Nieuwe technologie
mogelijk maken

Open Technologieprogramma

Project Title:

“A comprehensive prediction machine for long-term outcome after stroke”

Acronym: PrOS (Predicting Outcome of Stroke)

PrOS is offering clinicians a tool to predict outcome and stroke patients an opportunity to improve their quality of life

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1.3 Title

A comprehensive prediction machine for long-term outcome after stroke

1.4 Keywords

Stroke, Prognosis, Automated lesion detection, Long-term outcome, Rehabilitation, Decision tree added diagnosis, decision reliability estimation.

2. Summary

2.1 Research Summary

Stroke refers to a sudden incident (bleeding or blockage) in the blood circulation of the brain, resulting in nerve cell death and subsequent loss of neurological function. About 16 million new strokes occur per annum worldwide, and it is estimated that by 2030 this will be 23 million. In the Netherlands, every year more than 45,000 people suffer a first-ever stroke. About one-third of the patients die and a substantial number of survivors suffer long-term adverse effects. Stroke may cause functional, cognitive and emotional impairments. The true burden of stroke is the life long struggle to cope with these deficits, affecting patients, their families and their social environment. In addition to the personal and social costs, economic costs are also considerable (direct and indirect costs of stroke in 2010 were estimated at €63 billion in Europe and at $74 billion in the USA). Unfortunately, most impairments, especially cognitive and emotional disturbances, go undetected in the acute phase and are not addressed until they re-appear as complaints in the chronic phase.

Previous research of our group has yielded a battery of tests (the Utrecht Screening of COGnitive function, USCOG) that has shown a strong relationship between test and stroke outcome and has made it clear that it is possible to perform meaningful diagnostics in an early stage (<10 days).

The aim of this project is to develop a quantitative model for predicting stroke outcome.

For building this model we will extend a large database that is currently being constructed which combines detailed measurements of both **behavior** and **MRI** of patients who recently had a stroke, with a follow-up study to document the long-term outcome. Advanced use of neuroimaging sequences and analysis techniques holds great promise for improving neuroanatomical information regarding brain damage. We will build, utilizing state of the art deep-learning techniques for lesion segmentation, an accurate system for predicting the long-term functional, cognitive and emotional outcome. This comprises proficiency at daily activities, level of mental functioning, such as memory and language and symptoms of depression and agitation symptoms. On the basis of this prediction machine it will become possible to formulate reliable, tailor-made rehabilitation procedures on the basis of information in the sub-acute phase, in a cost-efficient manner. The model has three direct applications, aiming to:

a) provide reliable diagnoses for the long-term outcome of stroke
b) make a prediction of the functional, cognitive and emotional outcome
c) provide an overview of the most informative tests to make a diagnosis.

2.2 Utilisation Summary

Relevance: the utilisation concerns an efficient clinical tool that will significantly increase the precision and objectivity of the long-term prognosis after stroke. The advantages are threefold. First, this tool will reduce the amount of time that neurologists, neuropsychologists and radiologists need to spend on the diagnostic deduction process. The efficient use of clinician's time is achieved through an informed decision tree and automated processing of predictors. Second, this tool will provide a reliable prediction of the functional long-term outcome. Functional outcome refers to the degree that a patient is able to live independently and carry out everyday activities, such as personal hygiene, food preparation, travel, etc. and is usually assessed with standardized checklists or questionnaires. This information is central for clinicians to decide on the referral of stroke patients, such as transfer to a nursing home or a rehabilitation centre, or discharge destination home (with or without day care). Third, this tool will also provide detailed information regarding the long-term emotional and cognitive repercussions. This is important as about half of the patients that are discharged home will later present with problems in everyday life due to cognitive (e.g. memory, attention) or emotional (post-stroke depression) problems. The early diagnosis of cognitive and emotional problems provides a window of opportunity for early remedial action, such as dedicated rehabilitation procedures for memory problems. Early intervention has been shown to be more beneficial than post-hoc treatment after the patient has returned with his or her complaints, and in many cases may prevent the problems from appearing at all.

Implementation: the first-wave target group consists of the stroke units in academic and general hospitals and rehabilitations centres. These can easily be reached by the neurologist involved in this programme via their professional channels. The second wave target group are clinical institutes responsible for the treatment of other patient populations, such as traumatic head injury, brain infections, and brain tumours. This target group will be approached after the success of the prediction machine has been demonstrated in the first wave. As neurologists are in the main also responsible for these patient populations they can be easily contacted.

Approach: the target groups will be reached via professional platforms (scientific meetings, continuous education programmes, journals and books). It is envisaged that the prediction machine will become part of standard clinical

practice. The distal utilisation lies in the substantial societal gain as economic costs are extreme. Direct economic costs for acute health care, rehabilitation and long-term care for stroke patients are substantial and rising. Indirect costs include the employment implications and disability benefits. The majority of stroke survivors will not return to work. Another indicator of the economic cost of the chronic implications of stroke are the illness-related benefits claimed by patients. In a recent study from Finland it was found that stroke patients required a mean of 11 months of stroke-related income benefits. The amount of benefit claimed was, among other factors, related to cognitive impairment and lesion size. Direct and indirect costs of stroke in Europe in 2010 were estimated at 63 billion euros, and in the US, 74 billion dollars.

2.3 Summary STW's website

Stroke refers to a sudden incident (bleeding or blockage) in the blood circulation of the brain, resulting in nerve cell death and subsequent loss of neurological function. In the Netherlands, every year more than 45,000 people suffer a first-ever stroke, resulting in large numbers of patients with ***chronic disabilities***. We propose to build a ***prediction machine***, based on ***clinical*** data and ***advanced neuroimaging*** data that will help clinicians to predict ***long-term outcome*** in an efficient and reliable manner. This is important as about half of the patients that are discharged home will later present with problems in everyday life due to cognitive (e.g. memory, attention) or emotional (post-stroke depression) problems. An early diagnosis provides a window of opportunity for early ***remedial action***, such as dedicated rehabilitation procedures for memory problems.

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4. Scientific description

4.1 Research contents/Introduction

Ischaemic stroke refers to a sudden blockage of the blood circulation in the brain, resulting in nerve cell death and lesion formation in the area with obstructed blood supply and subsequent loss of neurological function (Sacco et al., 2013). In many developed countries, stroke is a leading cause of adult disability, responsible for more quality-adjusted life-years (QALY) than any other disease. In 2005, 16 million new strokes occurred worldwide causing almost six million deaths. Of the 10 million survivors, five million patients and their families and communities were facing permanent disability (Mackay, Mensah, World Health Organization, & Centers for Disease Control and Prevention (U.S.), 2004). By 2030, it is estimated that 23 million new strokes will occur per annum (Mackay, Mensah, World Health Organization, & Centers for Disease Control and Prevention (U.S.), 2004). Improved acute

health care is decreasing stroke-related mortality (Koton et al., 2014), leading to a paradoxical increase in global stroke burden in terms of number of patients and severity of symptoms (Feigin et al., 2015).
The clinical focus of stroke care has traditionally been on the substantial physical disturbances that may occur after stroke, such as loss of functional movement. However, it is now clear that impairments in cognitive (e.g. Kauranen et al, 2014; 2015; Nys et al, 2006, 2007; de Haan et al., 2006) and emotional functioning (e.g. Montage et al., 2007; 2008; Nys et al., 2006) are amongst the most devastating consequences of stroke. This is not only found after large cerebral infarcts and heamorraghes (e.g. Tveiten et al., 2014) but also after minor strokes such as lacunar infarcts (van Zandvoort et al., 2001, 2003, 2005). This is true for older and younger patients (Synhaeve et al., 2015; de Bruijn et al., 2014), and long-term cognitive impairments are common even after initial successful clinical recovery (Jokinen et al, 2015; Kauranen et al., 2013). The decrease in neuropsychological functioning in stroke patients affects the ability to regain the premorbid level of everyday functioning of the patient and quality of life of both patient and caregiver (Zinn et al., 2004; Tatemichi et al., 1994; Ferro et al., 2001). Long-term functional outcome is related to age, clinical indices of severity (e.g. de NIHSS), and radiological data (e.g. Mees et al., 2016; Kauranen, 2015; Nys et al, 2006).

