	R Precentral gyrus	416	0.972	31	-8	52
6	R Caudate	382	0.311	8	13	9
7	R cerebral white matter, R Lateral occipital cortex, superior division	367	0.370	25	-84	1
8	R Cerebral white matter	343	0.487	29	-32	8

Attention and working memory

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	L Superior corona radiata	8539	0.454	-22	-2	22
2	L Angular gyrus	8351	0.724	-39	-57	22
3	L Inferior frontal gyrus	2887	0.326	-43	8	20
4	R Insular cortex	2648	0.329	37	-1	12
5	R Cerebellum	2479	0.278	5	-53	-50
6	R Superior parietal lobe	898	0.400	33	-47	46
7	L Cerebral white matter, L Insular cortex	688	0.263	-29	20	8
8	R Cerebral white matter, R Supramarginal gyrus, anterior division	665	0.240	53	-27	35

Language

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	L Cerebral white matter, L Supramarginal gyrus, posterior division	1882	0.993	-38	-52	17
2	L Frontal operculum cortex	1586	0.422	-36	8	15
3	L Superior longitudinal fasciculus	828	0.411	-31	-16	33
4	L Thalamus	819	0.594	-15	-15	8
5	R Cerebral white matter, R Caudate	602	0.302	21	-10	28
6	R Putamen	371	0.333	32	-13	3
7	R Cerebellum	366	0.294	28	-72	-38
8	L Cerebral white matter, L Precentral gyrus	327	0.312	-35	-9	40

NIHSS language subscale at discharge

Cluster	Anatomical location	Number of voxels	Intensity	X	Y	Z
1	L Parietal operculum cortex	156580	0.980	-47	-3	39
2	R Lateral occipital cortex	1159	0.307	52	-58	16
3	R Middle frontal gyrus	946	0.137	30	2	55

Chapter 6

White matter integrity and cognitive performance in the subacute phase after ischemic stroke in young adults

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Abstract

Introduction

Reduced white matter integrity outside the stroke lesion may be a potential contributor of post-stroke cognitive impairment. We aimed to investigate how a stroke lesion affects the integrity of surrounding white matter, and whether the integrity of the non-lesioned part of white matter tracts is associated with cognitive performance after ischemic stroke in young adults.

Methods

Patients from the ODYSSEY study, aged 18–49 years, with a first-ever ischemic stroke, underwent 3T MRI and cognitive assessment within six months after the index event. Using TractSeg and free water imaging, we analyzed free water corrected fractional anisotropy (FA_T), free water corrected mean diffusivity (MD_T), and free water (FW) of all white matter tracts outside the stroke lesion. We calculated FA_T and FW in the lesioned white matter tracts at 2 mm incremental distances from the lesion, extending up to 10mm, represented as Z-scores using the diffusion measures of controls. We categorized patients as no/mild or major vascular cognitive disorder (VCD) and compared with a stroke-free control group (n = 23). Group differences in diffusion measures were examined. We investigated associations between FA_T, FW and cognitive performance across seven domains.

Results

Among 66 patients (median age 40.3 years (IQR 31.3–46.2); 54.5 % women), 22 had major VCD. In the different lesion expansions, we found differences in FA_T ($p = 0.009$) and FW ($p = 0.049$). Patients with major VCD had lower FA_T [range of Cohen's d (0.65; 1.65)] and higher FW [Cohen's d (−1.40; −0.64)] values compared to controls, both in the hemisphere affected by the lesion and the unaffected hemisphere. Performance in processing speed correlated with FA_T across eight tracts in the affected hemisphere [range of R^2_{adj} (0.30; 0.37)], and with FW in four tracts in the affected and three in the unaffected hemisphere [R^2_{adj} (0.28; 0.38)].

Discussion

In the first months after a stroke, we observed a trend of microstructural changes remote from the lesion that diminish as the distance from the lesion increases. Tissue changes in the white matter outside the lesion are present in both hemispheres, but are more pronounced in the hemisphere affected by the stroke, and may contribute to worse cognitive performance.

Introduction

Most young patients (aged 18-50 years) with an ischemic stroke experience important and lifelong consequences, including cognitive impairment as a notable outcome in almost half of these individuals.[135] Yet, the variability of cognitive impairment among young stroke patients is not completely understood. Age, education level, vascular risk factors, stroke severity, stroke location, and lesion volume are related to post-stroke cognitive impairment,[9, 10] but do not explain the whole range of cognitive performance and recovery after stroke at a young age.[156] A potential contributor to post-stroke cognitive impairment may be the presence of structural changes beyond the infarcted area of the brain, referred to as remote structural changes. Previous studies from our group have shown that years after an ischemic stroke focal lesions may not only have local effects on the brain, but also extend their impact remotely throughout both hemispheres, thus impacting long-term cognitive performance.[17] In 17 older patients with, predominantly silent, lacunar infarcts, alterations in white matter integrity have been found outside the stroke lesion. These white matter abnormalities attenuates with increasing distance to the primary lesion.[177] In addition, studies have shown that microstructural changes in the white matter influence cognitive performance, independent of the size of the lesion.[17, 177, 178] However, studies in the subacute phase after stroke are lacking in this young stroke population.

Given their usually long life of young stroke survivors, gaining a better understanding of the mechanisms underlying the development of poststroke cognitive impairment is important. The aim of the present study is therefore to investigate 1) how a stroke lesion affects the integrity of surrounding white matter in white matter tracts passing through the stroke lesion, and 2) whether the integrity of the non-lesioned part of the white matter tracts is associated with cognitive performance after ischemic stroke at young age.

Methods

Patients and Study Design

This study is a part of the 'Observational Dutch Young Symptomatic Stroke Study' (ODYSSEY).[22, 136] The present study included patients aged 18 to 49 years with a first-ever ischemic stroke with radiological evidence of cerebral ischemia. Patients were enrolled at the Radboudumc, Nijmegen, The Netherlands, and underwent an extensive MRI assessment, including Diffusion Weighted Imaging (DWI) protocol

at baseline, along with a comprehensive neuropsychological assessment. Patients were included between December 2016 and July 2021. Exclusion criteria were a history of stroke, retinal infarction, and cerebral venous sinus thrombosis. Detailed information regarding data collection has been provided elsewhere.[22] We recruited controls among the patients' spouses, relatives or social environment. Inclusion criteria for controls were: age between 18 and 50 years old without a history of any TIA or stroke at the moment of inclusion. We aimed for similar sex and age between controls and patients.

Standard Protocol approvals, Registrations, and Patient Consents

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study (NL41531.091.12). We obtained written informed consent from all participants.

Cognitive Assessment

Patients underwent an extensive neuropsychological assessment within six months (median three months after stroke). The seven most relevant cognitive domains included: (i) Episodic memory, (ii) Processing speed, (iii) Visuoconstruction, (iv) Executive functioning, (v) Visual neglect, (vi) Language deficits, and (vii) Attention and working memory. Using normative data, raw test scores were converted to Z-scores per test for each participant, using the individual's age, sex and/or education level. Further details regarding the collection and preparation of cognitive data can be found in the Supplementary Methods section and elsewhere.[136, 156]

Criteria for vascular cognitive disorder (VCD) were based on the criteria of the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG). We defined mild VCD as a composite Z-score of between −1.5 and −2.0 in one or more cognitive domains. We defined major VCD as a composite Z-score of <−2.0, in one more cognitive domains. Normally, mild VCD is defined as a Z-score in one or more cognitive domains between −1.0 and −2.0.[119] However, this represents 13.6 % of the normal population. By adjusting the cut-off criteria to −1.5 instead of −1.0 (representing 4.4 % of the normal population) we attain a higher specificity.

Other Measurements

Level of education was scored with a Dutch scoring system comprising seven categories[121] that align with the UNESCO international classification of education levels.[122] We assessed symptoms of depression using the Mini International Neuropsychiatric Interview (MINI)[123] and fatigue using the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R).[124] We used the Barthel Index[125] and modified Rankin Scale (mRS)[126] to assess functional outcome

at the time of the cognitive assessment. Additionally, we evaluated the etiology of stroke (based on modified Trial of ORG 10172 in Acute Stroke Treatment; TOAST)[151, 152] and severity at admission and discharge (National Institutes of Health Stroke Scale; NIHSS)[128], if necessary retrospectively, using a validated approach.[129, 130] We visually scored markers of small vessel disease (SVD) on MRI. Evaluation of 4 markers (lacunes, microbleeds, white matter hyperintensity Fazekas score, and enlarged perivascular spaces score) led to the total SVD burden score of 0–4.[179]

Neuroimaging Data Acquisition

MRI scans were performed on a 3T MRI scanner (Siemens Magnetom Trio, Erlangen, Germany). The imaging protocol included: (i) 3D T1 magnetization-prepared rapid gradient echo (MPRAGE) (TR/TE 2300/2.3 ms; flip angle 8; voxel size 0.9 × 0.9 × 0.9 mm), (ii) 3D fluid attenuated inversion recovery (FLAIR) (TR/TE 5000/394 ms; voxel size 1.0 × 1.0 × 1.0 mm), (iii) gradient echo susceptibility weighted imaging sequence (TR/TE 27/20 ms; 3mm slice), (iv) DWI (TR/TE 8700/67 ms; voxel size 2 × 2 × 2 mm; 3 unweighted scans, 100 diffusion-weighted scans, with non-co-linear orientation of the diffusion-weighting gradient, and b value 0.50(3x)/150(7x)/350(30x)/1000(60x) s/mm^2).

Neuroimaging Data Processing

Lesion segmentation

All stroke lesions were segmented semi-automatically using ITK-SNAP.[157] Lesions were segmented on DWI (n = 27) when identified within two weeks from the index event, on FLAIR (n = 38) if the lesion was identified after two weeks (except for one lesion which was identified after 10 days, but better visible on FLAIR), or if not available on T1 sequences (n = 1).The lesions were reviewed and manually adjusted if necessary. We calculated lesion volumes using FSLstats.[160] To generate a lesion probability map, all lesion masks were registered to a standard space and merged. Additional details of the normalization process can be found in the Supplementary Methods section.

Pre-processing

We pre-processed the diffusion data following these steps: (1) noise removal using the Marchenko-Pastur PCA algorithm[180-182] and removal of Gibbs ringing artifacts[183]; (2) correction for head motion and eddy current-induced distortions[184]; (3) correction for susceptibility-induced distortions using the 'topup' (using synthesized b0 image generated from the T1 image) algorithm[184]; and (4) correction for B1 field inhomogeneity. After pre-processing, the first eigenvector (V1) of the

diffusion map, specifically in the corpus callosum region, was visually inspected to confirm anatomical plausibility of its direction and to exclude significant artifacts. We used MRtrix 3.0 software,[185] Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; v6.0.3),[186] Synb0-DISCO,[187] and Advanced Normalization Tools (ANTs, v 2.1.0)[158] for these pre-processing steps. Due to the absence of a b0 image with reversed phase encoding in our DWI scans, 'topup' was performed based on a synthesized b0 image from the T1 image using Synb0-DISCO.[187]

Free water imaging and tract specific analysis

We calculated free water corrected fractional anisotropy (FA_T), free water corrected mean diffusivity (MD_T), free water corrected mode of anisotropy (MO_T), and free water (FW), using nonlinear regularised minimization process implemented in Matlab.[188] Free water elimination might enable better estimation of FA, MD and MO by minimizing the effect of cerebrospinal fluid (CSF) and vasogenic oedema.[188]

Next, we used TractSeg, a deep learning-based framework for automated white matter bundle segmentation, to segmentate 72 white matter fiber tracts.[189] For full names of the white matter tracts see Supplementary Methods section. We calculated the diffusion measures in the white matter tracts outside the stroke lesion. To reduce bias, we excluded the fornix to remove unavoidable CSF partial-volume effects, as well as the striatal projections, due to a high anatomical overlap with thalamic projections.[190] To reduce the number of comparisons, we classified tracts according to whether they were in the affected side (i.e., the side of the lesion) or unaffected side (i.e., the contralateral side) based on the lesion location. For supratentorial lesions, we regarded the infratentorial region as the unaffected side, and vice versa. For further details see Supplementary Methods section. For controls, we averaged the tract measures of left and right hemispheres.

Lesion expansion

We investigated FA_T, MO_T, and FW values within lesioned white matter tracts (i.e. every tract passing through the lesion) across lesion expansions of 2, 4, 6, 8, and 10 mm. The expansion distance was selected based on the voxel size of our DWI scans (2 mm), ensuring accurate value extraction for each expansion. To minimize the impact of lesion location variability, we registered the diffusion images of each control to each patient, see the Supplementary Methods section. For each control (now in patient's DWI space), we calculated the mean diffusion values at locations corresponding to the different lesion expansion distances. We calculated Z-scores for every patient for each lesion expansion distance, using the mean and standard deviation of the diffusion values of the controls. Finally, the Z-scores across all

expansions within lesioned tracts were averaged for the patients, resulting in a single Z-score per expansion distance for each diffusion measure.

MRI scans were visually checked at each step of processing to ensure the accuracy of registration.

Statistical Analysis

We compared baseline characteristics between patients with no/mild VCD versus major VCD and for patients versus controls, using the independent t-test or Mann-Whitney U test for continuous variables and Pearson's Chi-squared/Fisher's exact test for categorial variables. We compared Z-scores of the diffusion measures of the lesion expansions with analysis of variance (ANOVA) followed by Tukey's HSD for post-hoc comparison. To compare differences in overall diffusion measures between controls, patients with no/mild VCD, and major VCD, we used ANOVA followed by Tukey's HSD for post-hoc comparison. To compare differences in diffusion measures in the different white matter tracts between controls, patients with no/mild VCD, and major VCD, we used ANCOVA, controlling for depression. Missing data on depressive symptoms was imputed by the mode. Additionally, we controlled for lesion volume when comparing patients with no/mild VCD to those with major VCD. Additionally, we computed Cohen's d as an effect size measure for group comparisons for all white matter tracts. We conducted a linear regression analysis to investigate the relationship between the diffusion measures per tract and domain-specific Z-scores, while adjusting for lesion volume and depressive symptoms. FDR correction, using the Benjamini-Hochberg procedure, was applied to p-values in all analyses involving white matter tracts, and was performed separately for each analysis involving all affected and unaffected white matter tracts. If FDR correction was applied, only results that remained FDR-significant were reported in the text. To explore the impact of the time interval between the event and the MRI (within two weeks or thereafter) on our results, we performed post-hoc analyses for the differences in these groups for the Z-scores of the diffusion measures in the lesion expansions and for the differences in overall diffusion measures. In addition, we performed a linear regression analysis to analyze time to MRI on the overall diffusion measures. Additionally, to explore the impact of any SVD on the white matter integrity, we compared the overall diffusion measures after excluding patients with any SVD.

All statistical analyses were performed using RStudio 2022.02.01.

Table 1 Baseline characteristics

	Patients (n = 66)				Controls (n = 23)	p-value[b]
	Whole group (n = 66)	**No/mild VCD (n = 44)**	**Major VCD (n = 22)**	**p-value[a]**		
Median age, years (IQR)	40.3 (31.3–46.2)	41.3 (32.6–46.8)	38.8 (27.2–44.1)	0.495	34.5 (27.0–47.0)	0.722
Men, n (%)	30 (45.5)	26 (60.1)	4 (18.2)	**0.002**	12 (52.2)	0.578
Median time to cognitive assessment, days (IQR)	85 (50–141)	88 (48–138)	77 (55–148)	0.744	–	
Median education level (IQR)	5 (5–6)	5 (5–6)	5 (5–5)	**0.036**	6 (5–7)	**0.003**
Median NIHSS score at admission (IQR)	3 (1–5)	3 (1–5)	3 (2–4)	0.742	–	
Median NIHSS score at discharge (IQR)	0 (0–2)	0 (0–1)	2 (0–3)	**0.005**	–	
Median Barthel Index (IQR)	100 (100–100)	100 (100–100)	100 (95–100)	**0.002**	–	
Good outcome (BI≥85), n (%)	60 (96.7)	41(100)	19(90.5)		–	
Median mRS (IQR)	1 (1–2)	1 (0–1)	2 (1–2)	**<0.001**	–	
Good outcome (mRS 0-1), n (%)	42 (63.6)	36 (81.8)	6 (27.2)		–	
MINI symptoms of depression present, n (%)	6 (9.2)	3 (7.0)	3 (13.6)	0.399	1 (4.3)	0.457
Mean CIS-20R - fatigue severity (SD)	33.0 (11.8)	30.7 (11.8)	37.4 (10.8)	0.059	21.5 (10.2)	**<0.001**
No/mild fatigue < 36, n (%)	26 (53.1)	19 (59.4)	7 (41.2)		20 (90.9)	
Severe fatigue ≥ 36, n (%)	23 (46.9)	13 (40.6)	10 (58.8)	0.361	2 (9.1)	**0.002**

Table 1 Continued

	Patients (n = 66)				Controls (n = 23)	p-value[b]
	Whole group (n = 66)	No/mild VCD (n = 44)	Major VCD (n = 22)	p-value[a]		
TOAST, n (%)				0.553		
Atherothrombotic	1 (1.5)	0 (0.0)	1 (4.5)		–	
Likely atherothrombotic	3 (4.5)	2 (4.5)	1 (4.5)		–	
Small vessel disease	9 (13.6)	7 (15.9)	2 (9.1)		–	
Cardioembolic	17 (25.8)	13 (29.5)	4 (18.2)		–	
Rare causes	11 (16.7)	7 (15.9)	4 (18.2)		–	
Multiple causes	7 (10.6)	3 (6.8)	4 (18.2)		–	
Cryptogenic	18 (27.3)	12 (27.3)	6 (27.3)		–	

Education category 5, i.e. middle school / secondary vocational training. VCD: Vascular Cognitive Disorder; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; BI: Barthel Index; mRS: modified Rankin Scale; MINI: Mini International Neuropsychiatric Interview; CIS-20R: Checklist Individual Strength; TOAST: Trial of ORG 10172 in Acute Stroke Treatment. Missing data patients: NIHSS at discharge 2 (3.0 %); Barthel Index 4 (6.1 %); MINI symptoms of depression 1 (1.5 %); CIS-20R-fatigue 17 (25.8 %). Missing data controls: CIS-20R-fatigue 1 (4.3 %).

