Aus der Neurologischen Klinik und Poliklinik
der Universität Würzburg

Direktor: Professor Dr. med. Jens Volkmann

Relation between cerebral arterio-venous transit time and neuropsychological performance in patients with vascular dementia

Inaugural - Dissertation

zur Erlangung der Doktorwürde der

Medizinischen Fakultät

der Julius-Maximilians-Universität Würzburg

vorgelegt von

Benedikt Schmid

aus Würzburg

.

Würzburg, Juli 2012

Referent: Professor Dr. med. Wolfgang Müllges

Koreferent: Professor Dr. med. László Solymosi

Dekan: Prof. Dr. med. Matthias Frosch

Tag der mündlichen Prüfung: 13. Juni 2013

Der Promovend ist Arzt.

Gewidmet meinen Eltern Irene und Peter

In tiefer Dankbarkeit für ein Leben voller offener Türen

Table of contents

Abbreviations

AD	Alzheimer's disease
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CT	computed tomography
cTT	cerebral arterio-venous transit time
HAWIE	Hamburg-Wechsler intelligence test
ICD-10	International Classification of Diseases, 10th edition
WML	white matter lesions
MMSE	Mini-Mental State Exam
MRI	magnetic resonance imaging
NYHA	New York Heart association
TAP	Test of Attentional Performance
VaD	vascular dementia
VCI	vascular cognitive impairment
WHO	World Health Organization
WMH	white matter hyperintensities

1. Introduction

As populations of the so called developed countries tend to grow older as a result of increasing wealth and ever improving hygienic and medical standards, degenerative disorders progressively gain importance with respects to incidence and prevalence. Among those disorders, dementia in general as well as its various subtypes play an important role. A common feature of most degenerative medical conditions is the extensive irreversibility of their symptoms. This means once the damage is done, effective treatment will mostly be not available. Therefore, early detection of degenerative processes is crucial in order to prevent further damage. Given the fact that the number of (possible) patients is constantly increasing, reliable yet simple and widely available instruments for an early diagnosis are desirable. For one subtype of dementias, the so called vascular dementia (VaD), the measurement of cerebral arterio-venous transit time (cTT) has turned out to be a promising approach to fulfill these requirements in recent years. The study at hand seeks to investigate the relation between changes in cTT on the one hand and actual changes in neuropsychological performance of patients with VaD on the other.

1.1 Terminology and Classification of Dementias

The term Vascular Dementia has been known for more than 100 years [1], but still there is no satisfying definition to describe this condition. “Dementia” is widely associated with the clinical and neuropsychological findings in patients with Alzheimer's Disease (AD). Those patients present a relatively early and severe onset of impairment of episodic memory whereas attention and executive function may remain intact for a long time [2]. However, recent studies have shown that patients suffering from VaD show different patterns of cognitive impairment [3], with an emphasis on “executive/attentional functioning, and visuospatial and perceptual skills" [4]. A large review from 2003 comes to the conclusion that typical VCI (vascular cognitive impairment) symptoms “frequently include early impairment of attention and executive function, with slowing of motor performance and information processing" [4].

According to World Health Organization‘s current version of the ”International Classification of Diseases“ (ICD-10), the different types of dementia are grouped into three major categories: ”Dementia in Alzheimer‘s Disease“ (F00), ”Vascular Dementia“ (F01), and ”Dementia in other diseases classified elsewhere“ (F02) [5]. Sub-diagnoses of F00 are mostly characterized by the dynamics of onset, whereas dementia in sub-diagnoses of F02 is only an additional syndrome on top of an underlying condition, e.g. Creutzfeld-Jakob's disease (F02.1) or Parkinson‘s disease (F02.3). Eventually, vascular dementia is subdivided into several types, partly following the hypothesized etiology of the damage to brain tissue. This approach becomes apparent in the diagnoses ”multi-infarct dementia“ (F01.1) and ”subcortical vascular dementia“ (F01.2). Other sub-diagnoses remain more general, such as ”vascular dementia of acute onset“ (F01.1) or ”other vascular dementia“ (F01.8).

The mentioned traditional understanding of dementia with its focus on AD and the boldly distinct pattern of clinical symptoms makes it hard in many cases to be able to diagnose and treat VaD in early stages of the disease. For example,

the WHO's “International Classification of Diseases” criteria for VaD identify only 25% of “demented patients showing vascular lesions of the computed tomography scan” correctly [6].

Recent publications propose improved and more differentiated classification into subtypes than ICD-10, depending on clinical symptoms, neuroimaging findings and quality of cognitive impairment. The major subgroups are multi-infarct dementia, strategic infarct dementia, and small vessel VaD or subcortical dementia [1]. Another frequently used term would be post-stroke dementia, including all cognitive decline after an event of stroke, thus missing all clinically silent strokes. In order to overcome these shortcomings of terminology and diagnostic criteria, the term Vascular Cognitive Impairment (VCI) has been established in the 1990s [7]. Nowadays, VCI is a concept that embraces demented conditions of all kinds due to cerebrovascular disease. But also by definition non-dementia conditions are included into this terminology, as impairment of cognitive performance can be tarnishing to everyday life activities without meeting the strict criteria for dementia [8]. Eventually, also common cases of so called mixed dementia that show both degenerative and vascular pathologies [9] are represented by VCI. A recent retrospective autopsy study from 2010 showed that with increasing age, simultaneous existence of AD and vascular pathologies becomes more and more likely [10].