Interventions aiming to improve functioning have been widely developed (Cicerone et al., 2002,2005). These rehabilitation programmes may include cognitive training programmes (e.g. memory training), compensatory strategies (e.g. diary use), and tools to alleviate the impairments (e.g. web-based aids using smart phones). These interventions are important for coping with functional and cognitive limitations and gain a higher level of outcome and quality of life (e.g. Eslinger et al., 2002, and a recent report by Turner-Stokes et al. (2015) in *Cochrane Database of Systematic Reviews*). The majority of first-ever stroke patients are discharged home and are considered ´good stroke survivors´ with the prospect of successful spontaneous recovery. However, research (e.g. Kauranen et al, 2015; Nys et al., 2005; 2006) has demonstrated that in about 50% of these patients outcome is seriously hampered by functional limitations. The major problem of patients with a diagnosis “stroke destination home” is that they are considered to have a ‘good outcome’ and therefore are automatically disqualified from rehabilitation programmes and do not have access to other dedicated clinical services. It has now been shown that stroke patients benefit much more from neuropsychological interventions when this is started in the early phase (3 months post-stroke, Jenkins & Merzenich, 1987; Kleim & Jones, 2008; Musicco et al., 2003; Salter et al., 2006; Chen et al., 2002, 2005).

Our group has shown that neuropsychological assessment is possible in the very early stage (<10 days) after stroke (Van Zandvoort et al., 2005), and developed a test battery (USCOG) that reliably relates with functional outcome (Nys et al., 2005a; 2006). Recent research by other labs has validated this approach (Hurford, Charidimou, Fox, Cipolotti & Werring, 2013; Beaudoin, Fournier, Julien-Caron, Moleski, Simard, Mercier & Desrosiers, 2013; Jokinen, Melkas, Ylikoski, Pohjasvaara, Kaste, Erkinjuntti & Hietanen, 2015).

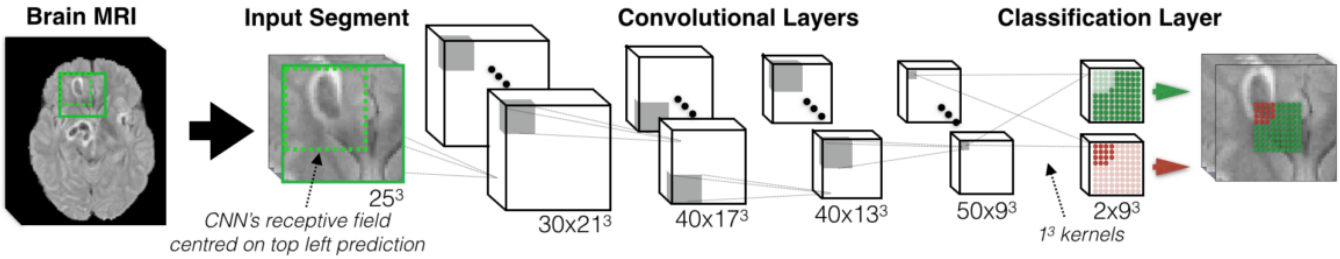

Fig 2. Overview of pipeline for automatic lesion segmentation using deep learning.

Magnetic Resonance Imaging (MRI) has proven to be a powerful clinical diagnostic tool for imaging stroke. The formation of lesions can be identified in an early stage after manifestation of the disease. Radiological information thus has become an important predictor for outcome (e.g. Gale and Pearson, 2012; Mandeville et al., 2016). Clear correlations between lesions data, notably lesion size, have been reported with functional outcome (e.g. Nys et al, 2006), with long-term neuropsychological outcome (e.g. Wong et al., 2015), and with income supplements after Stroke (e.g. Kauranen et al., 2015). Dijkhuizen et al. (2014) have recently argued that disrupted connectivity as assessed by resting state MR predicts may predict long-term outcome.Lesions can be automatically segmented using machine learning techniques. In the context of stroke, deep learning has shown to be a game changer in automatically segmenting lesions (see Fig 2) that appear highly different in size and structure (Kamnitsas et al., 2016). We will employ and extend this methodology.

The goal of the current project is to build a clinical tool for predicting functional long-term output based on imaging and behavioural data. For this we will use a database of about 1000 stroke patients that we are acquiring in the context of an ERC advanced project. These patients have completed an extended version of our original USCOG battery. Furthermore, they have undergone extensive MRI recordings which will be used for deep-learning

based lesion segmentation. These separate sources of information will be used to generate a model, using 60% of the data to make a model to predict the health outcome of the patient. This efficiency of this model will be evaluated using the remaining 40% of the data.
The final product will be an integrated prediction machine that uses imaging and behavioral data as input and a probabilistic prognosis of the functional long-term outcome as output. This will be done by generating a decision-tree that guides the clinician through the necessary diagnostic steps in order to reach a reliable estimate of the long-term emotional, physical and cognitive status with appropriate suggestions for treatment using the minimum of diagnostic steps. At each step of the decision tree, the machine will provide a predicted outcome in terms of physical, cognitive and emotional impairments and an indication of the reliability of these predictions. In addition, the algorithm will advise which additional data (more extensive testing or imaging) will increase the precision of the diagnosis and its reliability, thereby optimising both the costs and time expenditure of the diagnostic process. The approach will have three major repercussions on clinical practice:

1) It will provide clinicians with much more specific clinically relevant individual data allowing the tailoring of dedicated training programs.
2) It will facilitate fast-track rehabilitation, as the training programs can be applied immediately and early intervention has been shown to be more effective.
3) It will improve the cost effectiveness of the diagnostic process.

4.2 Existing infrastructure

The proposed study is embedded in the ERC funded programme “Functional Architecture of the Brain for Vision” of the main applicant, which provides the baseline information. In this programme, we are investigating a large cohort of stroke patients (N ~1000) and matched controls (N ~ 200). Stroke patients were eligible if they had either ischemic stroke or primary intracerebral hemorrhage. Data available from these patients include lesion characteristics based on extensive MRI recordings, the outcomes of the routine neurological and a neuropsychological assessment (USCOG) developed by us (Nys et al., 2005a) consisting of different behavioural tasks covering the domains of language, memory, visuo-spatial perception, praxis, emotion, and intellectual and executive abilities (see Box 1).

Patients are currently being included from the AMC, OLVG-O & OLVG-W (Amsterdam), UMCU & Diaconessen Ziekenhuis (Utrecht), UMCG (Groningen) and the UMC Radboud en Pantein ziekenhuis (Nijmegen en Boxmeer) and testing in the sub-acute phase is being carried out by the PhD students and assistants who are employed by the advanced ERC grant.