[a] p-value no/mild VCD compared to major VCD; [b] p-value patients compared to controls. Bold p-values represent significant differences.

Table 2 Imaging characteristics

	Patients (n = 66)			
	Whole group (n = 66)	**No/mild VCD (n = 44)**	**Major VCD (n = 22)**	**p-value**
Median time to MRI, days (IQR)	32 (5–90)	32 (5–76)	28 (6–108)	0.522
Lesion location, n (%)				0.969
Right supratentorial	28 (42.4)	19 (43.2)	9 (40.9)	
Left supratentorial	21 (31.8)	14 (31.8)	7 (31.8)	
Bilateral supratentorial	3 (4.5)	2 (4.5)	1 (4.5)	
Infratentorial	5 (7.8)	3 (6.8)	2 (9.1)	
Unilateral supratentorial and infratentorial	2 (3.0)	2 (4.5)	0 (0.0)	
Bilateral supratentorial and infratentorial	7 (10.6)	4 (9.1)	3 (13.6)	
Median lesion volume on MRI, mL (IQR)	1.00 (0.47–6.12)	0.89 (0.38–1.90)	3.99 (0.79–14.31)	**0.007**
Median total SVD score (IQR)	0 (0–0)	0 (0–0)	0 (0–1)	0.086

VCD: Vascular Cognitive Disorder; IQR: interquartile range; SVD: small vessel disease. Bold p-values represent significant differences.

Results

DWI and neuropsychological assessment at baseline were available for 66 ischemic stroke patients and 23 controls. Baseline characteristics of patients and controls are described in Table 1. Median age of patients at stroke onset was 40.3 years (IQR 31.3–46.2), 54.5 % were women (n = 36). Median NIHSS at admission was 3 (IQR 1–5), median time from index event to cognitive assessment was 85 days (IQR 50–141). Imaging characteristics are presented in Table 2. Median time to MRI was 32 days (IQR 5–90) and median lesion volume was 1.00 mL (IQR 0.47–6.12). Patients with major VCD were more frequent women (p = 0.002), had a lower education level (p = 0.036), a higher NIHSS at discharge (p = 0.005), a higher mRS (p < 0.001), and a larger lesion volume (p = 0.007) compared to patients with no/mild VCD. Supplementary Figure 1 shows an overlap of all stroke lesions.

Lesion expansion

Figure 1 shows the Z-scores FA_T and FW for the stroke lesion and the expansions in the lesioned white matter tracts. Absolute values of FA_T and FW are presented in Supplementary Figure 2. In the ANOVA models, we found differences in Z-scores of FA_T (p = 0.009) and FW (p = 0.049) in the different expansions. In the post-hoc analyses, the Z-scores for FA_T were lower in the 2 mm expansion compared with

the 6 mm (p = 0.037), 8 mm (p = 0.036) and 10 mm (p = 0.011). Other post-hoc comparisons were not statistically significant. To assess whether the relatively higher FA_T values in patients compared to controls can be explained by the loss of crossing fibers, we examined the Z-scores of MO_T in the lesion expansions (Supplementary Figure 3). We observed relatively high MO_T values across all lesion expansions in patients compared to controls.

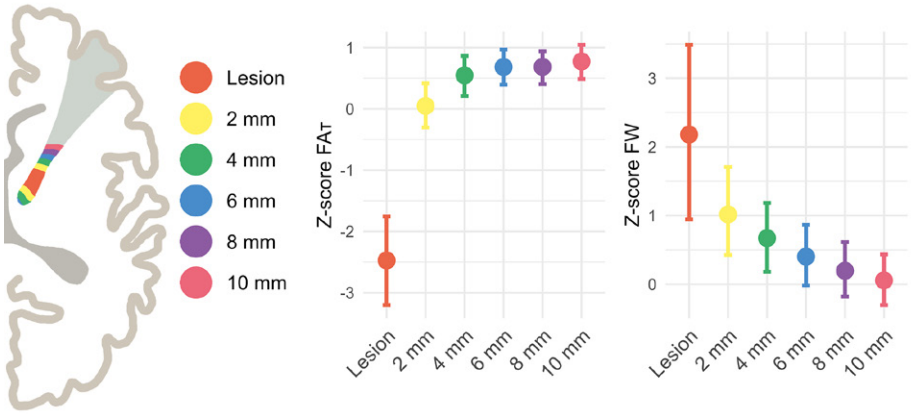


Figure 1 Z-scores with 95 % confidence interval of fractional anisotropy (FA_T) and free water (FW) in lesion expansions. Schematic figure of a part of a stroke lesion within a white matter tract and the 2, 4, 6, 8, and 10 mm expansions. Z-scores for FA_T and FW in patients across different lesion expansions. Z-scores were calculated using the diffusion measures of controls at the same location.

Group comparisons of the integrity of the white matter tracts

Patients with major VCD had an overall lower mean FA_T (p = 0.001) and a higher mean FW (p = 0.008) compared to controls (Figure 2A and C). For mean MD_T, there were no significant differences between groups (Figure 2B).

The major VCD group had lower FA_T values of most tracts on the affected side [range of Cohen's d (0.65; 1.65), range of p-value (<0.001; 0.05)], and lower FA_T values of some tracts on the unaffected side than controls[Cohen's d (0.85; 1.18), p-value (0.02; 0.03), Figure 3A]. Similarly, the major VCD group showed higher FW values in most on the affected side [Cohen's d (−1.40; −0.64), p-value (<0.001; 0.04)], and in some tracts on the unaffected side [Cohen's d (−1.09; −0.92), p-values all 0.03, Figure 3B]. The differences in FA_T and FW between patients with no/mild VCD versus major VCD were not significant, and the differences between controls and patients with no/mild there were only statistically significant in three tracts (all in the corpus callosum) for FW on the affected side after FDR correction (Supplementary Figure 4).

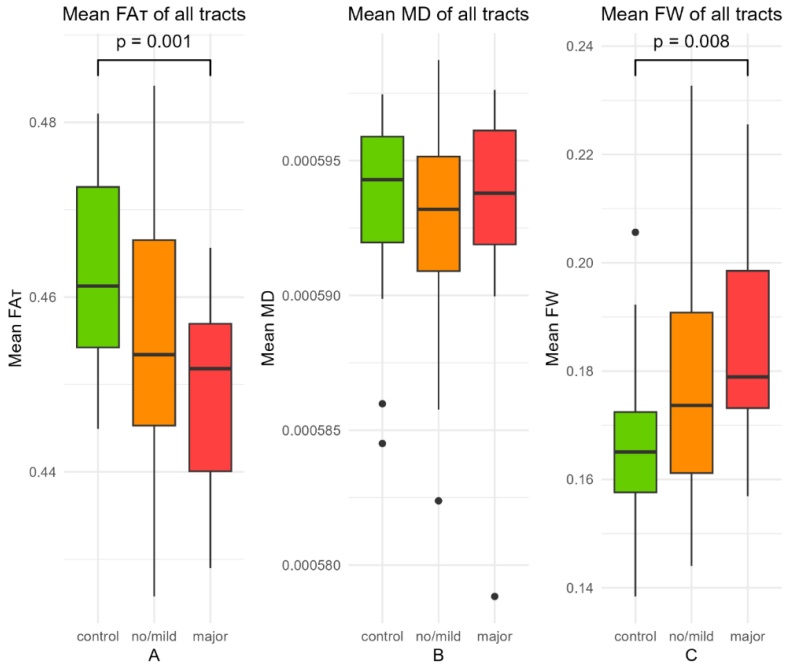


Figure 2 Group comparisons of overall white matter integrity. Group comparisons for controls (green), patients with no/mild VCD (orange), and major VCD (red). (**A**) Mean free water corrected fractional anisotropy (FA_T) across all tracts in. (**B**) Mean free water corrected mean diffusivity (MD_T) across all tracts. (**C**) Mean free water (FW) across all tracts.

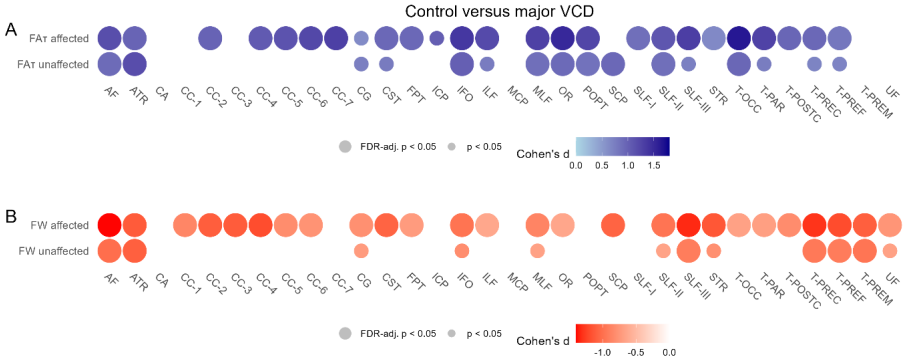


Figure 3 Group comparisons of free water corrected fractional anisotropy (FA_T) and free water (FW). Difference in (**A**) FA_T and (**B**) FW between controls and patients with major VCD quantified with Cohen's d represented by color. Circle size represents statistical significance level. Group differences were corrected for depressive symptoms. Group differences were presented for the tracts on the affected side, and the unaffected side. Correction for multiple comparisons was performed using false discovery rate (FDR). Large circles represent corrected p-values smaller than 0.05, small circles represent uncorrected p-values smaller than 0.05, and blank spaces represent uncorrected p-values greater than 0.05.

Association of cognitive performance with white matter integrity

In linear regression, processing speed was moderately associated with FA_T values in eight tracts on the affected side [range of R^2_{adj} (0.30; 0.37), range of p-values (0.02; 0.05), Figure 4A]. Processing speed was moderately associated with the FW values in four tracts on the affected side [R^2_{adj} (0.28; 0.34), p-value 0.02;0.05)], and the FW values of three tracts on the unaffected side [R^2_{adj} (0.33; 0.38), p-value (0.01; 0.04), Figure 4B]. Associations between the other cognitive domains, except for language deficits, and FA_T and FW were observed in various tracts. However, the associations, except for two tracts in executive functioning, were not statistically significant after FDR correction (Supplementary Figure 5).

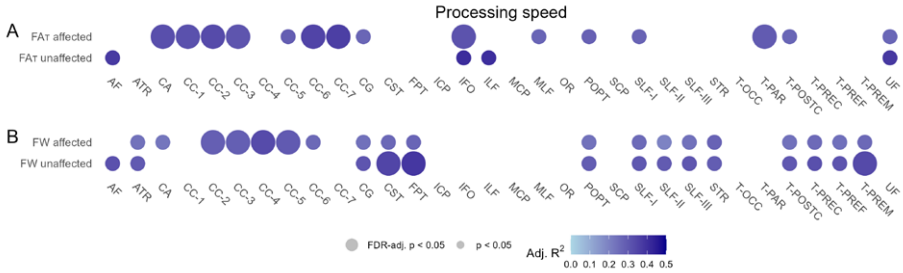


Figure 4 Association between processing speed and free water corrected fractional anisotropy (FA_T), and free water (FW). Effect sizes (adj. R^2) obtained from linear regression, adjusted for lesion volume, and depressive symptoms are presented by color. Circle size represents statistical significance level. Associations were presented for (**A**) the FA_T and (**B**) FW of the tracts on the affected side, and the unaffected side. Correction for multiple comparisons was performed using false discovery rate (FDR). Large circles represent corrected p-values smaller than 0.05, small circles represent uncorrected p-values smaller than 0.05, and blank spaces represent uncorrected p-values greater than 0.05.

Post-hoc analyses

We performed post-hoc analyses to investigate whether the timing of MRI was related to the diffusion parameters. We divided the group based on the timing of MRI: within 14 days after the stroke (n = 28) or thereafter. These analyses showed no significant differences in the Z-scores of FA_T and FW of lesion expansions, or the comparisons of the overall tract measures. In linear regression, time to MRI was not significantly associated with the overall diffusion measures.

Excluding patients with any SVD (n = 15) on their MRI did not influence the results of the group comparisons of overall white matter integrity.

Discussion

In this study of patients with a young ischemic stroke, we observed a trend that FA_T gradually increases, while FW gradually decreases along the lesioned white matter tracts, extending away from the stroke lesion. Furthermore, we found that lower white matter integrity outside the stroke lesion, which was more pronounced in the hemisphere affected by the stroke, is associated with worse cognitive performance, particularly in the cognitive domain processing speed.

In the present study, we observed diffusivity changes in white matter tracts remote from the stroke lesion that were not visible on conventional MRI. FA_T gradually increases with increasing distance from the lesion. However, only the FA_T in de 2 mm expansion was significantly lower than in the other expansions. The fact that this first rim around the lesion had lower FA_T values could be a partial volume effect. Interestingly, FA_T values in the expansions of the patients were higher compared to those in the same locations in the controls. This may be due to the degeneration of one or more fiber bundles in crossing fibers, resulting in a paradoxical increase in FA_T compared to controls.[191] The combination of higher values of FA_T and higher values of MO_T in the lesion expansions in our patients supports the notion that the increase in FA_T is most likely explained by the selective loss of fibers in the crossing-fiber areas. The extent of increased FW diminishes as the distance from the stroke lesion increases. However, in post-hoc analyses there were no differences between the different expansions. Our findings are consistent with a previous stroke study conducted in 17 older participants, predominantly with silent infarcts.[177] Although the confidence intervals of the Z-scores for FA_T and FW for most expansions overlap, our findings suggest that the process of microstructural changes might already begin in the first months after stroke. In our post-hoc analysis, we found no difference in white matter integrity between patients with a MRI scan within 14 days versus those scanned thereafter (up to six months). Additionally, the time to MRI was not associated with white matter integrity. Since all the MRI scans were made relatively early in the course after the event, a longer interval between the event and the MRI might reveal more pronounced differences in FA_T in the various lesion expansions.

In group comparisons, patients with major VCD exhibited lower FA_T values and higher FW compared to controls. When examining specific white matter tracts, we observed that this finding was not only present in the hemisphere affected by the stroke, but even in the unaffected hemisphere. While other group comparisons did not reach statistical significance, it appears that controls have the highest white

matter integrity, followed by patients with no or mild VCD, and finally, those with major VCD. While direct data linking FW to physiological changes are lacking, prior research has suggested that FW changes may be an early marker of white matter damage. Although the exact mechanisms underlying FW increases are unclear, several studies suggested that the FW changes reflect pathologic processes, including neuroinflammatory processes, blood-brain barrier dysfunction, vasogenic edema and intramyelinic vacuolization.[192, 193]

The pattern of reduced FA_T outside the stroke lesion is likely also not pathophysiology specific, but may be due to potential mechanisms, such as axonal degeneration and demyelination.[177, 194] Secondary degeneration occurs near the lesion side and spreads along the entire length of a damaged tract,[194] potentially extending to remote tracts. Prior stroke studies demonstrated reduced white matter integrity compared with controls in both ipsi- and contralesionally in the early phase after stroke[195] and even years after stroke.[53]

In contrast to the relatively high FA_T values in the lesion expansions, we observed an overall lower FA_T in patients. Another possible explanation is that the differences between groups, with respect to white matter integrity, were already present before the occurrence of the stroke. Individuals with greater cognitive reserve may have more robust white matter integrity.[196] This may relate to the significant difference in education level in our study population, as white matter integrity is positively correlated with intelligence, for which educational attainment is a proxy.[197] Additionally, lower intelligence might be associated in behaviors across the life-course that have impact on the white matter integrity.[197, 198] These behaviors may, for example, lead to lower white matter integrity in the normal appearing white matter.

Another explanation for the lower white matter integrity beyond the stroke lesion could be the presence of SVD that is not visible on conventional structural MRI.[199] Previous studies have suggested that focal SVD lesions represent only a fraction of the underlying pathology.[200] Since visible markers of SVD were not sufficiently explanatory for the differences in white matter integrity between groups in our study, it could be that these do not fully capture the burden of SVD-related brain damage.

Moreover, we investigated the association of white matter integrity with cognitive performance in specific domains. We found an association of FA_T and FW with processing speed performance in tracts in the affected hemisphere and for FW even

in some tracts in the unaffected hemisphere. Findings were independent of the lesion volume and depressive symptoms. An earlier study in young stroke patients also found an association between FA and processing speed, even in the unaffected hemisphere.[17] This may be explained by the fact that this study was performed almost 11 years after ischemic stroke. Since our scans were made approximately one month after the stroke, it is possible that secondary neurodegeneration may be ongoing at this point in time. Another study in older stroke patients also reported that white matter degeneration was associated with worse cognitive performance in multidomain impairments.[53] However, the question remains whether changes in white matter structure are directly causing cognitive impairment, whether they are an epiphenomenon, or possibly could even reflect a decrease in brain efficiency. In our study, we demonstrated that processing speed cannot be attributed to a specific tract or region, in agreement with the notion that it is a distributed cognitive ability that depends on the integrity of many anatomically widespread white matter tracts.[201] We only found associations between white matter integrity and processing speed and not for other cognitive domains. It is known that processing speed is a sensitive marker of white matter damage.[202]

Our study has several notable strengths. First, the prospective study design results in reliable information. While causal relationships cannot be established, these findings offer valuable insights into the underlying cerebral mechanisms. Second, the inclusion of patients with radiologically confirmed ischemic stroke ensured the absence of misdiagnosed patients. Third, we used extensive neurocognitive testing. Fourth, we used TractSeg for tract segmentation, which has a high accuracy in segmenting white matter tracts, thus enhancing the reliability of our study's findings. Finally, we used free water imaging, which might enable better estimation of diffusion measures by minimizing the effect of CSF and vasogenic oedema.