The focus of this study is supposed to be on subcortical dementia, so all the other subtypes, regardless whether they are proposed by ICD-10 or other studies, remain unconsidered in this paper.

1.2 Epidemiology

As various the definitions of VaD/VCI are, as diverse are data referring to its epidemiological features. A large Canadian prospective cohort-study estimated the prevalence of VCI (as described above) to two percent in a population of 65+ years, rising up to 13.7 percent in the 85+ years old. The prevalence was nearly equal in men and women. The most prevalent subgroup was VCI without dementia [11]. One other study showed prevalences for VaD of 0.3 percent in a group of 65 to 69 years and 5.2 percent in a group aged 90 years and older [12]. In 1996, a future estimation study predicted an increase of 40 percent of people with cognitive impairment in the UK over the following 30 years [13] .

Although present data do not allow unanimous estimations, dementias will probably be among the most prevalent and cost-intensive diseases in the near future.

1.3 Pathogenesis and Pathophysiology

The process of origination of subcortical VaD is not fully understood. Several mechanisms seem to be able to contribute to the clinical image. Microangiopathic lesions most probably lead to lacunar infarctions in the subgroup of subcortical dementia [4]. Those lesions are also likely to be related to the existence of brain white matter hyperintensities (WMH), whereas WMH have been proposed to origin from a kind of incomplete infarction [14]. The role of those brain White Matter Hyperintensities (WMH) in dementing processes as seen in magnetic resonance imaging remains to some extent unclear. A recent meta-analysis [15] shows a relation between the existence of such

hyperintensities (especially in the periventricular region) and the degree of cognitive impairment in several populations such as patients with AD or general dementia, or in community-based studies with healthy volunteers. Still, “the sole presence of WMLs [white matter lesions] cannot be considered as an index of cognitive deterioration, and nor can WMLs be assumed to be the only change in the brain responsible for cognitive decline in the elderly” [15]. Diseases that most commonly cause small vessel alterations are amongst others atherosclerosis, lipohyalinosis, cerebral amyloid angiopathy [1]. In the presence of diabetes mellitus the relative risk for developing VaD is 2.0, according to a large prospective study [16]. This also supports the theory of an atherosclerotic pathogenesis. More rare causes are genetic disorders, especially cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). In CADASIL, the Notch 3 gene seems to be mutated. This gene is responsible for smooth muscle cell proliferation and differentiation, thus explaining symptoms of migraine, lacunar stroke and dementia [17]. In general, the severity of cognitive impairment seems to be related to the location of lesions more than the total volume of damaged brain tissue [18]. A lesion-symptom mapping study from 2011 examined the connection of the location of WMH in CADASIL patients and their respective cognitive symptoms. It gives strong evidence that at least for the domain of processing speed, the anterior thalamic radiation and the forceps minor might be such critical locations where even small lesions can lead to significant functional damage [19].

2. Aim of the study

Vascular dementia is often diagnosed in stages of the disease where no more effective therapeutical means are available. However, more and more evidence emerges that there are early risk factors which can lead to cognitive impairment in later life. One meta-analysis states that “traditional cardiovascular risk factors such as hypertension, dyslipidemia and diabetes appear to increase the risk of developing dementia in old age“ [20], and more specifically that “older adults with diabetes have approximately double the risk of developing dementia and mild cognitive impairment compared to those who do not have diabetes“ . Moreover, another paper comes to the conclusion that “both high and low blood pressure play a part in the development and progression of cognitive impairment and dementia, depending on age“ [21]. Especially high systolic pressure in middle and old age as well as low diastolic blood pressure in elderly individuals is said to be a risk factor for developing dementia. An additional influencing factor may be high serum cholesterol and low-density lipoproteins [20], although the impact of dyslipidemia seems to be less powerful. One way or the other, all those conditions can only be treated effectively early in life, long before obvious symptoms of cognitive decline arise. Therefore, a reliable instrument which allows an early diagnosis of microvascular alterations is desirable in order to intensify prevention of risk factors or treatment, respectively. Possible instruments are magnetic resonance imaging, neuropsychological tests and measurement of cerebral arterio-venous transit time. The role of these procedures and their interactions shall be investigated in this study. Neuropsychological tests are to be considered the diagnostic gold

standard as they alone allow to directly quantify possible deficits in cognitive performance and even differentiate between the various domains affected. The detection of WMH is a more inaccurate marker. For one, there are various pathologies resulting in the radiological appearance of WMH, for example old infarctions or gliosis, which do not necessarily imply a vascular involvement. In addition to that, the extent of WMH most probably is not highly correlated with the clinical symptoms of the patient, as was mentioned above. Nevertheless, WMH were considered in this study as they are often found in patients with VCI.