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4.3 Time plan and division of tasks

The project can be construed of four work packages along different research lines:

WP 1: Follow-up tests and determination of outcome

Within this work-package the patients that participated in the ERC-FAB4 project will be contacted. The inclusion of the ERC program runs from the beginning of 2016 to 2019. We aim to see patients after 1 year for a follow-up evaluation, i.e. from the beginning of 2017. Based on our experience, we are confident that we will be able to include 50% of the original population (Patients are excluded if a second stroke occurs in the period between the first examination and the follow-up). This results in a group of 600 stroke patients for this study. This also means that follow-up tests will be started at the beginning of 2017, originally by the PhD students of the ERC program. A PhD will be hired who ios responsible for completing the follow-up tests up to Q4 of 2020. At follow-up, the PhD will either make an appointment to see the patient in one of the participating clinical centres or, if feasible, visit the patient at home. The assessment will involve measures for the four outcome parameters, i.e. functional outcome, emotional well-being, caregiver well-being, insight, and cognitive functioning. The outcome measures that will be obtained are in the functional and the cognitive domain (see table 1) and will take 60 ~ 70

Domain	Test
Functional outcome	Modified Ranking Scale & Frenchay Index (FAI)
Emotional Well-being	Becks Depression Inventory (BDI)
Caregiver Well-being	Sense of Competence Questionnaire (SCQ)
Insight	De Awareness Questionnaire (AQ)
Cognitive Functioning	USCOG

Table 1. Outcome measures collected at follow up.

minutes to complete. To ensure compliance an on-site visit will be required which will be executed using specially trained master students in clinical neuropsychology. This project will be supervised by Martine van Zandvoort, Jaap Kappelle and Edward de Haan.

WP 2: Lesion characterization

The lesion characterization line will be responsible for the automatic segmentation of the lesions (Q3 2017 until Q4 2019). The PhD working in this research line will first start on implementing the state of the art of machine learning on lesion segmentation, in collaboration with the team of Nico-Lab. Currently automatic lesion analysis is based on training samples that use approximately 60 subjects. The high quality and high number of subjects that this ERC project is providing will be a potential game changer in training automatic lesion segmentation algorithms and the impact of having a large N and the potential importance of high quality MRI recordings will be the target of the first paper from this project line (Q2-Q4 2018). This will also result in a trained lesion detection algorithm of which the IP will reside with Nico-Lab.

Box 1:

Physical and demographic data: Demographic factors include age (years), level of education (scored with 7 categories ranging from 1 = did not finish primary school to 7 = university degree (Hochstenbach, Mulder, van Limbeek, Donders, Schoonderwaldt, 1998), and sex. Vascular risk factors comprised previously diagnosed diabetes mellitus, hypertension, hypercholesterolemia TIA, smoking during the last 5 years, and alcohol consumption of more than 2 units per day. Factors associated with the patients' medical status on admission were body temperature > 38°C in the first week during hospital stay, admission glucose level, total serum cholesterol level at admission, systolic and diastolic blood pressure, stroke severity (assessed by means of the NIH Stroke Scale [NIHSS] (Brott, Adams, Olinger et al., 1989), and categorized as severe if NIHSS > 7 (DeGraba, Hallenbeck, Pettigrew, Dutka & Kelly, 1999), functional dependence (assessed by means of the modified Barthel Index [MBI] (Mahoney & Barthel, 1965), and categorized as present if MBI < 19 (Weimar, Ziegler, Amberger, et al., 2004), and weakness of either arm or leg (categorized as present if NIHSS items for either arm or leg > 1).

Neuropsychological assessment: This consists of a number of pen-and-paper and computer-based tasks. The constituent parts are derived from the 'proven means' as demonstrated in our own and others' studies. The tool will include a short semi-structured interview and standardized neuropsychological tasks covering seven major cognitive domains (Nys et al., 2005a; van Zandvoort et al., 2005); Reasoning: WAIS similarities, Raven Advanced Progressive Matrices – Short Form; Language : Boston Naming Task –Short Form, Tokentest – Short Form; Verbal Memory : Digit span, Rey Auditory Verbal Learning Task; Visual Memory : Corsi block span, Rey-Osterrieth Complex Figure – delayed Recall; Visual Perception and Construction : Benton Judgement of Line, Benton Facial Recognition Task, Rey-Osterrieth Complex Figure – copy; Executive Functioning: Verbal Fluency (letter), Brixton Visual Spatial Anticipation Task, The Every Day Attention: Visual Elevator; Neglect: Star cancellation. We will construct a testing procedure that is (a) standardised and economical, and (b) versatile in being able to cope with the diverse clinical pictures after stroke and the demands set by the problems of assessment in the subacute phase post-stroke. We will develop computer-based testing procedures when appropriate and develop automated scoring and data analyses procedures. This facilitates fast and standardised testing. Our group has extensive experience in developing automated testing procedures (e.g. De Haan et al., 1995; Kessels et al, 1999; 2000).

MRI Imaging data: T1, T2*, FLAIR and DWI

Within the ERC cohort we are both recording traditional FLAIR MRI recordings and measurements that provide modern 'synthetic' contrasts. Synesthetic contrast has, in theory, a sharper differentiation between T1 and T2* signals and should result in images that are more stable over different recording sites. During Q1-Q3 2019 the lesion characterization line will focus on comparing these different types of recordings by training automatic lesion detection algorithms either with FLAIR images or synthetic contrast images. Differences in the quality of FLAIR vs. synthetic contrast images can be evaluated by the performance of the differently trained lesion detection algorithms. This research line will also result in either a specialized exam-card for the Philips MRI scanning environment and/or tools within the Philips Analysis portal to measure and calculate synthetic MRI images. The IP of these latter steps will reside with Philips.

In the second half of this research line we will focus on clustering lesion images on the basis of these behavioral outcomes, which patterns of lesions correlate with specific behavioral outcomes. This will yield an atlas that can be used for an initial estimation of the outcome zone of a specific lesion on the basis of an MRI recording. During Q1 to Q3 of 2020 we will report on the initial taxonomy of this clustering and generate an atlas of this clustering than can be included in the Philips Analysis portal. Finally, we will report on how well this atlas predicts the functional outcome of new patients (Q4 2020 to Q2 2021). This project will be supervised by Matthan Caan & Edward de Haan.

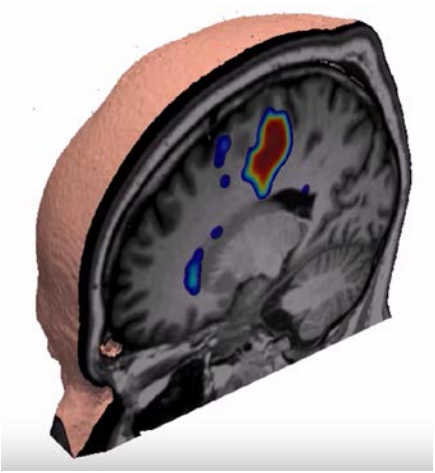


Fig 1. Result of automatic lesion detection by DeepMedic, the current state of the art in deep learning lesion segmentation.