However, there are several limitations that need to be addressed. First, the inclusion of patients from a tertiary care setting may have introduced a potential form of selection bias. Second, stroke severity, as measured by NIHSS and mRS, was relatively mild in our cohort. Therefore, our findings may not fully represent the complete range of the young stroke population. Third, we lacked information on pre-stroke cognitive functioning. Nonetheless, considering the relatively young age of our participants and the limited presence of other comorbidities, such as pre-existing vascular or degenerative disorder in this age group, the impact of pre-stroke cognitive functioning on post-stroke cognitive functioning is likely to be minimal. Fourth, MRI scans were not conducted at exactly the same time after the ischemic event. This variability in timing may have potentially resulted in

differences in microstructural changes at each timepoint. Fifth, the study may have insufficient power to detect statistically significant results. This could be attributed to either the relatively small sample size, the limited variability in diffusion metrics and the timing of the scanning. Lastly, our study is based on baseline neuroimaging data. While these provide valuable insights, longitudinal imaging data could offer a more comprehensive understanding of cerebral mechanisms and their relation with cognitive performance over time. Future research should prioritize the utilization of longitudinal imaging data, including more participants, and try to develop a prediction model for identifying patients at risk of post-stroke cognitive impairment.

In conclusion, among young stroke survivors, tissue changes in the white matter, especially in the affected hemisphere, are already present and may contribute to cognitive impairment in the subacute phase after stroke. These findings could provide valuable insights for identifying individuals at risk of cognitive impairment after a stroke and contribute to more effective risk stratification. Ultimately, this could facilitate early cognitive therapy, potentially improving outcomes by addressing cognitive impairments sooner in the rehabilitation process. In the future, it may also enable more targeted cognitive interventions during rehabilitation.

Supplementary data

Supplementary Methods

Cognitive assessment

The seven cognitive domains were assessed using multiple tests: *Episodic memory* (3-trial version of the Rey Auditory Verbal Learning Test), *Processing speed* (the written version of the Symbol-Digit Modalities Test, the abbreviated Stroop Color Word Test, parts I and II), *Visuoconstruction* (Rey-Osterrieth Complex Figure (ROCF)-copy trial), *Executive functioning* (Fluency test, Stroop interference score, Brixton Spatial Anticipation Test), *Visual neglect* (Star Cancellation of the Behavioral Inattention Test), *Language deficits* (Short Token Test), *Attention and working memory* (Digit Span subtest from the Wechsler adult Intelligence Scale – Fourth Edition). Normative data from the Advanced Neuropsychological Diagnostics Infrastructure (ANDI), which includes data of 26,000 healthy individuals across all age groups were employed for most tests. This allowed fine-grained adjustment based on age, sex and education level. For the written version of the Symbol-Digit Modalities Test (Smit A, 2010), we used the normative data from the test's manual. We used healthy controls from another stroke study for the Star Cancellation test (Nys GM et al., 2006).

Normalization

We first registered brain-extracted FLAIR images and DWI, along with the lesion mask, to brain-extracted T1-weighted images using the Functional MRI of the Brain Linear Image Registration Tool (FLIRT). Next, these T1-weighted images were registered, along with the lesion mask, to the Montreal Neurological Institute (MNI) standard space 152 template using FLIRT, followed by nonlinear registration using the Functional MRI of the Brain nonlinear registration tool (FNIRT). We used FSL 6.0.5 tools (Jenkinson M et al., 2012).

White matter tracts

Anterior thalamic radiation (ATR), Arcuate fascicle (AF), Commissure anterior (CA), Corpus callosum (Rostrum (CC-1), Genu (CC-2), Rostral body (CC-3), Anterior midbody (CC-4), Posterior midbody (CC-5), Isthmus (CC-6), Splenium (CC-7)), Cingulum (CG), Corticospinal tract (CST), Fronto-pontine tract (FPT), Inferior cerebellar peduncle (ICP), Inferior occipito-frontal fascicle (IFO), Inferior longitudinal fascicle (ILF), Middle cerebellar peduncle (MCP), Middle longitudinal fascicle (MLF), Optic radiation (OR), Parieto-occipital pontine (POPT), Superior cerebellar peduncle (SCP), Superior longitudinal fascicle I (SLF-I), Superior longitudinal fascicle II (SLF-II), Superior longitudinal fascicle III (SLF-III), Superior thalamic radiation (STR), Uncinate

fascicle (UF), Thalamo-occipital (T-OCC), Thalamo-parietal (T-PAR), Thalamo-postcentral (T-POSTC), Thalamo-precentral (T-PREC), Thalamo-prefrontal (T-PREF), Thalamo-premotor (T-PREM), Uncinate fascicle (UF).

Registration of DWI of controls to DWI of patients

We first registered DWI of controls to their brain-extracted T1-weighted imaged using the FLIRT. Next, brain-extracted T1-weighted images of controls were registered to the brain-extracted T1-weighted images of patients, along with the lesion mask of patients, using FLIRT, followed by FNIRT. Subsequently, spatial transformations were applied to convert DWI data from controls in T1 space of controls to the T1 space of patients. To enable the transformation of T1 space in patients to DWI space in patients, we first computed the inverse transformation matrix. Finally, we used FLIRT for the transformation of DWI of controls in T1 space of patients to the DWI space of patients. We used FSL 6.0.5 tools (Jenkinson M et al., 2012).

Dividing tracts ass in the affected or unaffected side based on the lesion location

Patients with supratentorial lesions:

- For unilateral supratentorial lesions, the supratentorial tracts at the side of the lesion are considered as affected, and the tracts at the contralateral side are considered as unaffected.
- For bilateral supratentorial lesions, the average of tract measures of the left and right hemisphere are considered affected, and there are no unaffected supratentorial tracts.
- All infratentorial tracts are considered unaffected, in case of two-sided tracts, the tract measures of left and right were averaged.
- Corpus Callosum I-VII and anterior commissure were considered as affected.

Patients with infratentorial lesions:

- All supratentorial tracts are considered unaffected, in case of two-sided tracts, the tract measures of left and right were averaged.
- All infratentorial tracts are considered affected, in case of two-sided tracts, the tract measures of left and right were averaged.

Patients with supra- and infratentorial lesions:

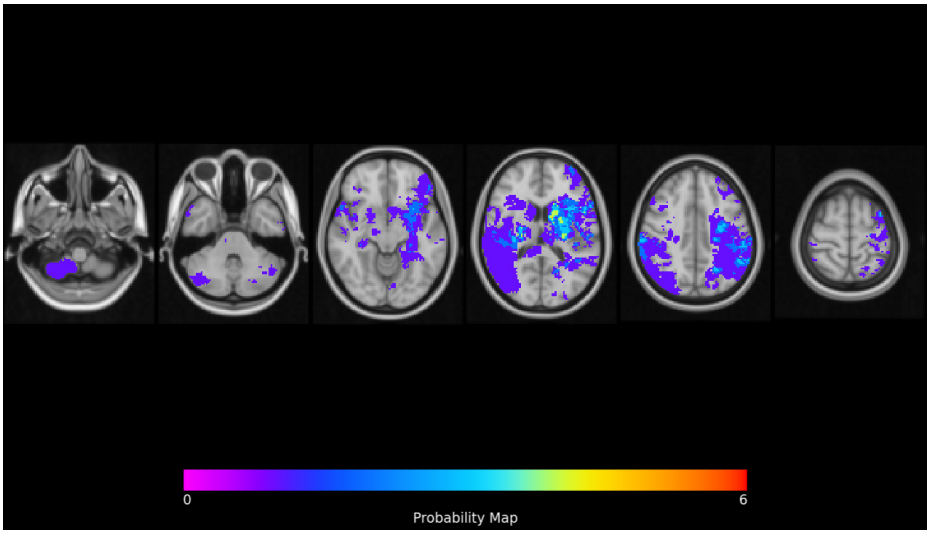
- For unilateral supratentorial lesions, the supratentorial tracts at the side of the lesion are considered as affected, and the tracts at the contralateral side are considered as unaffected.

- For bilateral supratentorial lesions, the average of tract measures of the left and right hemisphere are considered affected, and there are no unaffected supratentorial tracts.
- All infratentorial tracts are considered affected, in case of two-sided tracts, the tract measures of left and right were averaged.
- Corpus Callosum I-VII and anterior commissure were considered as affected.

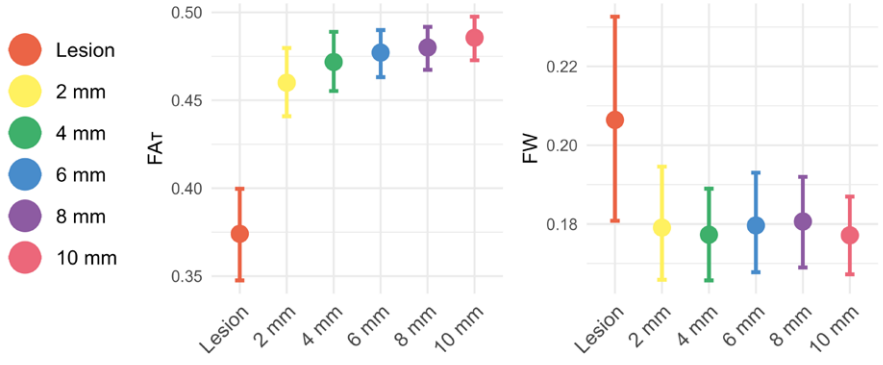
Controls:

- In case of two-sided tracts, the tract measures of left and right were averaged.

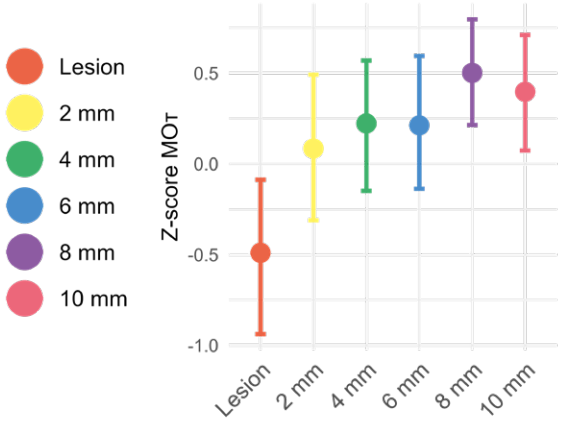
Supplementary Figures



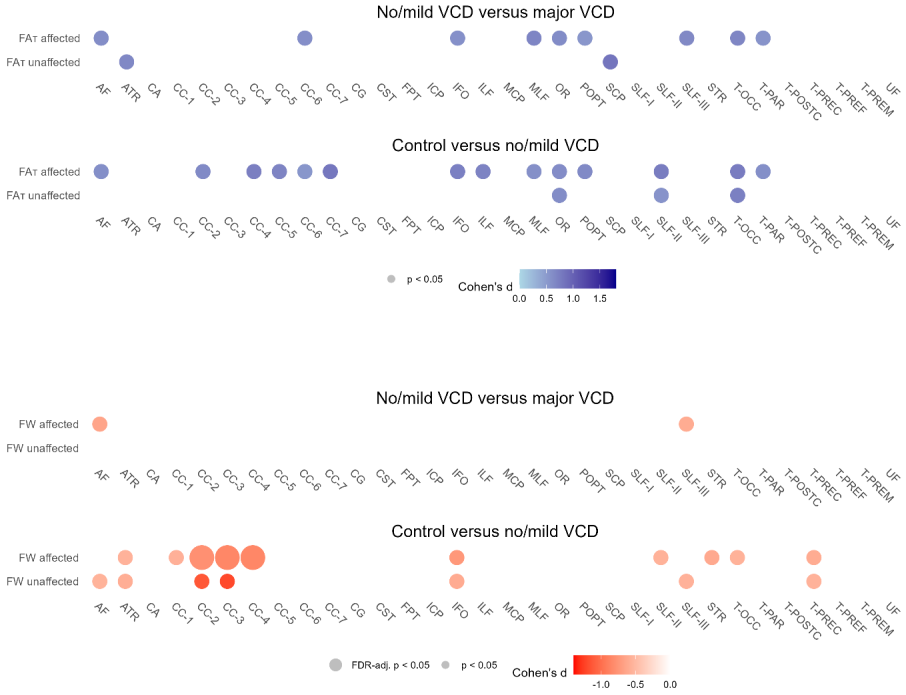
Supplementary Figure 1 Overlap of all stroke lesions in radiological orientation. This map displays an overlap across all stroke lesion by 6 slices at z=-60, z=-35, z =-10, z=15, z=40, and z=65. The color bar is ranging from 0 to 6, indicating the number of patients with a stroke lesion in that region



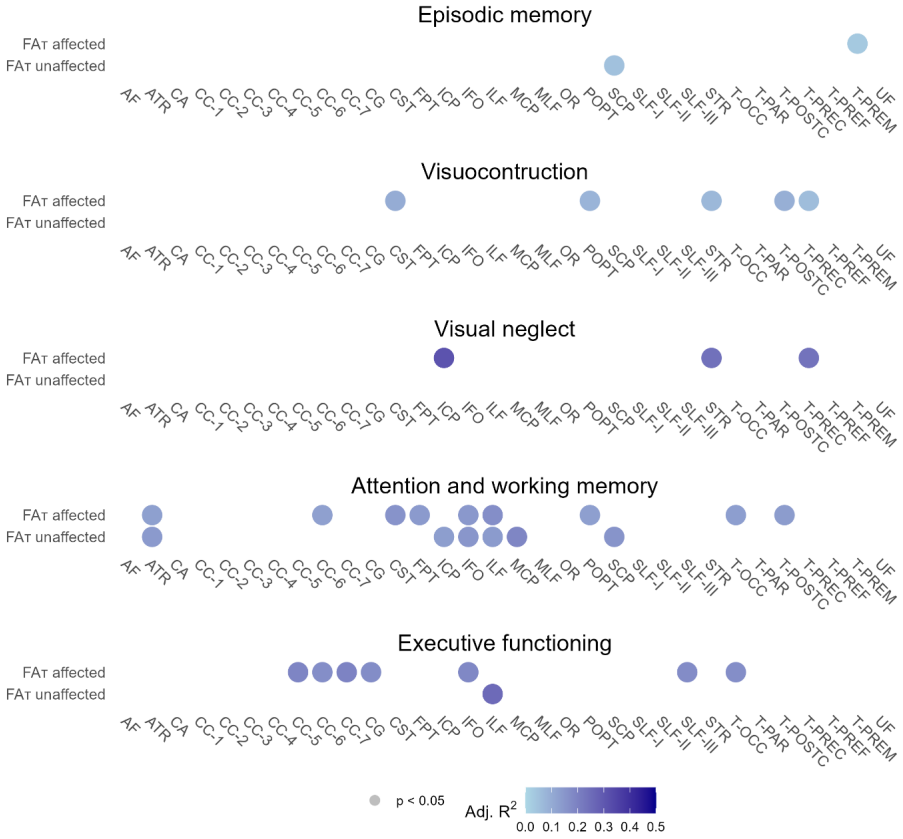
Supplementary Figure 2 Absolute values of free water corrected Fractional Anisotropy (FA_T) and Free Water (FW) (with 95% confidence interval) in lesion expansions of patients.



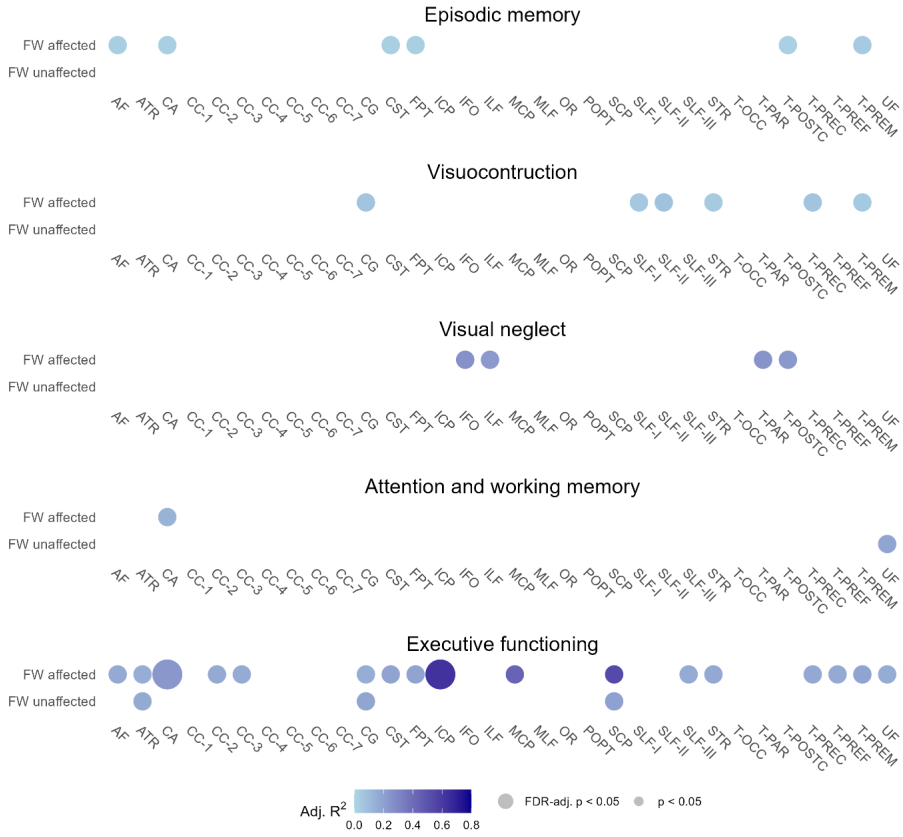
Supplementary Figure 3 Z-score with 95% confidence interval of free water corrected Mode of anisotropy (MO_T) in lesion expansions. Z-scores for MO_T in patients across different lesion expansions**.** Z-scores were calculated using the MO_T of controls at the same location).



Supplementary Figure 4 Group comparisons of free water corrected Fractional Anisotropy (FA_T) (blue) and Free Water (FW) (red). Difference in FA_T and FW between patients with no/mild VCD and major VCD, and between controls and patients with no/mild VCD and quantified with Cohen's d represented by color. Group differences were corrected for depressive symptoms and lesion volume. Group differences were presented for the FAT and FW of the tracts on the affected side, and the FAT and FW of the tracts on the unaffected side. Correction for multiple comparisons was performed using false discovery rate (FDR). In this figure circles are uncorrected p-values smaller than 0.05, and blank spaces represent uncorrected p-values greater than 0.05.



Supplementary Figure 5 Association between domain specific z-scores and free water corrected Fractional Anisotropy (FA_T), and Free Water (FW). Effect sizes (adj. R^2) obtained from linear regression, adjusted for lesion volume and the presence of depressive symptoms are presented by color. Associations were presented for the FA_T and FW of the tracts on the affected side, and the FA_T and FW of the tracts on the unaffected side. Correction for multiple comparisons was performed using false discovery rate (FDR). Large circles represent corrected p-values smaller than 0.05, small circles represent uncorrected p-values smaller than 0.05, and blank spaces represent uncorrected p-values greater than 0.05**Table 1** Continued



Supplementary Figure 5 Continued

Part IV

Impact of cognitive impairment on return to work

Chapter 7

Cognitive performance is associated with return to work after ischemic stroke in young adults: the ODYSSEY study

Published as:
Schellekens MM, Boot EM, Verhoeven JI, Ekker MS, Verburgt E, Immens MH, Mertens A, van Alebeek ME, Brouwers PJ, Arntz RM, van Dijk GW, Gons RA, van Uden IW, den Heijer T, van Tuijl JH, de Laat KF, van Norden AG, Vermeer SE, van Zagten MS, van Oostenbrugge RJ, Wermer MJ, Nederkoorn PJ, van Rooij FG, van den Wijngaard IR, de Kort PL, de Leeuw FE, Kessels RP, Tuladhar AM. Cognitive performance is associated with return to work after ischemic stroke in young adults: The ODYSSEY study.

Eur Stroke J. 2025 Mar 12:23969873251324400. Epub ahead of print.

Abstract

Introduction

Limited data exist on cognitive performance and return to work after ischemic stroke, especially in patients under 50 years. We investigated whether cognitive performance in the subacute phase after ischemic stroke in young adults was associated with unemployment and the inability to retain their jobs among those who returned to work.

Patients and methods

We conducted a multicenter prospective cohort study between 2013 and 2021, enrolling patients aged 18–49 years with first-ever ischemic stroke. Cognitive assessments were performed within 6 months following the index event, covering seven cognitive domains. We categorized patients with cognitive impairment (Z-score <-1.5 on a domain) and as no/mild or major vascular cognitive disorder (VCD) (Z-score <-2.0 in one or more domains). Cognitive performance and other predefined characteristics were chosen to identify factors associated with unemployment and, among patients who returned to work, the inability to maintain employment.

Results

Of 525 patients (median age 44.3 [IQR 38.0-47.4] years; 243 women [46.3%]); median follow-up of 6.6 [IQR 4.5-8.2] years), 426 patients (81.1%) returned to work. Sixty-five patients (15.3%) were unable to maintain employment. In multivariable logistic regression analysis, major VCD (OR=2.0; 95% CI 1.3-3.0; p=0.002) and cognitive impairment in processing speed (OR=2.0; 95% CI 1.3-3.3; p=0.004) were associated with unemployment, but not with the inability to maintain employment.

Discussion and Conclusion

In young patients after a first-ever ischemic stroke, major VCD and impaired processing speed in the subacute phase after stroke were independently associated with unemployment, but not with the inability to maintain employment.

Introduction

The incidence of stroke among young adults (aged 18-50 years) is increasing worldwide.[1, 2] Each year, over 2 million young adults experience a stroke globally.[1] Most young adults affected by a stroke are active participants of society, with demanding social lives, young families and busy (developing) careers. While most young stroke survivors have relatively mild strokes, measured with the National Institutes of Health Stroke Scale (NIHSS),[152] almost half of young adults experience cognitive impairment after stroke.[23] Moreover, they often experience other impairments, such as fatigue and mood disorders.[24, 203] These sequelae may result in unemployment, which has been shown to lead to lower levels of subjective well-being and life satisfaction.[20] In addition, not being able to return to work has a high socioeconomic impact.[204] Overall, about half to two-thirds of all working-age adults were able to return to work after their first stroke, although some studies report rates as high as 75%.[21, 205] In these studies, not only including young stroke patients (under 50 years), various factors were associated with return to work, such as age, sex, stroke subtype, etiology of ischemic stroke, aphasia, stroke severity, independence of daily living, depression, and type of work.[21, 205, 206] While other factors, including education level, fatigue, and cardiovascular risk factors, may also be related, and therefore warrant further attention.[205] Besides that, cognitive impairment appeared to be negatively associated with return to work.[21, 205] However, previous studies on post-stroke cognition and return to work were performed in small samples, did not cover all major cognitive domains, had a short follow-up duration, or predominantly included patients over 50 years. These older patients are closer to their retirement and may have, as a result, a poorer return to work rate than younger stroke survivors.[21] Additionally, there are limited data on the ability of young stroke patients to retain their jobs after returning to work. Furthermore, it remains unclear whether difficulties to keep one's job are associated with cognitive impairment.

The aim of this study was therefore to investigate (1) whether cognitive performance in the subacute phase after first-ever ischemic stroke in a large cohort of young patients was associated with unemployment median 6 years after stroke, and (2) the inability to maintain employment among patients who returned to work at least once during their follow-up.

Patients and methods

Patients and study design

This study is part of the *'Observational Dutch Young Symptomatic StrokE studY'*, a multicenter prospective cohort study examining risk factors and prognosis of stroke at young age.[22, 24] The present study included patients aged 18-49 years with a first-ever ischemic stroke with radiological evidence of cerebral ischemia, who underwent a cognitive assessment and had at least one follow-up moment with data on employment status. Patients were included between May 2013 and February 2021. Exclusion criteria were a history of stroke, retinal infarction, and cerebral venous sinus thrombosis. For this study, we also excluded patients who were not in paid employment or followed education/study prior to their stroke, and those who died during the follow-up before we could determine their employment status. Detailed information regarding data collection has been provided elsewhere.[22] This study involves human participants and was approved by the Medical Review Ethics Committee region Arnhem-Nijmegen approved the study (NL41531.091.12). We obtained written informed consent from all participants. If the patient was unable to provide informed consent, consent was provided by the patient's legal representative.

Cognitive assessment

Patients underwent an extensive neuropsychological assessment within 6 months after stroke. We assessed the seven most relevant cognitive domains using multiple tests: *episodic memory* (3-trial version of the Rey Auditory Verbal Learning Test), *processing speed* (the written version of the Symbol-Digit Modalities Test, the abbreviated Stroop Color Word Test, parts I and II), *visuoconstruction* (Rey-Osterrieth Complex Figure - copy trial), *executive functioning* (Fluency test, Stroop interference score, Brixton Spatial Anticipation Test), *visual neglect* (Star Cancellation of the Behavioral Inattention Test), *language deficits* (Short Token test), *attention and working memory* (Digit Span subtest from the Wechsler Adult Intelligence Scale - Fourth Edition).

Normative data from the Advanced Neuropsychological Diagnostics Infrastructure (ANDI), which includes data of 26,000 healthy individuals across all age groups were employed for most tests. This allowed fine-grained adjustment based on age, sex and education level.[115] For the written version of the Symbol-Digit Modalities Test, we used the normative data from the test's manual (n=1,307),[116] adjusted for age and education level. For the Star Cancellation Test, we used a cutoff value (<44) instead of Z-scores, to indicate cognitive impairment on the domain visuospatial neglect.[143] Further details regarding the collection and preparation of cognitive data can be found elsewhere.[24, 156]

Cognitive impairment on a domain was defined as an age and education-adjusted composite Z-score of <-1.5.[24, 118] Criteria for vascular cognitive disorder (VCD) were based on the criteria of the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG). We defined major VCD as a composite Z-score of <-2.0, in one or more cognitive domains.[120] All remaining patients were classified as no/mild VCD.

Return to work data

We collected follow-up data on return to work systematically through standardized, structured questionnaires by phone or by an online survey between November 2013 and February 2024. We classified patients as employed if they were working or studying at their last follow-up assessment. We defined unemployment as either (1) not having any paid employment in any capacity or studying during the follow-up period, or (2) having returned to work or study at least once during their follow-up, but not working or studying at the last follow-up assessment. The latter group was classified for the secondary analysis as unable to maintain employment. Due to the absence of an exact date of return to work, we used the dates of the follow-up moment for the moment of return to work. We gathered details of return to work from the first follow-up moment in which the patient reported having returned to work.

Other measurements

We scored level of education with a Dutch scoring system comprising seven categories[121] that align with the UNESCO international classification of education levels.[122] Lesion type was scored on available imaging data. Lesions were categorized as lacunar in the case of small subcortical infarcts, usually smaller than 20 mm.[207] We segmented all stroke lesions on MRI using ITK- SNAP,[157] registered them to a standard template using Advanced Normalization Tools (ANTs, v 2.1.0),[158] and calculated normalized lesion volumes using FSLstats.[160] At the time of the cognitive assessment, we assessed symptoms of depression using the Mini International Neuropsychiatric Interview (MINI)[123] and fatigue using the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R).[124] We assessed functional outcome using the Barthel Index[125] at the follow-up moment when a patient returned to work, or, if a patient did not returned to work, the last available follow-up moment. Additionally, we evaluated the cause of stroke (based on modified Trial of ORG 10172 in Acute Stroke Treatment; TOAST)[151, 152] and severity at admission and discharge (National Institutes of Health Stroke Scale; NIHSS)[128], if necessary retrospectively, using a validated approach.[129, 130] We assessed the following cardiovascular factors associated with an increased risk of stroke systematically through medical files and a standardized questionnaire at time of index event: hypertension, dyslipidemia, diabetes, smoking, excess alcohol use, and obesity.[208]

Statistical analysis

We compared baseline characteristics between patients who were employed (i.e. those who returned to work and were able to maintain employment) and those who were unemployed, using the independent t-test or Mann-Whitney *U* test for continuous variables and Pearson's Chi-squared test/Fisher's exact test for categorial variables. We performed univariate and multivariable logistic regression analyses to assess the associations between predefined factors based on literature (age, sex, education level, stroke severity, imaging characteristics, functional outcome, depressive symptoms, post-stoke fatigue, cognitive performance, stroke etiology, number of cardiovascular risk factors, and recurrent stroke)[21, 205, 206] and unemployment. Next, we assessed the associations between the predefined factors and the inability to maintain employment, compared to the patients who were able to maintain work participation, using univariate and multivariable logistic regression. We performed multiple imputation to handle the missing data for the multivariable logistic regression models. The logistic regression models were fitted to each of the imputed datasets. We then pooled the results to obtain a single odds ratio (OR) with a 95% confidence interval (CI) for each predefined factor. We calculated McFadden's pseudo R^2 (R^2_{McF}) for each multivariable logistic regression model across all imputed datasets to assess model fit. We pooled the R^2_{McF} values from the imputed datasets to obtain a single R^2_{McF} per model. Since only 1 (0.2%) patient scored as cognitively impaired on the visual neglect domain, we excluded this domain from the regression analyses. Multivariable analyses were performed using associated factors with alpha set at 0.10 in the univariate analyses. To address multicollinearity, we created two different multivariable models: one including the VCD score as the indicator of cognitive performance (VCD model) and the other including the separate cognitive domains (cognitive domains model). For the NIHSS we selected the score at discharge as the measure of stroke severity, since patients often recover during admission. Lesion volume was missing in 60 (11.4%) patients. The fatigue severity scores were missing in 83 (15.8%) of the patients. These missing data points were not at random, as patients without fatigue score showed lower rates of return to (and stayed at) work (p=0.013), higher NIHSS scores at discharge (p=0.012), more frequent a poor outcomes on the Barthel Index (p=0.019), more frequent depressive symptoms (p=0.050), and more frequent major VCD (p=0.009) (Supplementary Table 1). Therefore, we developed separate multivariable regression models that include lesion volume and the fatigue severity score. Significance level was predefined at 0.05 (2-tailed). All statistical analyses were performed using R, version 4.1.3.[161]

Results

Of the 1322 patients participating in the ODYSSEY study, 525 patients were included in this analysis (median age 44.3 [IQR 38.0-47.4] years; 243 women [46.3%]; Figure 1). Baseline characteristics, stratified by employment status, are described in Table 1. Median time to cognitive assessment was 85 (IQR 56-120) days. Median follow-up was 6.6 (IQR 4.5-8.2) years. Median NIHSS at admission was 2 (IQR 1-5) and at discharge 1 (IQR 0-2). In total, 426 (81.1%) patients returned to work at least once during their follow-up, and 361 (68.8%) patients were able to maintain work participation and were employed at their last follow-up assessment. The median time to the survey, when patients reported returning to work, was 1.3 (IQR 0.7-1.7) years. During the follow-up 45 patients (8.6%) experienced a recurrent stroke, all of which were ischemic. Additionally, 8 (1.5%) patients died, of whom 2 (0.4%) had returned to work before they died.

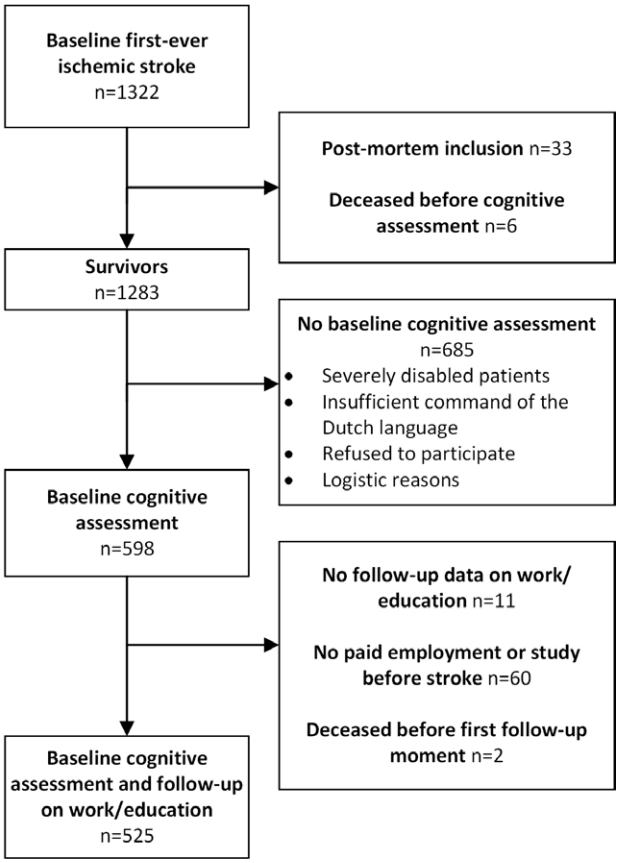


Figure 1 Flowchart of the study population

Table 1 Baseline characteristics

Characteristic	Patients, No. (%)			
	All (n=525)	Employed[a] (n=361)	Unemployed (n=164)	p-value
Age, median (IQR), years	44.3 (38.0-47.4)	43.9 (37.3-46.8)	45.3 (40.9-48.1)	0.002
18-29	58 (11.0)	43 (11.9)	15 (9.1)	0.053
30-39	101 (19.2)	78 (21.6)	23 (14.0)	
40-49	366 (69.7)	240 (66.8)	126 (76.8)	
Female	243 (46.3)	147 (40.7)	96 (58.5)	<0.001
Time to cognitive assessment, median (IQR), days	85 (56-120)	83 (57-119)	89 (56-120)	0.571
Follow-up, median (IQR), years	6.6 (4.5-8.2)	6.8 (4.6-8.3)	5.8 (4.5-7.8)	0.029
Follow-up to return to work, median (IQR), years	NA	1.3 (0.7-1.7)	NA	NA
Education level, median (IQR)	5 (5-6)	5 (5-6)	5 (5-6)	<0.001
6-7 (high)	200 (38.1)	155 (42.9)	45 (27.4)	0.002
5 (average)	260 (49.5)	168 (46.5)	92 (56.1)	
1-4 (low)	65 (12.4)	38 (10.5)	27 (16.5)	
NIHSS score at admission, median (IQR)	2 (1-5)	2 (1-4)	3 (1-6)	<0.001
≤ 3 (minor stroke)	340 (65.1)	250 (69.6)	90 (55.2)	0.002
> 3 (major stroke)	182 (34.9)	109 (30.4)	73 (44.8)	
NIHSS score at discharge, median (IQR)	1 (0-2)	1 (0-2)	1 (0-3)	<0.001
≤ 3 (minor stroke)	455 (87.0)	329 (91.4)	126 (77.3)	<0.001
> 3 (major stroke)	68 (13.0)	31 (8.6)	37 (22.7)	
Lesion type				
Lacunar	134 (25.5)	90 (24.9)	44 (26.8)	0.723
Territorial	391 (74.5)	271 (75.1)	120 (73.2)	
Normalized lesion volume (mL), median (IQR)	2.4 (0.6-13.8)	2.3 (0.7-12.6)	3.4 (0.6-18.7)	0.403
< 15 (small)	353 (75.9)	254 (78.1)	99 (70.7)	0.041
15-70 (medium)	96 (20.6)	64 (19.7)	32 (22.9)	
>70 (large)	16 (3.4)	7 (2.2)	9 (6.4)	
Barthel Index at follow-up, median (IQR)	100 (100-100)	100- (100-100)	95 (100-100)	<0.001
≥ 85 (good outcome)	514 (97.9)	360 (99.7)	154 (93.9)	<0.001
< 85 (poor outcome)	11 (2.1)	1 (0.3)	10 (6.1)	
Symptoms of depression	46 (9.0)	20 (5.7)	26 (16.3)	<0.001
CIS-20R - fatigue severity, mean (SD)	32.7 (11.9)	30.3 (11.3)	38.6 (11.2)	<0.001
< 36 (no/mild fatigue)	259 (58.6)	209 (66.5)	50 (39.1)	<0.001
≥ 36 (severe fatigue)	183 (41.4)	105 (33.4)	78 (60.9)	

Table 1 Continued

Characteristic	Patients, No. (%)			
	All (n=525)	**Employed[a] (n=361)**	**Unemployed (n=164)**	**p-value**
Cognitive impairment in [b]				
Episodic memory	97 (18.8)	59 (16.5)	38 (23.8)	0.068
Processing speed	152 (29.2)	79 (21.9)	73 (45.6)	<0.001
Visuoconstruction	182 (36.3)	126 (35.8)	56 (37.6)	0.780
Executive functioning	33 (6.3)	13 (3.6)	20 (12.3)	<0.001
Visual neglect	1 (0.2)	0 (0.0)	1 (0.6)	0.302
Language deficits	87 (17.4)	54 (15.4)	33 (22.3)	0.084
Attention and working memory	25 (4.9)	13 (3.6)	12 (7.9)	0.073
Vascular cognitive disorder [c]				
No/mild	358 (68.2)	270 (74.8)	88 (53.7)	<0.001
Major	167 (31.8)	91 (25.2)	76 (46.3)	
No. of cardiovascular risk factors [d]				
0	84 (16.0)	64 (17.8)	20 (12.2)	0.029
1-2	299 (56.9)	211 (58.4)	88 (53.7)	
≥ 3	142 (27.0)	86 (23.8)	56 (34.1)	
TOAST classification				
Atherothrombotic	20 (3.8)	8 (2.2)	12 (7.3)	0.006
Likely atherothrombotic	55 (10.5)	36 (9.9)	19 (11.6)	
Small vessel disease	74 (14.1)	44 (12.1)	30 (18.3)	
Cardioembolic	85 (16.2)	66 (18.3)	19 (11.6)	
Rare causes	113 (21.5)	74 (20.5)	39 (23.8)	
Multiple causes	33 (6.3)	23 (6.4)	10 (6.1)	
Cryptogenic	145 (27.6)	110 (30.5)	35 (21.3)	
Recurrent stroke during follow-up				
No	480 (91.4)	335 (92.8)	145 (88.4)	0.135
Yes	45 (8.6)	26 (7.2)	19 (11.6)	

IQR: interquartile range; NA: not applicable; NIHSS: National Institutes of Health Stroke Scale; CIS-20R: Checklist Individual Strength; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

Education category 5, i.e. middle school / secondary vocational training. Missing data: NIHSS ad admission 3 (0.6%); NIHSS at discharge 2 (0.4%); normalized lesion volume 60 (11.4%); MINI symptoms of depression 16 (3.0%); CIS-20R-fatigue 83 (15.8%); processing speed 5 (1.0%); episodic memory 8 (1.5%); visuoconstruction 24 (4.6%); executive functioning 1 (0.2%); visual neglect 11 (2.1%); language deficits 26 (5.0%); attention and working memory 22 (4.2%).