WP 3: Outcome modeling

With respect to the medical and neuropsychological data the starting point of the outcome modeling is the logistic regression analyses of our original studies (Nys et al., 2005, 2006). We will use the odd-ratios for identifying the most promising candidate variables for predicting outcome. As these odd-ratio are informative for a limited set of outcome measures, we will need to identify candidate predictor variables for the other outcome measures (e.g. emotional wellbeing, caregiver wellbeing, insight) based on the literature. The predictive power of MR measures will need to be developed from scratch. We suggest a two-pronged approach here. First and foremost, we will employ machine learning algorithms to find the most informative imaging parameters for predicting the different outcome measures. In addition, we will use cluster analyses to uncover possible templates of stroke damage and subsequently investigate the predictive power of these templates. Using advanced statistics (regression based with elastic net regularization) we will subsequently assess the predictive power of all the different predictor variables for the different outcome measures in the first batch of patients. These analyses will also take economic variables into account such as the cost of the diagnostic process (e.g. a neuropsychological test for language) and the cost of introducing a new diagnostic tool (it is cheaper to add a variable on the same diagnostic tool (e.g. adding MR resting state after one has done MR lesion segmentation is cheaper that adding a neuropsychological assessment). Finally, the analyses must use a time-line when which information may be accessible. For instance, a number of the medical variables will be known at admission. These data can then used to decide on further diagnostic interventions, such as neurological assessment, neuropsychological testing, MR scanning. At each point on the timeline, the prediction machine will provide a prognosis in terms of the chance to which a certain outcome is expected, the nature of then outcome (i.e. 60% risk of cognitive problems in the language realm), and which variables might increase the precision of the prognosis. These models are subsequently tested on an independent data set obtained from a second batch of patients. This project will be supervised by Steven Scholte, Martine van Zandvoort & Edward de Haan.

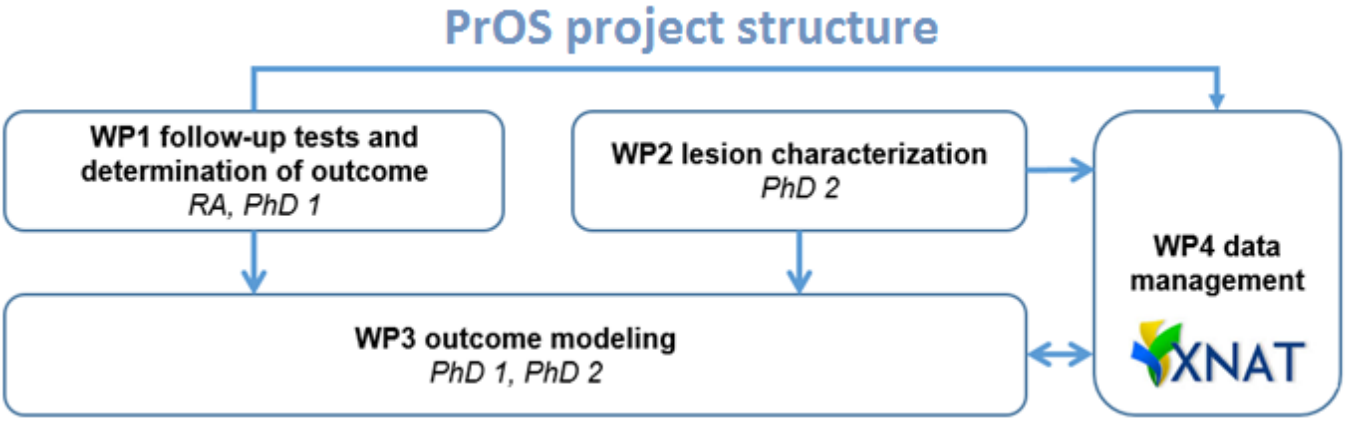
WP 4: Data management

Apart from measuring the outcome it is also of paramount importance to generate a secure, and anonymised database that combines the outcome data with the original test measurements and summary statistics of the lesion segmentations. Next to supervising the measurements of the outcome measures this will be the first responsibility (Q3 2017 to Q1 2018) of the PhD that will be hired to work on this project. Next this PhD student will make a first evaluation of the mutual information amongst the different tests, of both during the original measurements and the outcome measurements. Analyzing the data in this fashion will gently guide the PhD towards outcome modeling and will also provide the input for the first, paper (Q2 and Q3 2018) that will report on the information content of the different tests. After this (Q4 2018) there is enough data (~60%) to build a model regression model that relates the original measurements to the functional (Q2 to Q4 2019) and the neuropsychological outcome (Q1 to Q3 2020). After all follow-ups are completed we will use the last ~40% of the patients to evaluate our success in actually predicting functional and neuropsychological outcomes (Q4 2020) and report on both these effect sizes and the degree to which different tests are informative to establish these diagnoses (Q1 to Q2 2021). This project will be supervised by Steven Scholte, Martine van Zandvoort and Edward de Haan.

Risk and contingency plan

The power calculation is based on the results derived from our earlier studies as described in the pilot *results. The smallest difference in functional outcome for one measure (FAI) between patients with and* without cognitive impairments was 3 $\pm$ 7.6 (Van Zandvoort et al., 2003; Nys, 2005a). For the observed difference with respect to cognitive outcome (compound score) after six months this was 0.83 $\pm$ 0.37. For Quality of Life the minimal difference was 0.64 $\pm$ 0.98. When we apply these values as minimum detectable differences and when we assume to find the same standard deviations, our study will require a group sample size of 50 at a power and significance

level of respectively 0.9, 0.56, and 1 at a 0.05 level of significance (SISA). The current proposal is clearly overpowered for these three measures. However, we aim to investigate many more dependent variables (of which we have no reliable data for a power calculation), and more importantly, we want to develop a prediction machine based on several independent variables. Note that the prediction will be built on the basis of 400 patients and subsequently tested on 200 patients. In our view it is realistic to assume that we will be able to include about half of the patients who participated in the ERC baseline phase. With a total of 600 patients we should have enough power.



5. Utilisation plan

5.1 The problem and the proposed solution

Stroke refers to a sudden incident (bleeding or blockage) in the blood circulation of the brain, resulting in nerve cell death and subsequent loss of neurological function. About 16 million new strokes occur per annum worldwide, and it is estimated that by 2030 this will be 23 million. In the Netherlands, every year more than 45,000 people suffer a first-ever stroke. About one-third of the patients die and a substantial number of survivors suffer long-term adverse effects. Stroke may cause functional, cognitive and emotional impairments. The true burden of stroke is the life long struggle to cope with these deficits, affecting patients, their families and their social environment. In addition to the personal and social costs, economic costs are also considerable (direct and indirect costs of stroke in 2010 were estimated at €63 billion in Europe and at $74 billion in the USA). Unfortunately, most impairments, especially cognitive and emotional disturbances, go undetected in the acute phase and are not addressed until they re-appear as complaints in the chronic phase.

To improve the long-term outcome of stroke, we need to have access to outcome-related information as early and as reliably as possible. The effectiveness of stroke rehabilitation is critically dependent on detailed prognosis and early intervention. The best predictors of long-term outcome, apart from clinical measures such as the NIH stroke-scale, are lesion characteristics and neuropsychological status. The current proposal is meant to build an accurate system for predicting the long-term outcome based on information available in the early phase post-stroke. This prognosis will provide detailed information regarding the long-term functional (proficiency at daily activities), cognitive (level of mental functioning, such as memory, language, etc.) and emotional (depression, agitation, apathy, etc.) outcome and advice about which additional measures need to be collected during the sub-acute phase post-stroke.

The final product will be an integrated prediction machine that uses imaging and behavioural data as input and a probabilistic prognosis of the functional long-term outcome as output. The prognosis will have three major repercussions on clinical practice. First, it will allow clinicians to select dedicated training programmes that are tailor-made for the most important (predicted) impairments. Second, it will facilitate fast-track rehabilitation as the training programmes can be applied immediately. Early intervention has been shown to be more effective. Finally, the program will include a decision-tree that guides the clinician through the necessary diagnostic steps in order to reach a reliable estimate of the long-term emotional, physical and cognitive status with appropriate suggestions for treatment using the minimum of diagnostic steps. At each step of the decision tree, the machine will provide a predicted outcome in terms of physical, cognitive and emotional impairments and an index of the reliability of these predictions. In addition, the algorithm will advice which additional data (more extensive testing or imaging) will increase the precision of the diagnosis and its reliability, thereby optimizing both the costs and time expenditure of the diagnostic process.