[a] Patients working or studying at their last follow-up assessment.

[b] Cognitive impairment: composite Z-score < -1.5 in a cognitive domain.

[c] Major vascular cognitive disorder: composite Z-score of <−2.0 in one more cognitive domains.

[d] No. of cardiovascular risk factors was determined by the presence of hypertension, dyslipidemia, diabetes, smoking, excess alcohol use, and obesity.

Factors associated with unemployment

In the multivariable logistic regression model including VCD, without lesion volume and the fatigue score (R^2_{McF} = 0.148), the risk of unemployment was higher for women (OR=2.5; 95% CI 1.6-3.8; p<0.001), patients with average (OR=1.6; 95% CI 1.0-2.6; p=0.043) or low (OR=2.3; 95% CI 1.2-4.6; p=0.015) education level, major stroke at discharge (OR=2.9; 95% CI 1.6-5.4; p<0.001), poor functional outcome (OR= 9.0; 95% CI 1.1-78.1; p=0.045), depressive symptoms (OR=3.2; 95% CI 1.6-6.3; p= <0.001), major VCD (OR=2.0; 95% CI 1.3-3.0; p=0.002), atherothrombotic stroke (OR=3.9; 95% CI 1.3-11.9; p= 0.015), small vessel disease as the cause of stroke (OR=2.3; 95% CI 1.1-4.7; p=0.022), and other rare cause of stroke (OR=1.9; 95% CI 1.0-3.5; p= 0.039), compared with cryptogenic stroke (Table 2).

In the multivariable model including the cognitive domains, without lesion volume and the fatigue score (R^2_{McF} = 0.162), the risk of unemployment was higher for patients with cognitive impairment in processing speed (OR=2.0; 95% CI 1.3-3.3; p=0.004).

Cognitive impairment in executive functioning (OR=3.7; 95% CI 1.8-7.9; p<0.001) and in attention and working memory (OR=2.3; 95% CI 1.0-5.1; p=0.049) were associated with unemployment only in the univariate analysis.

In the multivariable model including VCD, with lesion volume and the fatigue score (R^2_{McF} = 0.180), the risk of unemployment was also higher for patients with severe fatigue (OR=2.6; 95% CI 1.5-4.4; p<0.001). In this model, average education level, functional outcome, and rare cause of stroke were no longer significant (Supplementary Table 2).

Table 2 Factors associated with unemployment

Factor	Unemployment					
	Univariate		Multivariable			
			VCD model		Cognitive domains model	
	Univariate OR (95% CI)	p-value	Multivariable OR (95%CI)	p-value	Multivariable OR (95%CI)	p-value
Age, years						
18-29	1 [Reference]	NA	NA	NA	NA	NA
30-39	0.8 (0.4-1.8)	0.660	NA	NA	NA	NA
40-49	1.5 (0.8-2.8)	0.201	NA	NA	NA	NA
Sex						
Male	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Female	2.1 (1.4-3.0)	<0.001	2.5 (1.6-3.8)	<0.001	2.5 (1.6-3.9)	<0.001
Education level						
6-7 (high)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
5 (average)	1.8 (1.2-2.9)	0.003	1.6 (1.0-2.6)	0.043	1.5 (1.0-2.5)	0.080
1-4 (low)	2.4 (1.4-4.4)	0.003	2.3 (1.2-4.6)	0.015	2.2 (1.1-4.4)	0.026
NIHSS score at admission						
≤ 3 (minor stroke)	1 [Reference]	NA	NA	NA	NA	NA
> 3 (major stroke)	1.8 (1.3-2.7)	0.001	NA	NA	NA	NA
NIHSS score at discharge						
≤ 3 (minor stroke)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
> 3 (major stroke)	3.1 (1.9-5.3)	<0.001	2.9 (1.6-5.4)	<0.001	2.8 (1.5-5.2)	<0.001
Lesion type						
Lacunar	1 [Reference]	NA	NA	NA	NA	NA
Territorial	0.9 (0.6-1.4)	0.644	NA	NA	NA	NA

Table 2 Continued

Factor	Unemployment					
	Univariate		Multivariable			
			VCD model		Cognitive domains model	
	Univariate OR (95% CI)	p-value	Multivariable OR (95%CI)	p-value	Multivariable OR (95%CI)	p-value
Normalized lesion volume (mL)						
< 15 (small)	1 [Reference]	NA	NA	NA	NA	NA
15-70 (medium)	1.2 (0.8-2.1)	0.313	NA	NA	NA	NA
>70 (large)	3.3 (1.2-9.5)	0.021	NA	NA	NA	NA
Barthel Index at follow-up						
≥ 85 (good outcome)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
< 85 (poor outcome)	23.4 (4.4-430.9)	0.003	9.0 (1.1-78.1)	0.045	8.4 (1.0-73.6)	0.055
Symptoms of depression						
No	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	3.2 (1.7-6.0)	<0.001	3.2 (1.6-6.3)	<0.001	3.2 (1.6-6.3)	<0.001
CIS-20R - fatigue severity						
< 36 (no/mild fatigue)	1 [Reference]	NA	NA	NA	NA	NA
≥ 36 (severe fatigue)	3.1 (2.0-4.8)	<0.001	NA	NA	NA	NA
Cognitive impairment in						
Episodic memory	1.6 (1.0-2.5)	0.053	NA	NA	1.0 (0.6-1.8)	0.889
Processing speed	3.0 (2.0-4.5)	<0.001	NA	NA	2.0 (1.3-3.3)	0.004
Visuoconstruction	1.1 (0.7-1.6)	0.704	NA	NA	NA	NA
Executive functioning	3.7 (1.8-7.9)	<0.001	NA	NA	2.2 (0.9-5.7)	0.104
Language deficits	1.5 (1.0-2.5)	0.064	NA	NA	1.3 (0.7-2.3)	0.348
Attention and working memory	2.3 (1.0-5.1)	0.049	NA	NA	0.9 (0.3-2.5)	0.780

Table 2 Continued

Factor	Unemployment					
	Univariate		Multivariable			
			VCD model		Cognitive domains model	
	Univariate OR (95% CI)	p-value	Multivariable OR (95%CI)	p-value	Multivariable OR (95%CI)	p-value
Vascular cognitive disorder						
No/mild	1 [Reference]	NA	1 [Reference]	NA	NA	NA
Major	2.6 (1.7-3.8)	<0.001	2.0 (1.3-3.0)	0.002	NA	NA
No. of cardiovascular risk factors						
0	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
1-2	1.3 (0.8-2.4)	0.313	1.2 (0.6-2.3)	0.553	1.2 (0.6-2.3)	0.583
≥ 3	2.1 (1.2-3.9)	0.017	1.3 (0.6-2.9)	0.463	1.2 (0.6-2.7)	0.590
TOAST classification						
Atherothrombotic	4.7 (1.8-12.9)	0.002	3.9 (1.3-11.9)	0.015	4.7 (1.5-14.4)	0.007
Likely atherothrombotic	1.7 (0.8-3.2)	0.141	1.7 (0.8-3.6)	0.203	1.9 (0.8-4.1)	0.124
Small vessel disease	2.1 (1.2-3.9)	0.013	2.3 (1.1-4.7)	0.022	2.8 (1.4-5.9)	0.006
Cardioembolic	0.9 (0.5-1.7)	0.758	1.3 (0.6-2.6)	0.511	1.5 (0.7-3.0)	0.291
Rare causes	1.7 (1.0-2.9)	0.069	1.9 (1.0-3.5)	0.039	1.9 (1.0-3.5)	0.051
Multiple causes	1.4 (0.6-3.1)	0.463	1.2 (0.4-3.0)	0.752	1.3 (0.5-3.5)	0.570
Cryptogenic	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Recurrent stroke during follow-up						
No	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	1.7 (0.9-3.1)	0.099	1.1 (0.5-2.3)	0.806	1.1 (0.5-2.3)	0.821

VCD: vascular cognitive disorder; OR: odds ratio; CI: confidence interval; NA: not applicable; NIHSS: National Institutes of Health Stroke Scale; CIS-20R: Checklist Individual Strength; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.
Education category 5, i.e. middle school / secondary vocational training. Multivariable regression models without lesion volume and CIS-20R - fatigue severity score.

Inability to maintain employment

Of the 426 patients who returned to work, 380 (89.2%) initially returned to their same job. Sixty-five (15.3%) patients were unable to maintain employment. Cognitive impairment in processing speed (OR=2.3; 95% CI 1.3-4.1; p=0.003) and the presence of a major VCD (OR=2.1; 95% CI 1.2-3.6; p=0.008) were associated with the inability to maintain employment only in the univariate analysis (Table 3).

In the multivariable model including VCD, without the fatigue severity score (R^2_{McF} = 0.162), this risk of the inability to maintain employment was higher for women (OR=2.9; 95% CI 1.6-5.2; p<0.001), for patients with average education level (OR=2.1; 95% CI 1.0-4.1; p=0.037), those with depressive symptoms (OR=3.3; 95% CI 1.3-8.3; p=0.011), atherothrombotic stroke (OR=6.1; 95% CI 1.6-23.4; p= 0.009), and small vessel disease as the cause of stroke (OR=3.4; 95% CI 1.3-8.9; p=0.011), compared to patients with cryptogenic stroke. For patients aged 30-39 years, the risk of the inability maintain employment was lower (OR=0.3; 95% CI 0.1-0.8; p=0.026) compared to patients aged 18-29.

The multivariable model including VCD and with the fatigue severity score (R^2_{McF} = 0.171) is presented in Supplementary Table 3. Fatigue was not significantly associated with the inability to maintain employment.

Table 3 Factors associated with the inability to maintain employment

Factor	Inability to maintain employment					
	Univariate		Multivariable			
			VCD model		Cognitive domains model	
	Univariate OR (95% CI)	p-value	Multivariable OR (95%CI)	p-value	Multivariable OR (95%CI)	p-value
Age, years						
18-29	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
30-39	0.3 (0.1-0.8)	0.026	0.3 (0.1-0.8)	0.026	0.2 (0.1-0.8)	0.020
40-49	0.9 (0.4-2.0)	0.775	0.8 (0.3-2.0)	0.651	0.7 (0.3-1.8)	0.500
Sex						
Male	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Female	2.3 (1.4-4.0)	0.002	2.9 (1.6-5.2)	<0.001	2.9 (1.6-5.3)	<0.001
Education level						
6-7 (high)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
5 (average)	2.3 (1.3-4.4)	0.006	2.1 (1.0-4.1)	0.037	1.9 (1.0-3.8)	0.060
1-4 (low)	1.2 (0.4-3.3)	0.736	1.3 (0.4-4.0)	0.637	1.2 (0.4-3.8)	0.710
NIHSS score at admission						
≤ 3 (minor stroke)	1 [Reference]	NA	NA	NA	NA	NA
> 3 (major stroke)	1.3 (0.7-2.2)	0.376	NA	NA	NA	NA
NIHSS score at discharge						
≤ 3 (minor stroke)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
> 3 (major stroke)	2.7 (1.3-5.3)	0.007	2.0 (0.9-4.6)	0.092	2.0 (0.9-4.8)	0.081
Lesion type						
Lacunar	1 [Reference]	NA	NA	NA	NA	NA
Territorial	0.8 (0.5-1.5)	0.465	NA	NA	NA	NA

Table 3 Continued

Factor	Inability to maintain employment					
	Univariate		Multivariable			
			VCD model		Cognitive domains model	
	Univariate OR (95% CI)	p-value	Multivariable OR (95%CI)	p-value	Multivariable OR (95%CI)	p-value
Normalized lesion volume (mL)						
< 15 (small)	1 [Reference]	NA	NA	NA	NA	NA
15-70 (medium)	1.3 (0.6-2.6)	0.423	NA	NA	NA	NA
>70 (large)	1.8 (0.3-8.0)	0.449	NA	NA	NA	NA
Barthel Index at follow-up						
≥ 85 (good outcome)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
< 85 (poor outcome)	11.4 (1.1-248.1)	0.048	11.3 (0.6-199.2)	0.098	10.5 (0.6-195.5)	0.116
Symptoms of depression present						
No	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	3.4 (1.6-7.6)	0.002	3.3 (1.3-8.3)	0.011	3.5 (1.4-8.6)	0.008
CIS-20R - fatigue severity						
< 36 (no/mild fatigue)	1 [Reference]	NA	NA	NA	NA	NA
≥ 36 (severe fatigue)	2.1 (1.2-3.9)	0.011	NA	NA	NA	NA
Cognitive impairment in						
Episodic memory	1.4 (0.7-2.7)	0.300	NA	NA	NA	NA
Processing speed	2.3 (1.3-4.1)	0.003	NA	NA	1.8 (0.9-3.4)	0.073
Visuoconstruction	1.0 (0.5-1.7)	0.905	NA	NA	NA	NA
Executive functioning	2.2 (0.7-6.5)	0.141	NA	NA	NA	NA
Language deficits	1.1 (0.5-2.1)	0.895	NA	NA	NA	NA
Attention and working memory	0.9 (0.1-3.4)	0.908	NA	NA	NA	NA

Table 3 Continued

Factor	Inability to maintain employment					
	Univariate		Multivariable			
			VCD model		Cognitive domains model	
	Univariate OR (95% CI)	p-value	Multivariable OR (95%CI)	p-value	Multivariable OR (95%CI)	p-value
Vascular cognitive disorder						
No/mild	1 [Reference]	NA	1 [Reference]	NA	NA	NA
Major	2.1 (1.2-3.6)	0.008	1.4 (0.8-2.7)	0.254	NA	NA
No. of cardiovascular risk factors						
0	1 [Reference]	NA	NA	NA	NA	NA
1-2	1.9 (0.9-4.9)	0.121	NA	NA	NA	NA
≥ 3	1.4 (0.5-3.9)	0.515	NA	NA	NA	NA
TOAST classification						
Atherothrombotic	6.9 (2.0-23.4)	0.002	6.1 (1.6-23.4)	0.009	6.0 (1.6-23.3)	0.009
Likely atherothrombotic	1.5 (0.5-4.2)	0.429	1.5 (0.5-4.8)	0.475	1.5 (0.5-4.9)	0.471
Small vessel disease	2.9 (1.3-6.9)	0.013	3.4 (1.3-8.9)	0.011	3.6 (1.4-9.4)	0.008
Cardioembolic	0.8 (0.3-2.3)	0.728	1.1 (0.4-3.2)	0.914	1.1 (0.4-3.4)	0.824
Rare causes	1.8 (0.8-4.3)	0.136	2.2 (0.9-5.3)	0.089	2.0 (0.8-5.0)	0.122
Multiple causes	2.4 (0.8-6.9)	0.113	2.1 (0.6-7.1)	0.221	2.1 (0.6-7.2)	0.220
Cryptogenic	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Recurrent stroke during follow-up						
No	1 [Reference]	NA	NA	NA	NA	NA
Yes	1.5 (0.6-3.7)	0.326	NA	NA	NA	NA

VCD: vascular cognitive disorder; OR: odds ratio; CI: confidence interval; NA: not applicable; NIHSS: National Institutes of Health Stroke Scale; CIS-20R: Checklist Individual Strength; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.
Education category 5, i.e. middle school / secondary vocational training. Multivariable regression models without CIS-20R - fatigue severity score.

Discussion

In this prospective cohort study of young ischemic stroke patients, we found that cognitive performance, measured by the presence of a major VCD in the subacute phase after stroke, was independently associated with unemployment 6 years post-stroke. Processing speed was the key cognitive domain affecting return to work. The presence of a major VCD and impaired processing speed were not independently associated with the inability to maintain employment.