The tool will be initially developed on the Philips experimental platform and its implementation which will be available to the core clinical team. During acceptance in routine clinical this will be transformed in a basic application.

5.2 Potential users

Core clinical experts & user committee: The acceptance of our new approach in clinical practice will require deep involvement of the clinical experts in the field. Therefore, we closely collaborate with several leading clinicians, with a strong background in stroke assessment and they will be, for this project, the core clinical experts: Professor Jaap Kappelle (UMCUtrecht; co-applicant), professor Frank Erik de Leeuw (Radboud UMC), dr. Paul Nederkoorn (AMC Amsterdam) and dr. Gert Jan Luijckx (UMCGroningen). The use committee will be extended with representatives from Nico-Lab and Philips. Their contribution will be essential in the adoption of the developed tools in the clinical arena.

Company/Institute	Contact	Full contact details	Company size > or <250 empl.	Attendance user committee yes/no	Support letter yes/no	Contri-bution yes/no
Philips MR Clinical Science Neuroscience BIU ADI MR	Dr. Liesbeth Geerts	Veenpluis 4-6, Building QR-0121, 5684 PC Best, The Netherlands. liesbeth.geerts@philips.com	>	Yes	Yes	Yes
Nico-Lab	Dr. Robert Kuipers, CEO	Amsterdam Health And Technology Center Paasheuvelweg 25, Wing 5D 1105BP Amsterdam, The Netherlands info@nico-lab.com	<	Yes	Yes	Yes
UMCU	Prof. Jaap Kappelle	Universitair Medisch Centrum Utrecht, Heidelberglaan 100, 3584 CX Utrecht. l.kappelle@umcutrecht.nl	>	Yes	No	No
UMCG	Dr. GertJan Luijckx	Universitair Medisch Centrum Groningen, Hanzeplein 1 9713 GZ Groningen. g.j.luijckx@umcg.nl	>	Yes	Yes	No
AMC	Dr. Paul Nederkoorn	Academisch Medisch Centrum Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam. p.j.nederkoorn@amc.uva.nl	>	Yes	Yes	No
UMCR	Prof. Frank Erik de Leeuw	Radboud Universitair Medisch Centrum, Reinier Postlaan 4, 6525 GC Nijmegen. frankerik.deleeuw@radboudumc.nl	>	Yes	Yes	No

Clinicians and Researchers: The PIs and the PhD students will present details of this study, including the prediction machine, at national and international scientific meetings for stroke clinicians and MR imaging experts. Furthermore, to initiate, and further stimulate, the adaption of these tools developed in our research group we will organize a symposium together with the users committee in year 3/4 of the project. MRI vendors, clinicians, insure companies and other companies in our network will be invited for this symposium and we will try to organize this as a satellite to the national meeting of stroke professionals.The direct aim of the satellite conference will be to initiate a second-wave of users, tightly connected to the core clinical group that will allow us to extend the database and keep continuing the quality of the prediction machine.

Commercial users: Philips Medical Instruments and Nico-Lab have expressed a formal interest in the expected products of this programme (see Appendix II). To Philips several key components of this project proposal are relevant for their MR Imaging product offering. First of all, during this project several prominent research sites will collaborate to draft a consensus protocol for stroke imaging using MR. Currently, every MR expertise center more or less optimizes their own protocols – which results in poor between site comparibility of the results and different expectations per site. Optimized consensus protocols, drafted by well-respected members of the MR community, are an elegant way to facilitate and improve the protocol offering on the scanner. Secondly, as part of the “lesion characterization” task during this project advanced segmentation software will be developed for stroke lesion

detection. It's expected that this software – even without the prediction component – will enhance and facilitate stroke reading in clinical practice. Last, but not least, stroke outcome prediction is extremely relevant to complete the stroke imaging portfolio.

Dissemination: The findings of this programme regarding the diagnostic and the rehabilitation tools will be described in scientific articles in international peer-reviewed journals and presented at international scientific conferences and symposia for clinicians. These publications will serve to form the basis for the manuals that will be produced subsequently. Finally, the testing procedures in the sub-acute phase and the prediction machine will be published and marketed commercially.

5.3 Past performance

In a series of clinical studies, we demonstrated that a neuropsychological examination in the early stage after a first ever stroke is both feasible and valid in the majority of the patients (NHS 2000.23) (van Zandvoort et al., 2005; Nys et al., 2006; 2005a&b). More importantly, we found that cognitive impairment in the early stage post-stroke (mean (sd)= 8 (4.5) days) is the most powerful predictor (even beyond medical and demographic predictors) for functional, cognitive and emotional outcome after six months, as well as the well-being of the primary caregivers (van Zandvoort et al., 2005; Nys et al., 2005b) These results were observed in a representative stroke population admitted to a stroke-unit including patients ranging from 1 to 5 on the Modified Rankin Scale. From this sample (n=111) 58% of the patients were considered 'good stroke survivors' and subsequently received @ discharge destination home (DDH) (n=64). However, after six months 1 out of every 2 of these DDH patients experience neuropsychological limitations interfering with their everyday life (instrumental ADL Frenchay Activities Index: R^2 =0.26; p<.0001), as well as with their Quality of Life (Visual Analogue Scale: R^2=0.16; p<.01), the presence of post-stroke depression Montgomery Åsberg Depression Rating Scale: R^2=0.12; p<.01), and their caregivers' well-being (n=66) (Sense of Competence Questionnaire: R^2=0.13; p<.05) all corrected for age (van Zandvoort et al., 2005) Patients with DDH do not meet the criteria for rehabilitation programmes, and interventions aimed to improve their outcome are not readily available to them. In a multicentre trial performed in our group the effectiveness of an 'outreach nursing stroke care' specifically aimed at stroke patients with DDH was assessed (Boter et al, 2004). This programme offered patients and caregivers the opportunity to receive information and reassurance from specialised nurses who used ´supportive listening´ as intervention strategy. Patients were contacted three times by telephone 10 to 14 weeks after the stroke and were paid a visit at home by one of the nurses. Nevertheless, this outreach nursing stroke care did not improve the quality of life of the DDH patients or the well-being of the carers, suggesting that general attention and information is not helpful.

It is envisaged that the prediction tool will also include a facility that suggests specific treatments options. From the abovementioned study in the DDH patients (Nys et al., 2005), we learned that distinct cognitive domains are important for outcome. Functional outcome (p<.0001) and caregivers' well-being (p<.05) are predicted by impairments in executive functioning, whereas quality of life in the DDH patients is predicted by impairments in memory (p<0.001) and language (p<.05). These treatment suggestions are based on existing, evidence-based intervention protocols (e.g. Berg et al., 1991; Cicerone et al., 2002; 2005). Our work has been instrumental in this endeavour. We have devised novel neuropsychological intervention programmes based on proven cognitive rehabilitation techniques (Kessels et al., 2003a&b; Dijkerman et al., 2004; Fasotti et al., 2000; de Haan et al., 2000; Doornhein & de Haan, 1998). In addition, there proven rehabilitation strategies for time-management (Fasotti et al, 2000; Levine et al., 2000), attention (e.g. Harmsen et al., 2004), memory (e.g. Cicerone K. et al. 2002; 2005; Kessels et al., 2003a&b), communication (e.g. Eames et al., 2003; Brouwer et al., 2002; Gupta et al., 2003), tools to enhance emotional coping, and psycho-education (Visser-Meily, 2005).

To connect these lines, at the level of relating outcome to predictive algorithms we have used machine learning we have furthermore developed the actual algorithm that is now considered to be capable of determining whether a depressed patient will respond to electroconvulsive therapy (Van Waarde, Scholte et al., 2015) and an algorithm to make a 0.8+ reliable prediction of whether the person under consideration is dyslectic on the basis of an anatomical recording (Tamboer et al. 2016).

Finally, in terms of managerial and commercial experience, amongst the applicants are a founder of a successful commercial spin-off company (8 fte, double digit growth for 3 years), the previous dean of the faculty of social science, a co-founder of a recently started spin-off company and all are experienced researcher managers.

Edward de Haan Project Coordinator	**Organisation Full name / Department** University of Amsterdam, Department of Psychology.
Role: Together with Steven Scholte, Jaap Kappelle, Martine van Zandvoort and Matthan Caan, Edawrd de Haan has initiated this proposal, and if funded, we will be coordinating the programme together. What brings us together is a drive to develop better models of brain processes, brain imaging, machine learning. The relevant expertise he brings to this programme concerns (1) carrying out basic research within a clinical setting, (2) extensive knowledge of the human brain, (3) the development of new theoretical concepts, (4) research	

management.

Education and Qualifications
1983 Doctoral (MSc) Psychology, University of Groningen, The Netherlands.
1989 PhD Experimental Psychology, University of Lancaster, UK.
2008 Consultant Clinical Neuropsychologist (NL: BIG art 14: KNP)

Appointments
2008 – present Professor of Neuropsychology, University of Amsterdam, NL.
1991 – 2008 Professor of Neuropsychology, University & Academic Hospital Utrecht, NL.
1983 – 1991 Research Fellow, MRC Neuropsych. Unit, Radcliffe Infirmary, Oxford, UK.

Publications: I am a (co)author of over 300 scientific papers, 25 chapters and (co)editor of 4 books. ***My H-index (WoS) is*****: 50** (Google Scholar H-index = 66). Five recent publications are:

Pinto,Y, Neville, DA, Otten, M, Corballis, PM, Lamme, VAF, de Haan, EHF, Foschi, N & Fabri, M. (in press) Split brain: divided perception but undivided consciousness. ***Brain.***

Kessels, RPC, Montagne, B, Hendriks, AW, Perrett, DI & De Haan, EHF (2014) Assessment of perception of morphed facial expressions using the Emotion Recognition Task (ERT): normative data from healthy participants aged 8-75.***Journal of Neuropsychology, 8,***75-93

Schoo, L.A., van Zandvoort, M.J.E. Biessels, G.J., Kappelle, L.J., Postma, A. and De Haan, E.H.F. (2011) The posterior parietal paradox: Why do functional magnetic resonance imaging and lesion studies on episodic memory produce conflicting results? ***Journal of Neuropsychology, 5*****, 15-38.**

De Haan, E.H.F. and Cowey, A. (2011) On the usefulness of what and where. ***Trends in Cognitive Sciences, 15,*** 460-466.

Poljac, E., Montagne, B. and de Haan, E.H. (2011) Reduced recognition of fear and sadness in post-traumatic stress disorder. ***Cortex, 47***, 974-980.

Funding ID: Since his PhD, h has obtained continuous external support for his research. His current research is funded by a NWO Horizon programme grant "*Knowledge and culture"* (€ 2.000.000.00) and an ERC Advanced grant "Functional architecture of the brain for vision" (€ 2.500.000.00).

Major contributions to early careers of excellent researchers: He has supervised 35 PhD students (and served as external examiner of over 60 PhD theses

H.Steven Scholte	**Organisation Full name / Department** University of Amsterdam, Department of Brain & Cognition, Department of Informatics.

Role: Dr Scholte will be responsible for recordings and the reconstruction of the MRI data and the analysis of the BOLD-MRI data. He will co-supervise the development of the prediction algoritmes using machine learning.

Expertise: Dr Scholte has expertise in the areas of functional and anatomical neuro-imaging, mid-level perception and modelling the visual system. He has a master in biology (1998) and psychology (2001) and a PhD in Medical Physics (2003). He worked shortly as a post-doc but obtained an assistant professorship in 2004 and became associate professor in 2009. In 2014 he became head of the imaging centre of the Spinoza Center REC-L.

Publications: He is the author of 65 peer reviewed international papers and has an h-index of 21. Five representative papers of the last 3 years are:

Van Waarde JA, Scholte HS, van Oudheusden LJB, Verwey B, Denys D & van Wingen GA (2014). A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. ***Molecular psychiatry***. AOP.

Ramakrishnan K, Scholte HS, Groen IIA, Smeulders AW, Ghebreab S (2014). Visual dictionaries as intermediate features in the human brain. ***Frontiers in Computational Neuroscience 8***, 168

Visser RM, Scholte HS, Beemsterboer T, Kindt M (2013). Neural pattern similarity predicts long-term fear memory. ***Nature neuroscience 16(4),*** 388-390.

Groen IIA, Ghebreab S, Lamme VAF, Scholte HS (2012). Spatially pooled contrast responses predict neural and perceptual similarity of naturalistic image categories. ***PLoS computational biology 8***, 10.

Groen IIA, Ghebreab S, Prins H, Lamme VAF, Scholte H (2013). From Image Statistics to Scene Gist: Evoked Neural Activity Reveals Transition from Low-Level Natural Image Structure to Scene Category. The

Journal of Neuroscience 33(48), 18814-18824.

Major contributions to early careers of excellent researchers: He was the co-promotor of 8 PhD students and currently supervises and additional 4 PhD students. He has obtained 2,3 mE in subsidies either the primary (1.2 mE) or secondary applicant.

L. Jaap Kappelle MD	**Organisation Full name / Department** University Medical Centre Utrecht, Department of neurology.

Role: Professor Kappelle will be responsible for the selection and recruitment of the stroke patients and will supervise the clinical aspects of the project

Education and Qualifications
1983-8 Resident in neurology, University Medical centre Utrecht, The Netherlands.
1992 Visiting Associate at the University of Iowa, USA
1998 Visiting Associate University of Western Ontario, Canada

Appointments
2000 Professor of Neurology, University Medical centre Utrecht, The Netherlands
1988 Assistant professor of neurology, Utrecht University, The Netherlands

Publications: He is (co)author of over 500 scientific papers, Five recent publications are:
Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol. 2015;14:329-40.
Biesbroek JM, van Zandvoort MJ, Kappelle LJ, Schoo L, Kuijf HJ, Velthuis BK, Biessels GJ, Postma A; Utrecht VCI study group. Distinct anatomical correlates of discriminability and criterion setting in verbal recognition memory revealed by lesion-symptom mapping. Hum Brain Mapp. 2015;36:1292-303.
Biesbroek JM, van Zandvoort MJ, Kuijf HJ, Weaver NA, Kappelle LJ, Vos PC, Velthuis BK, Biessels GJ, Postma A; Utrecht VCI Study Group.. The anatomy of visuospatial construction revealed by lesion-symptom mapping. Neuropsychologia. 2014;62:68-76.
Kant N, van den Berg E, van Zandvoort MJ, Frijns CJ, Kappelle LJ, Postma A. Functional correlates of prospective memory in stroke. Neuropsychologia. 2014;60:77-83.
Heringa SM, Bouvy WH, van den Berg E, Moll AC, Kappelle LJ, Biessels GJ. Associations between retinal microvascular changes and dementia, cognitive functioning, and brain imaging abnormalities: a systematic review. J Cereb Blood Flow Metab. 2013;33:983-95.