In this cohort, 81% of the patients who were previously working or studying returned to work at least once after a median of 6 years after stroke, and 69% remained employed. This is a relatively high percentage of patients compared to earlier studies, reporting overall return to work proportions of 51% and 66%.[21, 205] Patients in most previous studies were closer to retirement age than those in our study, potentially resulting in a lower number of patients returning to work. Besides that, most patients in our study have had a relatively mild stroke (median NIHSS 2) and all were able to complete a cognitive assessment, potentially resulting in higher return to work rates.

Patients with a major VCD were twice as likely to be unemployed compared to patients with no or mild VCD. This was controlled for demographic and clinical factors, as well as depression and fatigue. Processing speed independently affected unemployment, whereas executive functioning and attention and working memory were associated with unemployment only in univariate analysis. This is line with other studies reporting that, next to independence in Activities of Daily Living (ADL), cognitive ability was the second most common factor influencing return to work and may be a limiting factor for those who have an otherwise good functional recovery.[21] However, cognitive disorders were evaluated using a variety of assessments and questionnaires in those studies. In studies focusing on specific cognitive domains, processing speed and executive functioning were associated with unemployment.[90, 209] However, sample sizes of previous studies were more than three times smaller,[90, 209] not all cognitive domains were assessed,[90] the assessments were conducted 7 years post-stroke, [90] or the follow-up period was limited to 6 months.[209] There were also studies that found no association between cognitive performance on specific cognitive domains and employment.[210, 211] However, these studies were not restricted to young stoke patients and had a follow-up duration that did not exceed 12 months.

Of the patients who returned to work at least once during their follow-up, 15% was unable to maintain employment. This highlights that a notable percentage

of patients struggle to maintain employment after initially returning to work. It is noteworthy that patients in the 30-39 age group were more likely to stay employed after returning to work. Possible reasons include longer employment duration, more stable work contracts, and greater familial responsibilities, such as children relying on their income. Better guidance could potentially lead to higher rates of successful return to work. However, to date, limited data are available with evidence regarding the effectiveness of interventions to promote return to work.[212] Cognitive impairment in processing speed and the presence of a major VCD were univariately associated with the inability to maintain employment. However, these associations did not persist in multivariable analysis. Overall, processing speed seems to be the most important domain in relation to return to work and maintain employment, as it is crucial for maintaining productivity, adaptability, and effective communication in the workplace.

In line with other studies, we found a higher odds ratio of unemployment for women, patients with a low or average education level, those who experienced a major stroke, patients with a poor functional outcome, patients affected by a depression, those experiencing severe fatigue, and those with atherothrombotic stroke, small vessel disease, and other rare cause of stroke, compared with cryptogenic stroke.[21, 205, 206] Our data suggest that less visible impairments, such as symptoms of a depression, severe fatigue, and cognitive impairment, also play an important role in unemployment in young stroke patients, besides motor impairment.

Our study has several strengths. Firstly, this is a large prospective cohort of young adults who experienced a first-ever, radiologically confirmed ischemic stroke. Secondly, we used extensive neuropsychological testing, with limited missing data. Thirdly, we have a long follow-up period, making it likely that if patients returned to work, it is captured within this timeframe.

However, some study limitations need to be addressed. Firstly, the exact dates of return to work were not collected. At subsequent follow-up moments, we surveyed patients regarding their then-current employment status. The first follow-up assessment, conducted at a median of one year, may have contributed to the relatively long return to work intervals, as we used the date of the follow-up assessment as the return to work date. Additionally, for patients who had not returned to work at their first follow-up assessment, it remains unclear whether they were employed at any time between their stroke and the first follow-up moment. Secondly, we did not collect data on the percentage of hours worked compared to the original number of hours. Binary representation of work status

may not fully capture nuances of patients who experience varying degrees of reduced work capacity. Thirdly, cognitive data were unavailable for patients who were unable or refused to participate, often due to severe stroke. Consequently, our study includes patients with relatively mild strokes. This could potentially lead to an overrepresentation of the number of patients returning to work, and likely leads to an underrepresentation of the effect of cognitive impairment. A shorter stroke-specific cognitive screening assessment[132] may be used in future research to get an estimate of the cognitive status of individuals unable to complete a full comprehensive assessment, providing a more accurate understanding of the relationship between cognitive impairment and return to work outcomes. Fourthly, the fatigue severity score is missing in almost 16% of our patients, and these missing data were not at random; patients without a fatigue score had poorer motor and cognitive performance. Since fatigue was a strong associated univariate factor, we analyzed its impact in a separate multivariable model after imputing the missing data. Fifthly, the prevalence of some factors (e.g. the Barthel Index) in the logistic regression was rare, making it harder to detect significant results or resulting in large confidence intervals. Finally, we did not have data on pre-stroke levels of stress and depression. These factors could influence return to work, with pre-stroke stress and depression potentially having a negative impact, possibly even independently of post-stroke depression.

In rehabilitation, return to work is an important goal for young stroke patients. The recognition of key drivers for the (in)ability to return to work and the subsequent development of cognitive rehabilitation programs may facilitate this process.[97] Future studies should focus on developing and improving methods to enhance cognitive function and accurately assess its effects on everyday activities.[97] Additionally, there is need for controlled studies to evaluate interventions to promote return to work.[212]

Conclusion

In conclusion, in young patients after a first-ever stroke, cognitive performance in the subacute phase after stroke was independently associated with unemployment, but not the inability to maintain employment. Neuropsychological assessments or cognitive screenings may be considered in the young stroke population to obtain information regarding cognitive status, which may enable better predictions of return to work outcomes, and may be helpful facilitating successful return to work.

Supplementary data

Supplementary Table 1 Characteristics of patients with and without assessment of fatigue

Characteristic	Patients No. (%)		
	Fatigue score (n=442)	No fatigue score (n=83)	p-value
Age, median (IQR), years	44.3 (38.5-47.4)	44.3 (37.0-47.5)	0.964
18-29	48 (10.9)	10 (12.0)	0.583
30-39	82 (18.6)	19 (22.9)	
40-49	312 (70.6)	54 (65.1)	
Female	203 (45.9)	40 (48.2)	0.795
Follow-up, median (IQR), years	6.9 (4.5-8.2)	6.3 (4.6-7.8)	0.165
Return to (and stayed at) work	314 (71.0)	47 (56.6)	0.013
Education level, median (IQR)	5 (5-6)	5 (5-6)	0.218
6-7 (high)	174 (39.4)	26 (31.3)	0.374
5 (average)	215 (48.6)	45 (54.2)	
1-4 (low)	53 (12.0)	12 (14.5)	
NIHSS score at admission, median (IQR)	2 (1-5)	3 (1-5)	0.051
≤ 3 (minor stroke)	295 (66.9)	45 (55.6)	0.066
> 3 (major stroke)	146 (33.1)	36 (44.4)	
NIHSS score at discharge, median (IQR)	1 (0-2)	1 (0-3)	0.012
≤ 3 (minor stroke)	388 (88.0)	67 (81.7)	0.170
> 3 (major stroke)	53 (12.0)	15 (18.3)	
Normalized lesion volume (mL), median (IQR)	2.4 (0.7-13.0)	1.9 (0.5-26.3)	0.801
< 15 (small)	304 (77.4)	49 (68.1)	0.206
15-70 (medium)	77 (19.6)	19 (26.4)	
>70 (large)	12 (3.1)	4 (5.6)	
Barthel Index at follow-up, median (IQR)	100 (100-100)	100 (100-100)	0.875
≥ 85 (good outcome)	436 (98.6)	78 (94.0)	0.019
< 85 (poor outcome)	6 (1.4)	5 (6.0)	
Symptoms of depression	34 (7.9)	12 (15.6)	0.050
Cognitive impairment in [a]			
Episodic memory	76 (17.4)	21 (26.3)	0.087
Processing speed	115 (26.1)	37 (46.3)	<0.001
Visuoconstruction	149 (35.0)	33 (44.0)	0.171
Executive functioning	24 (5.4)	9 (10.9)	0.099
Language deficits	7 (16.4)	17 (23.6)	0.185
Attention and working memory	20 (4.6)	5 (7.0)	0.377

Supplementary Table 1 Continued

Characteristic	Patients No. (%)		
	Fatigue score (n=442)	No fatigue score (n=83)	p-value
Vascular cognitive disorder [b]			
No/mild	312 (70.6)	46 (55.4)	0.009
Major	130 (29.4)	37 (44.6)	
No. of cardiovascular risk factors [c]			
0	72 (16.3)	12 (14.4)	0.805
1-2	249 (56.3)	50 (60.2)	
≥ 3	121 (27.4)	21 (25.3)	
TOAST classification			
Atherothrombotic	15 (3.4)	5 (6.0)	0.377
Likely atherothrombotic	49 (11.1)	6 (7.2)	
Small vessel disease	61 (13.8)	13 (15.7)	
Cardioembolic	77 (17.4)	8 (9.6)	
Rare causes	93 (21.0)	20 (24.1)	
Multiple causes	26 (5.9)	7 (8.4)	
Cryptogenic	121 (27.4)	24 (28.9)	

IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of ORG 10172 in Acute Stroke Treatment. Education category 5, i.e. middle school / secondary vocational training.

[a] Cognitive impairment: composite Z-score < -1.5 in a cognitive domain.

[b] Major vascular cognitive disorder: composite Z-score of <−2.0 in one more cognitive domains.

[c] No. of cardiovascular risk factors was determined by the presence of hypertension, dyslipidemia, diabetes, smoking, excess alcohol use, and obesity.

Supplementary Table 2 Multivariable regression model of factors associated with unemployment, including lesion volume and fatigue

Factor	Unemployment	
	VCD model OR (95% CI)	p-value
Sex		
Male	1 [Reference]	NA
Female	2.2 (1.4-3.4)	<0.001
Education level		
6-7 (high)	1 [Reference]	NA
5 (average)	1.6 (1.0-2.6)	0.066
1-4 (low)	2.3 (1.1-4.6)	0.021
NIHSS score at discharge		
≤ 3 (minor stroke)	1 [Reference]	NA
> 3 (major stroke)	2.7 (1.4-5.3)	0.003
Normalized lesion volume		
Small	1 [Reference]	NA
Medium	1.0 (0.6-1.9)	0.872
Large	2.1 (0.6-7.0)	0.230
Barthel Index at follow-up		
≥ 85 (good outcome)	1 [Reference]	NA
< 85 (poor outcome)	7.6 (0.8-69.2)	0.073
Symptoms of depression		
No	1 [Reference]	NA
Yes	2.4 (1.2-4.7)	0.017
CIS-20R - fatigue severity		
< 36 (no/mild fatigue)	1 [Reference]	NA
≥ 36 (severe fatigue)	2.6 (1.5-4.4)	<0.001
Vascular cognitive disorder		
No/mild	NA	NA
Major	1.9 (1.2-3.0)	0.005
No. of cardiovascular risk factors		
0	1 [Reference]	NA
1-2	1.1 (0.6-2.3)	0.699
≥ 3	1.3 (0.6-2.9)	0.512

Supplementary Table 2 Continued

Factor	Unemployment	
	VCD model OR (95% CI)	**p-value**
TOAST classification		
Atherothrombotic	4.1 (1.3-13.1)	0.019
Likely atherothrombotic	1.9 (0.8-4.2)	0.132
Small vessel disease	2.6 (1.2-5.5)	0.015
Cardioembolic	1.2 (0.6-2.4)	0.640
Rare causes	1.7 (0.9-3.3)	0.087
Multiple causes	1.1 (0.4-2.8)	0.922
Cryptogenic	1 [Reference]	NA
Recurrent stroke during follow-up		
No	1 [Reference]	NA
Yes	1.0 (0.5-2.1)	0.958

VCD: vascular cognitive disorder; OR: odds ratio; CI: confidence interval; NA: not applicable; NIHSS: National Institutes of Health Stroke Scale; CIS-20R: Checklist Individual Strength.
Education category 5, i.e. middle school / secondary vocational training.

Supplementary Table 3 Multivariable regression models of factors associated with the inability to maintain employment, including fatigue score

Factor	Inability to maintain employment	
	VCD model OR (95% CI)	**p-value**
Age, years		
18-29	1 [Reference]	NA
30-39	0.3 (0.1-0.9)	0.033
40-49	0.9 (0.4-2.2)	0.793
Sex		
Male	1 [Reference]	NA
Female	2.6 (1.3-4.8)	0.002
Education level		
6-7 (high)	1 [Reference]	NA
5 (average)	2.0 (1.0-4.0)	0.045
1-4 (low)	1.3 (0.4-4.1)	0.631
NIHSS score at discharge		
≤ 3 (minor stroke)	1 [Reference]	NA
> 3 (major stroke)	2.2 (0.9-5.0)	0.071
Barthel Index at follow-up		
≥ 85 (good outcome)	1 [Reference]	NA
< 85 (poor outcome)	8.7 (0.5-146.7)	0.135
Symptoms of depression present		
No	1 [Reference]	NA
Yes	2.7 (1.0-6.9)	0.045
CIS-20R - fatigue severity		
< 36 (no/mild fatigue)	1 [Reference]	NA
≥ 36 (severe fatigue)	1.8 (0.9-3.6)	0.092
Vascular cognitive disorder		
No/mild	NA	NA
Major	1.4 (0.8-2.7)	0.256
TOAST classification		
Atherothrombotic	5.9 (1.5-23.2)	0.011
Likely atherothrombotic	1.6 (0.5-5.3)	0.414
Small vessel disease	3.6 (1.4-9.5)	0.009
Cardioembolic	1.0 (0.3-3.1)	0.949
Rare causes	2.1 (0.9-5.2)	0.106
Multiple causes	1.9 (0.6-6.4)	0.304
Cryptogenic	1 [Reference]	NA

VCD: vascular cognitive disorder ; OR: odds ratio; CI: confidence interval; NA: not applicable; NIHSS: National Institutes of Health Stroke Scale; CIS-20R: Checklist Individual Strength.
Education category 5, i.e. middle school / secondary vocational training.

Part V

Discussion and future perspectives

Chapter 8

Summary

Around 10–15% of first-ever strokes occur in adults aged 18 to 50 years, affecting approximately 2 million young individuals worldwide each year.[1] Experiencing a stroke at a young age can have devastating and lifelong consequences. [6] Among these, post-stroke cognitive impairment is particularly impactful, influencing social life, quality of life, and the ability to return to work—often even independently of physical recovery.[21] Most young adults suffering from a stroke are active participants of society, with demanding social lives, young families and busy careers. Despite its clinical importance, research on post-stroke cognitive impairment in young stroke patients remains limited. Therefore, the aim of this thesis was to investigate the prevalence, longitudinal course, underlying mechanisms and impact on return to work of cognitive impairment after ischemic stroke in young adults.

This thesis comprises one narrative review and five chapters presenting original data, based on the ODYSSEY study—a Dutch multicenter prospective cohort study investigating risk factors and prognosis of 1492 patients aged 18–49 years with a first-ever ischemic stroke or intracranial hemorrhage with radiological evidence. These patients were recruited from 17 centers across the Netherlands between 2013 and 2021. The studies included in this thesis focused exclusively on patients with an ischemic stroke.

In **Part II** of this thesis, I studied the prevalence and longitudinal course of cognitive impairment after ischemic stroke in young adults.

In **Chapter 3**, I investigated the prevalence of cognitive impairment in the subacute phase after ischemic stroke, in patients with and without physical impairments 24 hours after symptom onset. I investigated factors associated with a major vascular cognitive disorder (VCD), defined as a Z-score <-2.0 in one or more cognitive domains. Additionally, I examined the prevalence of subjective cognitive complaints and their relation with objective cognitive performance. We conducted cognitive assessments in 598 patients within six months after their ischemic stroke, covering seven cognitive domains: episodic memory, processing speed, visuoconstruction, executive functioning, visual neglect, language deficits, and attention and working memory. I found that a substantial proportion of patients performed worse across multiple cognitive domains compared to healthy controls at a median of three months post-stroke, even after full recovery from focal neurological deficits. Cognitive impairment was common, in up to 37% of the patients, across five domains. I observed that patients with a major VCD were more likely to have severe strokes (as indicated by higher NIHSS scores), stroke lesions in the left frontal lobe, and lower education levels compared to patients without

VCD. Furthermore, about two-thirds of patients reported subjective memory and executive complaints, although these were only weakly associated with objective cognitive performance.

> *Main finding:* Cognitive impairment across a wide range of cognitive domains, along with subjective cognitive complaints, was prevalent the subacute phase in young patients after ischemic stroke, even after full recovery from focal neurological symptoms.

In **Chapter 4**, I focused on the cognitive trajectory during the first year after ischemic stroke in young adults and aimed to identify predictors for cognitive recovery. A total of 393 patients completed cognitive assessments within six months and after one year following stroke. Overall, more than 50% of patients showed no cognitive change. However, approximately 20% exhibited cognitive improvement, while around 10% of the patients experienced decline. Cognitive recovery in patients with cognitive impairment at baseline was seen in 20–40% of patients in processing speed, visuoconstruction and executive functioning. I was unable to predict cognitive recovery in individual patients.

> *Main finding:* The majority of patients showed no cognitive change after the first months after ischemic stroke at a young age. However, approximately 20% improved, while 10% experienced cognitive decline.

In **Part III**, I explored the underlying mechanisms of cognitive impairments from an imaging perspective.

In **Chapter 5**, I investigated stroke location as one of the determinants of post-stroke cognitive impairment. Lesion-symptom mapping (LSM) has provided evidence for the role of strategic infarct location in post-stroke cognitive impairment. However, a comprehensive map of lesion locations and their associations with cognitive performance is still lacking in young adults. In this study, which included 522 patients, I demonstrated that various stroke lesion locations, identified from routine clinical MRI, were associated with poorer cognitive performance across multiple domains in patients with a young ischemic stroke. Additionally, I found that stroke lesions in the cerebellum—often overlooked in the context of stroke and cognition—also contributed to worse cognitive performance in multiple domains. This may help explain why patients with lesions in different locations can all experience cognitive problems.