Major contributions to early careers of excellent researchers: He has supervised 38 PhD students

Martine van Zandvoort	**Organisation Full name / Department** Utrecht University, Department of Psychology & University Medical Centre Utrecht, Department of Neurology.

Role: Dr van Zandvoort will be responsible for the selection of the cognitive and emotional test and will supervise the neuropsychological assessment.

Education and Qualifications
1996 - MSc.: Experimental Psychology - Universiteit Utrecht.
2001 - Ph.D.: Neuropsychology - Helmholtz Research Institute.
2011 - Consultant *Clinical Neuropsychologist*

Appointments
2003 assistant professor, Utrecht University, The Netherlands
2010 associative professor, Utrecht University, The Netherlands

Publications: She is (co)author of over 150 scientific papers, and her H-index = 24 (WoS). Five recent, relevant publications are:
Boerboom, Wendy, van Zandvoort, Martine J E, van Kooten, Fop, Khajeh, Ladbon, Visser-Meily, Johanna M A, Ribbers, Gerard M. & Heijenbrok-Kal, Majanka H. (2016). Long-term fatigue after perimesencephalic subarachnoid haemorrhage in relation to cognitive functioning, mood and comorbidity. ***Disability and Rehabilitation*****,** in press.
Claessen, Michiel H G, Van Der Ham, Ineke J M & Van Zandvoort, Martine J E (04-05-2015). Computerization of

the standard corsi block-tapping task affects its underlying cognitive concepts - A pilot study. ***Applied Neuropsychology:Adult, 22,*** 180-188.
Huenges Wajer, Irene M C, Cremers, Charlotte H P, van Zandvoort, Martine J E, Vergouwen, Mervyn D I, van der Schaaf, Irene C., Velthuis, Birgitta K., Dankbaar, Jan Willem, Vos, Pieter C., Visser-Meily, Johanna M A & Rinkel, Gabriel J E (2015). CT perfusion on admission and cognitive functioning 3 months after aneurysmal subarachnoid haemorrhage. ***Journal of Neurology, 262,*** 623-628.
Schoo, Linda A., Van Zandvoort, Martine J E, Reijmer, Yael D., Biessels, Geert Jan, Kappelle, L. Jaap & Postma, Albert (12-06-2014). Absolute and relative temporal order memory for performed activities following stroke. ***Journal of Clinical and Experimental Neuropsychology, 36***, 648-658.
van Stralen, H.E., van Zandvoort, M.J.E., Hoppenbrouwers, S.S., Vissers, L.M., Kappelle, L.J. & Dijkerman, H.C. (2014). Affective touch modulates the rubber hand illusion. ***Cognition, 131,*** 147-158.

Major contributions to early careers of excellent researchers: She has (co)supervised over 10 PhD students.

Matthan W.A. Caan	**Organisation Full name / Department** Department of Radiology, Academic Medical Center, University of Amsterdam.

Role: Dr Caan will be responsible for the development of the prediction algorithms using machine learning and the acquisition and reconstruction of the MRI data.

Expertise: Dr Caan is physicist, with an expertise in MRI, neuroimaging and machine learning. He is involved in the spin-off company Nico-lab, a core lab for imaging and analysing stroke data. He earned a PhD in Physics in 2010 from Delft University of Technology (The Netherlands). He is currently assistant professor at the AMC.

Publications: He is the author of 55 peer reviewed international papers and has an h-index of 14. Five representative papers of the last 3 years are:

Van Dalen JW, Scuric EEM, Van Veluw SJ, Caan MWA, Nederveen AJ, Biessels GJ, Van Gool WA, Richard E. Cortical microinfarcts detected in vivo on 3 tesla MRI: Clinical and radiological correlates. Stroke 2015;46:255–257. doi: 10.1161/STROKEAHA.114.007568.
Steenwijk MD, Pouwels PJW, Daams M, van Dalen JW, Caan MW a, Richard E, Barkhof F, Vrenken H. Accurate white matter lesion segmentation by k nearest neighbor classification with tissue type priors (kNN-TTPs). NeuroImage. Clin.
Su T, Wit FWNM, Caan MWA, et al. White matter hyperintensities in relation to cognition in HIV-infected men with sustained suppressed viral load on cART. AIDS 2016:2329–2339.
de Rooij SR, Caan MWA, Swaab DF, Nederveen AJ, Majoie CB, Schwab M, Painter RC, Roseboom TJ, Prenatal famine exposure has sex-specific effects on brain size. BRAIN 2016;139 (8):2136-2142
Van Dalen JW, Caan MWA, van Gool WA, Richard E, Neuropsychiatric symptoms of cholinergic deficiency occur with degradation of the projections from the nucleus basalis of Meynert. BRAIN IMAGING BEHAV 2016

Major contributions to early careers of excellent researchers: He is the co-promotor of 5 PhD students and 1 postdoctoral researcher.

6. Intellectual property

6.1 Contracts

Dr. Scholte has a research agreement with Philips Healthcare on population imaging with MR in psychology. This will provide the research group with premium support for the development of advanced sequences. This research agreement does not obstruct the utilization of the research performed within this project. In the current setup we will base the lesion segmentation algorithm on existing work in the public domain. The IP still needs to be divided amongst the participants.

6.2 Patents

There are a number of patents for the segmentation of lesions (US8155405, US20090097727, US20070031020) and the prediction of stroke outcome (US20070032736, EP20120704430). The stroke outcome patents either use biomarkes (level of endostatin and FasL) or EEG. In none of these methods multiple markers are used in combination and none of the markers used in these methods are included in the current approach. The lesion segmentation patents are on the generic side of the equation. Whether the proposed techniques infringe on the

generic sides (for instance evaluation whether a voxel is part of a lesion on the basis of its neighbors) of these patents is a matter for the judicial process.

The protection of intellectual property for a machine learning application is first and foremost the data used for the model. Given a lack of access to training data it cannot be easily copied. At the same time the model will improve with the addition of more data.

The outcome of this project potentially qualifies for a number of new patents. In that case the research team will contact both STW and the technology transfer office of their own institutions and discuss if the results should be patented.

7. Positioning of the project proposal

7.1 Uniqueness of the proposed project

The project is unique in that it is, to our knowledge, the first to use a database of a substantial size in combination with modern machine learning techniques. Furthermore the database has a diverse set of predictions. Also, the data-base is, in all probability, large enough for both building, and, crucially testing a predictive model.

7.2 Embedding of the proposed project

The proposed study is embedded in the ERC funded programme “Functional Architecture of the Brain for Vision” of the main applicant, which provides the baseline information. In this programme, we are investigating a large cohort of stroke patients. The Netherlands is uniquely positioned for a large-scale cohort study. There are major academic teaching hospitals in relatively close proximity. The four medical centres that participate in this programme (AMC Amsterdam, UMC Utrecht, UMC Groningen and UMC Nijmegen) all have excellent neurological, neuropsychological and neuro-imaging facilities, and there are well established collaborations between the academic medical centres within the framework of the “Parelsnoer” initiative in the areas of dementia (http://www.parelsnoer.org/page/De-Parels/Neurodegeneratieve-hersenziekten) and stroke (http://www.parelsnoer.org/page/De-Parels/Cerebro-vasculair-accident-CVA). This means that it is possible to organize (1) access to a large number of patients, (2) a comprehensive and comparable neurological and neuropsychological clinical assessment, and (3) detailed neuroimaging using the availability of 3T facilities. The expected number of patients to be included is 1200. The testing in the sub-acute phase will be carried out by four PhD students who are employed by the ERC grant and seconded to the four hospitals.