Main finding: Ischemic stroke lesions in multiple brain regions, including the cerebellum, are associated with poorer cognitive performance in multiple cognitive domains, which might explain why patients with lesions in different locations can all experience cognitive problems.

In **Chapter 6**, I conducted a study to examine how an ischemic stroke lesion affects the integrity of surrounding white matter in the brain, and whether the integrity of this non-lesioned part of the white matter tracts is associated with cognitive performance after ischemic stroke in young adults. For this study, I included 66 patients who all underwent a 3T MRI and a neuropsychological assessment within six months after their stroke. Using Diffusion Tensor Imaging (DTI), I observed that microstructural changes remote from the lesion gradually diminish with increasing distance. Specifically, free water corrected fractional anisotropy (FA_T) gradually increased, while free water (FW) gradually decreased along the lesioned white matter tracts, extending away from the stroke lesion. Furthermore, I found that lower white matter integrity outside the stroke lesion, which was more pronounced in the hemisphere affected by the stroke, was associated with worse cognitive performance, particularly in the cognitive domain processing speed.

Main finding: Among young stroke survivors, lower white matter integrity outside the stroke lesion—measured by decreased FA_T and increased FW—especially in the affected hemisphere, is already present in the subacute phase after stroke and may contribute to cognitive impairment.

In **Part IV**, I examined the impact of cognitive impairment on return to work.

In **Chapter 7**, I analyzed cognitive performance in the subacute phase after stroke, along with other predefined characteristics, to identify factors associated with unemployment. Among patients who returned to work at least once during their follow-up, I also examined factors related to the inability to maintain employment. Of the 525 patients, 81% returned to work at least once during a median follow-up period of six years. However, 15% were unable to maintain employment. Patients with reduced processing speed or the presence of a major VCD were twice as likely to be unemployed at the end of their follow-up. This association was independent of demographic and clinical factors, as well as depression and fatigue. Cognitive impairment was not independently associated with the inability to maintain employment.

Main finding: In young patients after an ischemic stroke, major VCD and impaired processing speed were independently associated with unemployment.

Chapter 9

General discussion

In this chapter, I will begin with a discussion of the main findings. I will then address the methodological considerations of the studies included in this thesis. Finally, I will discuss the clinical implications of my findings and conclude with future research opportunities.

Discussion of main findings

In this part, I place the main findings of this thesis in a broader context, by three different themes: (1) the prevalence and recovery of cognitive impairment, (2) underlying mechanisms from an imaging perspective, and (3) impact of cognitive impairment on return to work in young adults after ischemic stroke.

Prevalence and recovery of cognitive impairment after stroke in young adults

In this thesis, I investigated the prevalence and recovery of cognitive impairment after ischemic stroke at young age. In **Chapter 3**, I demonstrated that cognitive impairment across a wide range of cognitive domains was highly prevalent in young stroke patients, even in those who have fully recovered from focal neurological symptoms. These findings are not entirely unexpected, as previous studies in young stroke populations have already shown cognitive deficits compared to healthy controls in both the short[3-5] and long term[6, 7]. However, many of these earlier studies were limited by small sample sizes, did not assess all cognitive domains, or lacked radiological confirmation of stroke. The FUTURE study, a single center prospective observational cohort study in the Netherlands, previously reported that up to 50% of young stroke survivors exhibited below-average cognitive performance or cognitive impairment even 11 years post-stroke, particularly in processing speed, working memory and attention.[6] While our results are in line with these prior findings, the ODYSSEY cohort provides several important strengths. Our study includes a well-defined patient population with radiologically confirmed stroke, in both general and academic hospitals, and a large proportion of participants that underwent comprehensive neurological assessment, making our findings more robust compared to earlier research.

The ODYSSEY study assessed cognition after stroke in a prospective way, whereas previous studies were often cross-sectional. In **Chapter 3 and 4** I investigated clinical factors associated with cognitive impairment in both the subacute and chronic phase after stroke, as well as factors associated with cognitive recovery. While I found that factors as stroke severity, lesion location, and education level

may play a role, I were unable to reliably predict either the presence or recovery of cognitive impairment in individual patients. To date, predicting cognitive impairment in young stroke survivors remains challenging. An interesting and evolving concept to explain the differences between the extent of brain damage observed in an individual and its clinical manifestation is the concept of reserve.[65] Two models, brain reserve and cognitive reserve, may help to clarify this phenomenon. The brain reserve model views reserve as a physical trait, suggesting that individuals with larger pre-stroke brain capacity can compensate for more neurological damage before exhibiting impairments. The cognitive reserve model emphasizes the brain's flexibility and adaptability, allowing cognitive networks to actively compensate for damage. Since cognitive reserve cannot be measured directly, various proxies—such as education, premorbid IQ, occupation, and leisure activities—are often used to estimate it. These factors may help maintain cognitive function despite underlying brain pathology. Although this reserve theory may contribute to our understanding, it alone may not be sufficient to explain the wide variation of cognitive functioning among patients after stroke.

In the ODYSSEY study, we may not have fully captured all factors influencing cognitive performance after stroke to predict development of cognitive impairment after a stroke. While gaining a better understanding of these predictive factors is important, one might also question how much further research is needed in this area. Given the high prevalence of cognitive impairment after young stroke, physicians could consider cognitive screening at least one time after stroke.

From a patient perspective, this would be a meaningful approach. Rather than focusing on predicting which individuals will develop cognitive impairment, clinicians should prioritize simply recognizing the problem and detecting cognitive deficits. At the same time identifying factors associated with cognitive impairment may provide potential targets for interventions, making it a valuable area of research. However, the first and most crucial step is recognizing the problem. The fact that the 'Young Stroke' medical protocol from the Radboudumc does not mention cognition at all perhaps highlights just how much this issue is overlooked. The Dutch guideline 'Herseninfarct en hersenbloeding' recommends assessing all stroke patients for cognitive impairment using at least the Montreal Cognitive Assessment (MoCA) in the acute/subacute phase. If the cognitive screening is positive, referral for cognitive rehabilitation is advised. Even if screening is negative, cognitive complaints should be explicitly addresses during follow-up, and psychoeducation should always be provided. However, many barriers exist before implementation in clinical practice occurs.

Another important finding, described in **Chapter 3**, is the high prevalence of subjective cognitive complaints among young stroke survivors. However, these complaints were only weakly associated with objective cognitive impairment. This suggests that factors contributing to subjective cognitive complaints might differ from factors contributing to objective impairment. Besides depression and fatigue, which I adjusted for in the analyses, potential contributors include psychological distress, coping strategies, personality traits and social factors, none of which were assessed in the ODYSSEY study. An alternative explanation is that individuals with severe cognitive impairment may lack insight into their deficits and therefore report fewer complaints, whereas those with very mild cognitive deficits (or even only subjective complaints) may experience significant daily challenges, particularly in demanding work and social environments. This raises an important question: What is more disabling—severe cognitive impairment that a patients is unaware of, or mild cognitive deficits that significantly impact daily life? This leads to the discussion whether clinicians should primarily focus on objectively measured cognitive deficits or also consider subjective complaints. There is currently little attention for the subjective complaints after stroke as well. Furthermore, another relevant question arises: Which aspect should be targeted in treatment to maximize quality of life and reduce social-economic impact? Understanding how to best support young stroke survivors—whether through cognitive rehabilitation, coping strategies, or workplace accommodations—should be priority for future research.

Underlying mechanisms from an imaging perspective

The FUTURE study previously observed a lower white matter integrity—even in the contralateral hemisphere—in cognitively impaired young stroke patients, years after the event.[17] Our findings in **Chapter 6** suggest that a lower white matter integrity was already present in the subacute phase after stroke. The increased free water (FW) in the non-lesioned white matter, which I used in our study as a marker of reduced white matter integrity, might be due pathological processes, including neuroinflammation, blood-brain barrier dysfunction, and vasogenic edema. The reduced free water corrected fractional anisotropy (FA_T) may result from mechanisms such as axonal degeneration and demyelination, which were already observable in the subacute phase.

Additionally, in **Chapter 6,** I explored the relationship between white matter integrity and cognitive performance in a specific domain. I found associations only for processing speed, primarily in the hemisphere affected by the stroke. Colleagues from the FUTURE study also found associations for processing speed and white matter integrity, even in the unaffected hemisphere.[17] Since our scans

were acquired approximately one month after the stroke, whereas the FUTURE study assessed patients 11 years after stroke, it is possible that secondary neurodegeneration in our study was still ongoing at the time of the MRI scan. A longitudinal study examining changes in white matter integrity over time would be valuable to determine whether these findings support the hypotheses of neurodegeneration as an underlying process.

Diffusion studies have gained popularity among clinicians and researchers in recent years. However, the Diffusion Tensor Imaging (DTI) models, like I used in our study , are not yet suitable for routine stroke care, and its value as a diagnostic tool for cognitive performance remains uncertain. Given that cognitive function is unlikely to be strictly localized in the brain and that many other underlying factors contribute to cognitive impairment, the added value of DTI models in clinical practice may remain limited, even in the future. From this perspective, one might question the necessity of further research on white matter integrity and its association with cognition in young stroke patients, especially in an era in which we must consider the scarcity of healthcare resources and research funding.

In **Chapter 5**, I demonstrated that various lesion locations are associated with poorer cognitive performance across multiple domains in young stroke patients. In recent years, increasing attention has been given to the role of the exact stroke location and the clinical consequences. Our findings are in contrast with previous studies in older stroke patients, which have not identified widespread bilateral brain regions, including locations in the cerebellum, associated with poorer cognitive performance.[9, 13] Lesion location data could be valuable in a prediction model and, when combined with demographic, personal, clinical, and other imaging data, may improve the prediction of cognitive impairment after young stroke. However, for young patients, such a prediction model does not yet exist, and it is unknown whether these specific locations would be helpful in this context.

Furthermore, it remains uncertain whether the widespread areas represent distinct regions, or if they are part of a larger brain network. It could be that younger patients are more reliant on such a network, which could explain why a lesion in an area of that network might disrupt it and lead to poorer cognition. However, there is no evidence for this yet. Another important question is whether our neuropsychological tests truly assess specific cognitive functions. It might be the case that we are not solely testing one single distinct cognitive domain when conducting a neuropsychological test, and that this contributes to our finding of widespread regions involved in various cognitive domains.

Impact of cognitive impairment on return to work

In **Chapter 7**, I found that 31% of the young stroke survivors were unemployed at the end of their follow-up. Major VCD and impaired processing speed were independently associated with unemployment. However, among patients who returned to work at least once, these factors were not associated with the inability to maintain employment. Although the proportion of patients returned to work is a relatively high percentage of patients compared to earlier studies—reporting overall return to work proportions of 51% and 66%—[21, 205] the 31% who remain unemployed still represents a significant group. This was despite the fact that most patients in our study had a mild stroke. Moreover, for those who did return to work, it remains unclear whether they were able to perform the same tasks as before. So the proportion of patients who returned to work in their previous capacity might be even lower. As there is insufficient attention for cognitive impairment and cognitive complaints after stoke, there may also be too little focus on ensuring a successful return to work. This also highlights the need for controlled studies to evaluate interventions aimed at assisting the transition back to work after stroke.[212]

Methodological considerations

The methodology of a study plays a crucial role in interpreting the results. Cohort studies are prone to various types of bias. In the following sections, I will discuss the potential sources of bias affecting the studies in this thesis.

Internal validity

Internal validity refers to the extent to which a study can establish a causal relationship between the variables being examined. The internal validity of observational studies is vulnerable to three main types of bias: selection bias, information bias, and confounding.

Selection bias

Selection bias occurs when the selection of the participants into a study leads to a result that is systematically different to the target population. This bias can be further subdivided into non-response bias and attrition bias.

Non-response bias might occur when participants who are not able or refuse to participate are different from those who enter the study. In the ODYSSEY study, the median NIHSS was 3—a relatively low score—which may indicate a selection bias favoring patients with less severe stroke. Patients with severe strokes might

have been underrepresented, as they or their legal representatives might have been less inclined to consent to participation. Additionally, cognitive data were lacking for patients who were unable (e.g. due to severe aphasia) or who refused to undergo a neuropsychological examination. This resulted in even lower NIHSS scores for patients with a cognitive assessment compared to all the participants participating in the ODYSSEY study. However, this selection bias would most likely lead to underestimation of the actual cognitive deficits.

In the study investigating the associations of white matter integrity and cognitive performance, all patients underwent an extensive MRI protocol and were recruited from an academic hospital. This may have introduced selection bias, as some patients may have been specifically referred (e.g. due to an unexplained cause of their stroke), which could further limit the generalizability of the findings.

Attrition bias might occur when systemic differences occur between participants who drop out of a study and those who continue. In the ODDYSEY study, cognitive data of patients who were unable or refused to participate in the follow-up cognitive assessment were lacking. Patients who completed cognitive assessments at both baseline and follow-up had a lower median NIHSS score compared to those who completed only one assessment. This likely results in an even more selective patient group with less severe strokes. However, once again, this selection bias would most likely lead to underestimation of the actual cognitive deficits.

Information bias

Information bias arises when key study variables are inaccurately measured or classified.

To reduce misclassification, neuro-imaging confirmation of ischemic stroke was required in the ODYSSEY study. Additionally, to minimize observer bias the baseline data of the ODYSSEY study were consistently gathered by four researchers.

However, over the years, the neuropsychological assessments were conducted by different researchers, which could have affected the consistency and accuracy of the measurements. To address this observer bias, two trained researchers retrospectively reviewed all the cognitive assessments that were administered.

Furthermore, due to logistic reasons, not all neuropsychological tests were performed at the same time after the stroke. Baseline assessments were conducted up to six months after stroke, which might have influenced the results, as recovery could have occurred in the initial weeks after stroke.

Additionally, in the ODYSSEY study, we used an extensive neuropsychological assessment to evaluate the cognitive performance. While this approach provides a comprehensive evaluation of patient's cognition, measurement validity, and more specifically construct validity, may play a role. The key question is whether a test accurately measures the intended cognitive domain—for example, whether an executive function test also relies on attention or language. Besides that, several cognitive tests we used exhibited a ceiling effect, reducing their sensitivity and limiting their ability to differentiate between individuals.

Confounding

Confounding occurs when a variable is related to both the determinant (independent variable) and the outcome (dependent variable), but not part of the causal pathway, thereby distorting the observed relationship between the determinant and the outcome.

For most cognitive tests, I used the normative data from the Advanced Neuropsychological Diagnostics Infrastructure (ANDI), enabling adjustment for age, sex and/or education level, where appropriate. Additionally, in the analyses on return to work, I adjusted for age, sex, education level, stroke severity, imaging characteristics (e.g. lesion volume), functional outcome, depressive symptoms, post-stoke fatigue, stroke etiology, number of cardiovascular risk factors, and recurrent stroke.

However, I did not collect data on all potential confounders. Factors that were not gathered in the ODYSSEY study, but could be important confounders—particularly in relation to subjective cognitive complaints and return to work—include patients coping strategies and the support system surrounding the patient. Furthermore, I did not collect data on all interventions that patients may have received, such as cognitive rehabilitation, which could have influenced cognitive recovery and impacted our results.

External validity

External validity refers to the extent to which conclusions of a study are generalizable to daily practice.

The ODYSSEY study is expected to be representative of the Dutch population, as it included patients from 17 centers across the country, encompassing both academic and general hospitals. However, since patients who were able to undergo an extensive neuropsychological examination may have been those with less

severe strokes, the incidence of cognitive impairment might be underestimated, while the proportion of return to work could be overestimated. Nevertheless, given that cognitive impairment is already common in this population, this suggests that cognitive difficulties are likely more prevalent than currently recognized.

Clinical implications

Given the increasing incidence of ischemic stroke in young adults, clinicians are more often likely to encounter young patients in clinical practice. Due to the demanding phase these patients face, it is important to understand the causes and prognosis following ischemic stroke in young adults. This knowledge will enable clinicians to provide accurate information to these young patients and their caregivers, addressing a key question they often have: "What will this mean for my future?"

The frequent occurrence of cognitive impairment in young stroke patients should make clinicians aware that this is a common issue following ischemic stroke in this age group, even in patients with mild strokes. Since cognitive impairment is not always immediately apparent, clinicians should be vigilant in recognizing it. Additionally, the question arises as to whether all young stroke patients should undergo at least once neuropsychological assessment or cognitive screening. This decision must be carefully considered, especially when rising healthcare costs are a concern. However, given that young stroke survivors are more likely to be discharged to home without rehabilitation than older adults, and only 15% of them received some form of cognitive screening in the acute setting, their cognitive and psychological needs may often remain unmet.[92] Therefore, it may be justifiable to conduct a cognitive screening at least once in the acute setting or during follow-up. These data could at least be used to inform patients and their caregivers. Hopefully, in the future, these findings could also serve as a basis for referral to evidence-based cognitive rehabilitation.

In this thesis, I aimed to identify associations of clinical and imaging predictors of cognitive performance. Although I found associations between white matter integrity, measured using DTI, and cognitive impairment, this MRI technique is not yet suitable for clinical practice for this purpose. Since the analyses of these diffusion-weighted sequences are time-consuming, and won't lead to any changes in treatment or clinical decision-making, we cannot currently utilize this technique in clinical practice.

Future research opportunities

In this thesis, I demonstrated that cognitive impairment is common in young adults following stroke. However, based on the studies conducted in this thesis, I am still unable to predict which patients will develop cognitive impairment and which will not. Although I have found group-level associations between cognitive performance in the subacute phase after stroke and factors such as education level, stroke severity, and stroke location, I was not yet able to make reliable predictions for individual patients. This also applies to the likelihood of cognitive recovery or decline. It could be of added value to develop a prediction model specifically for young ischemic stroke patients, allowing for a better estimation of the risk of cognitive impairment and the longitudinal course. Artificial Intelligence (AI) based algorithms might be helpful to evaluate all these data at once to provide individualized cognitive outcome predictions. Earlier studies using AI-based models for the prediction of post-stroke cognitive impairment demonstrated promising results in older patients.[213] However, before implementation of AI in clinical practice, validation in young patients and integration with clinical systems should be carried out.