This project is formulated in close collaboration with two commercial companies. Philips Medical is a global multinational technology company and a major producer of medical equipment, such as magnetic resonance imaging. They are very interested in the development of MR applications predicting health related parameters. Nico-Lab is a company that is working at the front-end of designing automated learning algorithms for stroke based on deep-learning, with an interest in extending their IP to stroke lesions measured with MRI.

7.3 Request for support elsewhere

None.

8. Financial planning

8.1 Personnel positions

Position	Category[1] *PhD, Postdoc, NSP, SP, PDEng*	fte	Months	Tariff (zie salaristabel)*	Name (optional)
1	PhD	1	48	€ 191364	Follow-up stroke cohort
1	PhD	1	48	€191364	Lesion segmentation, modelling outcome, machine design
1	PhD	1	48	€191364	Neuropsychologist

[1] (N)SP (non-)scientific personnel; PDEng Professional Doctorate in Engineering

Twp PhDs will be employed by the UvA and one by the UU/UMC.

8.2 Consumables

The patients included in the baseline studies were recruited from all over the Netherlands. Therefore, either the patient, or the neuropsychologist (at home testing), will need to travel in most cases. It is estimated that the travel costs will be on average €50 x 600 = €30,000 for the patients. The 200 control subjects, who need to be retested also need to be reimbursed for their travel: 200 x €50 = €10,000.
Test materials (clinical tests, etc.) is estimated at €6,000.
National travel of the PhDs and PIs is estimated at €5,000.
Total = €51,000.

8.3 Travel abroad

The PhD students and the applicants will present the results of these studies at international conferences for image analyses, such as MICCAI, and at neurological and neuropsychological stroke meetings. Because of the importance of not only sharing the scientific results, but also advertising the usability, we plan to attend a substantial number of meetings. This requires €2,000 per PhD per year (€24,000) plus €1,500 for the PIs per year (€ 6,000).
Total = € 30,000.

8.4 Investments

Testing equipment (2 x laptop) are estimated at €4,000, and a Workstation with GPU for lesion segmentation €6,000.
Total = € 10,000.

8.5 Contribution from users

Philips will provide in-kind support by making our Clinical science keys (CSK's) and our PRIDE platform for post-processing available (valued @ 25.000 EUR/year). Next to this, Philips will contribute in-kind support in protocol optimization and review from various senior individuals from the R&D and clinical science groups of Philips. Furthermore, Philips will take part in the user committee of this project. It is estimated that the total in-kind value of the scientific support (man-hours spend) over the 4 year program is € 5,000.

Nico-lab will provide support in developing a deep learning segmentation algorithm estimated at a value of € 15,000.

8.6 Cost breakdown

Total project costs	€ 785092
Total contribution in cash	€
Total contribution in kind	€ 120,000
Requested from STW (STW-bijdrage)	€ 665092

8.7 Letters of support

Dr. Ir. Liesbeth Geerts	Philips Healthcare
Dr. Robert Kuipers	Nico-Lab
Prof.dr. Pim A. van Gool	AMC, Voorzitter van de Gezondheidsraad
Prof.dr. Louise Gunning-Schepers	UvA, AMC; Oud-voorzitter van de Gezondheidsraad
Prof.dr Frank Erik de Leeuw	Neurologie, Radboud Medisch Centrum
Dr. Gert Jan Luijckx	Neurologie, Universitair Medisch Centrum Groningen
Dr. Paul Nederkoorn	Neurologie, Academisch Medisch Centrum Amsterdam

9. References

9.1 Selection of key publications research group

De Haan, E.H.F*.* and Cowey, A. (2011) On the usefulness of what and where. ***Trends in Cognitive Sciences, 15,*** 460-466.

De Haan, E.H.F., van Zandvoort, M.J.E., Nys, G.M.S. (2009) Neuropsychological sequelea of cerebellar stroke. **Journal of the Neurological Sciences, 283**, 269-269.

Dijkerman, H.C. and **de Haan, E.H.F.** (2007) Somatosensory processes subserving perception and action. ***Behavioral and Brain Sciences, 30***, 189-201***.***

Kessels, R.P.C., Montagne, B., Hendriks, A.W., Perrett, D.I. & **De Haan, E.H.F**. (2014) Assessment of perception of morphed facial expressions using the Emotion Recognition Task (ERT): normative data from healthy participants aged 8-75. ***Journal of Neuropsychology, 8,*** 75-93

Kreijkamp-Kaspers, S. , Kok, L., Grobbee, D.E., **de Haan, E.H.F.,** Aleman' A., Van der Schouw, Y.T. (2004) Soy protein with isoflavones and cognitive function in postmenopausal women; A randomised placebo-controlled double-blind trial. ***Journal of the American Medical Association***, 292, 65-74.

Nys, G.M.S, ***v*an Zandvoort, M.J.E.,** de Kort, P.L.M, Jansen, B.P.W., Van der Worp, H.B., **Kappelle, L.J.** & **de Haan, E.H.F.** (2006) Domain specific cognitive recovery after first-ever stroke. ***Journal of the International Neuropsychological Society, 11***, 795-806.

Nys, G.M.S, **van Zandvoort, M.J.E.,** de Kort, P.L.M, van der Worp, H.B., Jansen, B.P.W., Algra, A**., de Haan, E.H.F., Kappelle, L.J.** (2005) The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. ***Neurology, 64,*** 821-827.

Nys, G.M.S, **van Zandvoort, M.J.E.,** Van der Worp, H.B. and **de Haan, E.H.F***.* (2006) Neuropsychological and neuro-anatomical correlates of motor perseveration in acute stroke. ***Brain, 129,*** 2148-2157.

van Oers, C.A.M.M., Vink, M., **van Zandvoort, M.J.,** van der Worp, H.B., **de Haan, E.H.F. Kappelle, L.J.,** Ramsey, N.F. and Dijkhuizen, R.M. (2010) Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. ***NeuroImage, 49,*** 885-893.

Rouw, R. & **Scholte, H.S.** (2007). Increased structural connectivity in grapheme-color synesthesia. ***Nature neuroscience 10*** (6), 792-797.

Tamboer, P., Vorst, H.C.M., Ghebreab, S. & **Scholte, H.S.** (2016). Machine learning and dyslexia: Classification of individual structural neuro-imaging scans of students with and without dyslexia. ***NeuroImage: Clinical*** 11, 508-514.

Van Waarde, J.A., **Scholte, H.S.**, van Oudheusden, L.J.B., Verwey, B., Denys, D. & Van Wingen, G.A. (2015). A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. ***Molecular psychiatry 20*** (5), 609-614.

9.2 List of publications cited

Berg, I. et al. (1991) Long term effects of memory rehabilitation: a controlled study. *Neuropsychological Rehab*ilitation, 1, 97-111.

Boter, H. (20040 HESTIA Study Group. Multimember randomized controlled trial of an outreach nursing support program for recently discharged stroke patients. Stroke, 35, 2867-72.

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10. Abbreviations and acronyms

mRS	modified Rankin Scale
mBI	modified Barthell Index
BDI	Becks Depression Inventory
AQ	Awareness Questionnaire
FAI	Frenchay Activity Index
NIHSS	National Institute of Health Stroke Scale
USCOG	Utrecht Screening of Cognitive function
QALY	Quality-Adjusted Life-Years
DWI	Diffusion Weighted Imaging
FLAIR	

MRI	Magnetic Resonance Imaging
AMC	Academic Medical Centre
UMC	University Medical Centre
TIA	Transient Ischeamic Attack
ERC	European Research Council