Additionally, I highlighted focal lesion locations in the brain, which were associated with poorer cognitive performance. Another future research opportunity is to explore whether these regions interact within larger functional brain networks. Such research could help clarify whether cognitive impairments arise from focal lesions or network disruptions and help us better understand the underlying mechanisms.

Another important question is how to best treat cognitive impairment once it has been identified. Young stroke patients report that rehabilitation programs are not adapted to their age and often express frustration about the invisibility of their cognitive symptoms.[93] This highlights the need for age-tailored cognitive rehabilitation programs in this patient population. Currently, several forms of cognitive rehabilitation exists. Restorative cognitive retraining focuses on behavioral interventions aimed at restoring impaired cognitive function. While these training programs have shown to improve cognitive performance,[99] their generalization to daily functioning is absent or at best limited.[100] Another approach, compensatory strategy training, teaches individuals how to compensate for cognitive impairments in daily activities. However, randomized controlled trials specifically targeting young stroke individuals are lacking. Future research should explore the effectiveness of different cognitive rehabilitation approaches, including

their timing, and intensity— ensuring that treatment strategies align the real-world needs of young stroke survivors.

Besides rehabilitation training, repetitive transcranial magnetic stimulation (rTMS) is an example of a treatment that might be effective in improving cognitive functioning in young ischemic stroke patients. This is a noninvasive brain stimulation technique in which neuronal networks are stimulated by a pulsed magnetic field. There are several small rTMS studies, mostly in older adults with stroke, that show potential benefit on cognitive outcomes.[108] However, rTMS is currently not recommended for treatment of post-stroke cognitive impairment in young adults, due to limited evidence supporting the use of rTMS in stroke rehabilitation. Future studies, specifically in young stroke patients are needed to investigate whether rTMS is effective in improving cognitive performance and functional outcome.

Finally, I believe it is essential to involve young stroke patients and their caregivers themselves more actively in future research. It is important to understand their needs and identify areas in which they would like to see improvements.

Concluding remarks

This thesis underscores the ongoing relevance of research into the prognosis of ischemic stroke in young patients. I demonstrated that cognitive impairment after stroke in young adults is prevalent, however, predicting its individual presence and longitudinal course remains challenging. This work highlights the need to develop personalized treatments that optimize outcomes for young stroke survivors with cognitive impairment.

Chapter 10

Nederlandse samenvatting | Dutch summary

Een beroerte is een verzamelnaam voor een herseninfarct, een transiënte ischemische aanval (TIA) en een hersenbloeding. Bij een herseninfarct en een TIA sluit een stolsel een bloedvat in de hersenen af. Bij een hersenbloeding scheurt een bloedvat in de hersenen. Ongeveer 10–15% van alle beroertes treft volwassenen tussen de 18 en 50 jaar. Dit komt wereldwijd neer op circa 2 miljoen jonge mensen per jaar met een beroerte. Een beroerte op jonge leeftijd kan ingrijpende en blijvende gevolgen hebben.

Een belangrijk gevolg van een beroerte is het optreden van cognitieve stoornissen, zoals problemen met de snelheid van informatieverwerking, taal of het geheugen. Deze stoornissen hebben vaak een grote impact op het dagelijks functioneren, sociale relaties, de kwaliteit van leven en het vermogen om terug te keren naar werk, zelfs als het lichamelijk herstel goed verloopt. De meeste jonge mensen met een beroerte zitten midden in het leven, met een intensief sociaal bestaan, een jong gezin en een drukke carrière. Toch is er nog relatief weinig onderzoek gedaan naar cognitieve stoornissen na een beroerte op jonge leeftijd.

Dit proefschrift bestaat uit één overzichtsartikel en vijf hoofdstukken met originele onderzoeksresultaten. De hoofdstukken zijn gebaseerd op de ODYSSEY-studie: een Nederlands onderzoek naar de risicofactoren en prognose van 1492 patiënten van 18 tot 49 jaar met een eerste beroerte, waarbij bij alle deelnemers de beroerte werd bevestigd met beeldvorming van de hersenen. De patiënten werden tussen 2013 en 2021 geïncludeerd in 17 ziekenhuizen verspreid over Nederland. In dit proefschrift werden uitsluitend patiënten met een herseninfarct geïncludeerd.

In **Deel II** onderzocht ik hoe vaak cognitieve stoornissen voorkomen bij jonge mensen na een herseninfarct en hoe deze zich in de tijd ontwikkelen.

In **Hoofdstuk 3** keek ik naar het voorkomen van cognitieve stoornissen in de eerste maanden na een herseninfarct, bij patiënten met én zonder lichamelijke klachten 24 uur na het ontstaan van symptomen. Ik onderzocht ook welke factoren samenhangen met het hebben van een ernstige vasculaire cognitieve stoornis- dat wil zeggen: een cognitieve stoornis veroorzaakt door schade aan de bloedvaten in de hersenen, gekenmerkt door een zeer slechte score op één of meer cognitieve domeinen. Daarnaast bekeek ik hoe vaak patiënten zelf cognitieve klachten rapporteerden, en of dit overeenkwam met de resultaten van de cognitieve testen. We voerden cognitieve testen uit bij 598 patiënten binnen zes maanden na hun herseninfarct. De testen besloegen zeven domeinen: episodisch geheugen, verwerkingssnelheid, visueel-ruimtelijke vaardigheden, executieve functies (zoals

plannen en schakelen), visueel neglect (verminderde aandacht voor één kant van de ruimte), taal, en aandacht/werkgeheugen. Ik vond dat een groot deel van de patiënten slechter scoorde dan gezonde mensen op meerdere cognitieve domeinen, zelfs als zij volledig hersteld waren van hun lichamelijke uitvalsverschijnselen. Cognitieve stoornissen kwamen vaak voor, tot bij 37% van de patiënten, in vijf domeinen. Patiënten met een ernstige vasculaire cognitieve stoornis hadden vaker een ernstiger herseninfarct, een infarct in de linker frontaalkwab, of een lager opleidingsniveau dan patiënten zonder een ernstige vasculaire cognitieve stoornis. Ongeveer twee derde van de patiënten gaf aan geheugen- of executieve klachten te ervaren, maar deze subjectieve klachten hingen slechts zwak samen met de objectieve testresultaten.

Belangrijkste conclusie: Cognitieve stoornissen en subjectieve cognitieve klachten komen vaak voor in de eerste maanden na een herseninfarct op jonge leeftijd, zelfs bij patiënten die lichamelijk goed hersteld zijn.

In **Hoofdstuk 4** keek ik naar het verdere beloop van het cognitief functioneren in het eerste jaar na het herseninfarct. In totaal ondergingen 393 patiënten zowel binnen zes maanden als na een jaar na hun herseninfarct cognitieve testen. Bij meer dan de helft van de patiënten trad er geen cognitieve verandering op. Ongeveer 20% liet cognitieve verbetering zien, en bij 10% verslechterde het cognitief functioneren. Bij patiënten met een cognitieve stoornis op het eerste meetmoment, herstelden de domeinen verwerkingssnelheid, visueel-ruimtelijke vaardigheden en executief functioneren het vaakst (bij 20–40% van de patiënten). Het bleek echter niet mogelijk om per patiënt te voorspellen wie zou herstellen.

Belangrijkste conclusie: Bij de meeste patiënten verandert het cognitief functioneren niet na de eerste maanden na een herseninfarct op jonge leeftijd. Echter, bij ongeveer 20% treedt cognitieve verbetering op, terwijl bij 10% de cognitie achteruitgaat.

In **Deel III** onderzocht ik de mogelijke onderliggende mechanismen van cognitieve stoornissen, met behulp van MRI-scans van de hersenen.

In **Hoofdstuk 5** onderzocht ik de rol van de locatie van het herseninfarct. Eerder onderzoek heeft aangetoond dat infarcten op bepaalde plekken in de hersenen eerder tot cognitieve klachten leiden. Toch ontbrak tot nu toe een volledig overzicht van deze locaties bij jonge mensen. In dit onderzoek analyseerde ik de MRI-scans van de hersenen van 522 patiënten. Daaruit bleek dat infarcten op verschillende

locaties in de hersenen geassocieerd waren met slechtere prestaties in verschillende cognitieve domeinen. Opvallend was dat ook infarcten in de kleine hersenen, een gebied dat vaak over het hoofd wordt gezien in de context van cognitieve stoornissen na een beroerte, bijdroegen aan slechter cognitief functioneren. Dit kan helpen verklaren waarom mensen met een infarct op verschillende plekken toch allemaal cognitieve stoornissen kunnen hebben.

> *Belangrijkste conclusie:* Infarcten op meerdere plaatsen in de hersenen, ook in de kleine hersenen, hangen samen met slechter cognitief functioneren in meerdere domeinen. Dit kan verklaren waarom patiënten met verschillende infarctlocaties allemaal cognitieve stoornissen hebben.

In **Hoofdstuk 6** onderzocht ik hoe een herseninfarct de witte stof beïnvloedt – de verbindingsbanen in de hersenen. Ik keek daarbij ook of de integriteit van de witte stof buiten het infarctgebied samenhangt met het cognitief functioneren. Voor dit onderzoek analyseerde ik MRI-scans en cognitieve testen van 66 patiënten binnen zes maanden na hun herseninfarct. Met behulp van Diffusion Tensor Imaging, een geavanceerde MRI-techniek, zag ik een verminderde integriteit van de witte stof buiten het infarct. Deze veranderingen in de integriteit van de witte stof verminderden naarmate de afstand tot het infarct groter werd. Vooral in de hersenhelft waar het herseninfarct plaats vond was de integriteit van de witte stof verminderd. Dit hing samen met slechtere prestaties op de cognitieve testen, met name op het gebied van verwerkingssnelheid.

> *Belangrijkste conclusie:* Al in de eerste maanden na een herseninfarct bij jonge mensen is er een verminderde integriteit van de witte stof buiten het infarctgebied, vooral in de hersenhelft waar het herseninfarct zich bevindt. Deze verminderde integriteit kan bijdragen aan cognitieve stoornissen.

In **Deel IV** keek ik naar de gevolgen van cognitieve stoornissen voor de terugkeer naar werk.

In **Hoofdstuk 7** analyseerde ik de relatie tussen het cognitief functioneren in de eerste maanden na het infarct en de terugkeer naar werk. Bij patiënten die gedurende de follow-up tenminste eenmaal terugkeerden naar werk, keek ik ook of ze dit werk konden behouden en welke factoren daarmee samen hingen. Van de 525 patiënten keerde 81% gedurende de mediane follow-up van zes jaar ten minste één keer terug naar werk. Toch bleek dat 15% van de patiënten die terug keerden naar werk het werk niet kon volhouden. Mensen met verlaagde verwerkingssnelheid

of een ernstige vasculaire cognitieve stoornis hadden tweemaal zoveel kans om aan het einde van de follow-up werkloos te zijn. Deze associatie bleef bestaan, ook na correctie voor demografische en klinische factoren, evenals voor depressie en vermoeidheid. Cognitieve stoornissen waren niet geassocieerd met het onvermogen om werk te behouden, nadat men eenmaal was teruggekeerd.

Belangrijkste conclusie: Bij jonge mensen na een herseninfarct zijn een ernstige vasculaire cognitieve stoornis en een verlaagde verwerkingssnelheid geassocieerd met werkloosheid.

Appendices

Research data management

Ethics and privacy

Studies in this thesis, using data from the Observational Dutch Young Symptomatic StrokE studY" (ODYSSEY) study, are based on the results of research with human participants. Studies were conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). The recognized Medical Ethics Review Committee 'METC Oost-Nederland' has given approval to conduct data for the ODYSSEY study (file number: NL41531.091.12). The institutional ethical review committee CMO Radboudumc, Nijmegen, the Netherlands has given approval to conduct this study (CMO Radboudumc dossier number: 2013-010).

The privacy of the participants in these studies was warranted by the use of pseudonymization. The pseudonymization key was stored on a secured network drive that was only accessible to members of the project who needed access to it because of their role within the project.

We obtained written informed consent from all participants used for the studies in this thesis. If the patient was unable to provide informed consent, consent was provided by the patient's legal representative. The consent covers sharing data to the researchers during the course of the study.

Data collection and storage

Data collection for the ODYSSEY study started in 2013, with ongoing collection of follow-up data. Paper (hardcopy) data were stored at the neurology department of the Radboudumc. Data was stored in the online data management system Castor EDC. Clinical data (e.g. Castor exports) is archived on a Radboud server. Imaging data is archived on a Radboudumc server and in a project folder of the storage of the Donders Centre for Cognitive Neuroimaging (DCCN). Raw data from patients are archived in a Data Acquisition Collection (DAC) with closed access in the Radboud Data Repository. DOI: https://doi.org/10.34973/r4t5-3d49.

Data sharing according to the FAIR principles

Findable and Accessible

Data are stored in the repository: 'Cognitive impairment after stroke in young adults'. DOI: https://doi.org/10.34973/r4t5-3d49. Metadata describe the data in line with the metadata standard of the Radboud Data Repository. The Radboudumc is legal owner of the data. All published studies for this thesis are published open access.

Interoperable and Reusable

Documentation (codebook) was added to the data sets to make the data interpretable. We used interoperable file formats where possible. The data were stored in the following file formats: .xlsx (Microsoft Office Excel), .R (RStudio, R Project) and .RData (RStudio, R Workspace).

Data in this thesis will be archived for 15 years in a DAC with closed access of the Radboud Data Repository. The PI's Frank-Erik de Leeuw and Anil Man Tuladhar are responsible for the DAC.

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Gelukkig zijn er al veel mooie stukken uit de data geschreven, en er zullen er vast nog vele volgen. Het was daarnaast ook ontzettend leuk om met jullie samen te werken. Vrijdagavonden MRI scans maken in het Radboud maken met Esther, onder het genot van chocolade, gebracht door Anil. Pizza en wijn in een hotelkamer met Jamie in Rotterdam. Kletsen over werk, kinderen en het leven met Merel, die naast een topneuroloog en onderzoeker ook een fantastische fotograaf is.

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About the author

Mijntje Schellekens was born on October 15th 1992 in Boxtel, the Netherlands. She graduated cum laude from the Jacob-Roelandlyceum Boxtel in 2010 and started medical school that same year at the Radboud University Nijmegen. In 2016, she performed a research internship at the Department of Neurology of the Radboud university medical Center under supervision of Prof. dr. Frank-Erik de Leeuw. She investigated the long-term risk of recurrent ischemic events in young stroke patients with a hypercoagulable state.

After obtaining her medical degree in 2017 (cum laude), Mijntje started working as a neurology resident at the Radboud university medical center under the guidance of Dr. Bart Post and Prof. dr. Karin Klijn. During her residency program, she started a PhD project in 2020 on cognitive impairment after stroke in young adults. The results of her PhD research, conducted under the supervision of Prof. Dr. Frank-Erik de Leeuw and Dr. Anil M. Tuladhar, are described in this thesis and were presented at international stroke conferences.

In addition to being a doctor and researcher, Mijntje tries to be a dedicated mother of two young children, a loving partner, a true family person, a sociable friend, and a passionate athlete.

Portfolio

Courses and workshops	Organizer	Year
Introduction Day	Donders Graduate School	2020
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	NFU BROK Academie	2020
Statistics for PhDs by using SPSS	Radboud University	2021
Statistics for Clinical Researchers	Radboudumc	2023
Presenteren & Promoveren	Spies & Spreken	2023
Scientific Integrity Course	Donders Graduate School	2025

Conferences	Role	Year
European Stroke Organisation Conference, Lyon	Presentation	2022
European Stroke Organisation Conference, Munich	Poster Presentation	2023
European Stroke Organisation Conference, Basel	Presentation	2024
European Stroke Organisation Conference, Helsinki	Presentation	2025
European Stroke Organisation Conference, Helsinki	Poster	2025

Project supervision	Duration	Year
R. Springer	3 months	2022
D. van Lingen	3 months	2022
M. Wijnands	6 months	2023
A. Papounidou	6 months	2023

List of publications

Publication in this thesis

1. **Schellekens MM**, Boot EM, Verhoeven JI, Ekker MS, van Alebeek ME, Brouwers PJ, Arntz RM, van Dijk GW, Gons RA, van Uden IW, den Heijer T, de Kort PL, de Laat KF, van Norden A, Vermeer SE, van Zagten MS, van Oostenbrugge RJ, Wermer MJ, Nederkoorn PJ, van Rooij FG, van den Wijngaard IR, de Leeuw FE, Kessels RP, Tuladhar AM. Subacute cognitive impairment after first-ever transient ischemic attack or ischemic stroke in young adults: The ODYSSEY study. Eur Stroke J. 2023 Mar;8(1):283-293. Epub 2022 Oct 31.
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1. **Schellekens MMI**, Li H, Wijnands M, Papounidou A, Boot EM, Verhoeven JI, Ekker MS, van Alebeek ME, Brouwers PJAM, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, van Tuijl JH, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, van Rooij FG, van den Wijngaard IR, de Kort PLM, Piai V, de Leeuw FE, Kessels RPC, Tuladhar AM. Lesion locations are associated with cognitive impairment after ischemic stroke in young adults.
2. **Schellekens MMI***, Li H*, Piai V, PhD, Kessels RPC, Tuladhar AM, de Leeuw FE. Understanding cognitive performance after stroke at young age.

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1. **Schellekens MMI**, van Alebeek ME, Arntz RM, Synhaeve NE, Maaijwee NAMM, Schoonderwaldt HC, van der Vlugt MJ, van Dijk EJ, Rutten-Jacobs LCA, de Leeuw FE. Prothrombotic factors do not increase the risk of recurrent ischemic events after cryptogenic stroke at young age: the FUTURE study. J Thromb Thrombolysis. 2018 May;45(4):504-511.
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* Shared first authorship

Dissertations of the cerebrovascular diseases research group

- Liselore Snaphaan. Epidemiology of post stroke behavioral consequences. Radboud University Nijmegen, 12 March 2010
- Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, 29 November 2011
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- Renate M. Arntz. The long-term risk of vascular disease and epilepsy after stroke in young adults. Radboud University Nijmegen, 16 February 2017
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