Following the concept of a mainly microangiopathic genesis in subcortical dementia, cerebral arterio-venous transit time (cTT) was shown to be a reliable indicator for small vessel damage which may consequently cause cognitive impairment [22]. This study aims to examine the qualitative and, if proven to exist, the quantitative relation of cTT prolongation with the decline of cognitive performance. Therefore detailed neuropsychological assessment covering all major domains of cognition was carried out and cTT was measured in all participants. Moreover, the influence of WML on cognitive decline and its possible relation with cTT alterations shall be investigated. Finally, statistical analysis shall show if cTT is able to predict cognitive impairment sufficiently in order to ease the diagnosis of VCI without the need for complex neuropsychological testing or cost-intensive neuroimaging. Altogether, this proof-of-principle study intends to examine whether cTT measurement is an appropriate procedure to detect early-stage cognitive decline and thus make vascular cognitive impairment better treatable, eventually.

3. Methods

3.1 Time span of investigation and population

All patients included in this study were in-patients on one of the neurological wards of the Würzburg University Hospital any time between August 2009 and December 2010. Regular screening of all MR images taken during that time lead to a further evaluation whether the respective patient fitted the inclusion criteria. Patients were preselected subsequently by random if an diffusion-weighted MRI excluded acute stroke lesions but showed signs of cerebral microangiopathy. A total number of 80 patients to be included were proposed. When a pre-planned interim analysis at the count 35-40 patients turned out to sufficiently proof the hypothesized principles, further requisition of patients was refrained of.

3.2 Inclusion criteria

In order to be included in the study, patients needed to show periventricular or subcortical white matter lesions of any extent on computed tomography (CT) or magnetic resonance imaging (MRI), respectively, being in line with the criteria pointed out in 3.4.

Moreover, a sufficient temporal bone window as detected in routine brain-artery doppler sonography had to be found in all patients, thus being crucial to measure cerebral arterio-venous transit time (cTT).

Every patient gave informed consent to their participation in the study and the anonymized evaluation of medical data. The local ethics committee had no

concerns regarding the implementation of the study (application no. 38/09).

3.3 Exclusion criteria

Several reasons were determined that led to a patient's exclusion from the study.

First, all patients showing clinical signs of recent stroke (ischemic or hemorrhagic) in cranial imaging could not participate.

Also, patients with hemodynamically relevant stenoses (>70% of lumen) of one or both internal carotid arteries detected in Doppler or Duplex sonography were excluded.

Further exclusion criteria were missing ability to sit for at least 45 minutes, severe dysfunction of fine motor skills as needed in neuropsychological tests, impaired vision, or the existence of contraindications for the ultrasound contrast-agent (Levovist®, Fa. Schering). Those include amongst others galactosaemia, myocardial infarction within the last two weeks, and cardiac insufficiency NYHA III and higher.

3.4 Magnetic resonance imaging (MRI)

Cranial MRI scans performed were medically necessary within the patients' regular diagnostic procedures. Due to ethical considerations, no MR scan was performed only for investigational purposes. Evaluation of MR imaging was performed by neuroradiologic consultants. All patients were grouped by the extent of white matter hyperintensities (WMH) found in MRI as follows (adapted from [23]). Group A is defined to show no WMH in MR imaging. Patients in group B (mild WMH) showed one subcortical WMH ≤ 3mm or one periventricular WMH ≤ 5mm. Group C (moderate WMH) showed 1 to 10 subcortical WMHs sized 4 – 10 mm or periventricular lesions sized 6 – 10 mm. Patients were assigned to group D (severe WMH) if more than ten subcortical WMHs or confluent WMHs or periventricular WMHs ≥11 mm were present. MRI classification was performed blinded for any other test results and vice versa.

3.5 Cerebral arterio-venous transit time (cTT)

Measurement of the cTT has been shown to be a trustworthy method to detect microangiopathic dysfunction of brain tissue [24].

For this examination, the P2 segment of the posterior cerebral artery and the vein of Galen are depicted in one axial slice of power-mode Duplex sonography. Enhanced by an ultrasound contrast agent, the time from the increase of signal intensity in the artery to the increase in the vein is recorded thus reflecting the function of the microvascular bed. The contrast agent consists of transpulmonary stable micro bubbles formed in a galactose suspension. It increases the signal intensity by approximately 25 dB.

Two repeat measurements are being performed with injection of each 2g of Levovist® (Bayer-Schering, Germany) and arithmetically averaged. Repeated intraindividual measurements have proven to be stable [24].

All cTT examinations were performed in a certified Ultrasound Laboratory by one experienced examiner in order to prevent possible examiner-related aberrations.

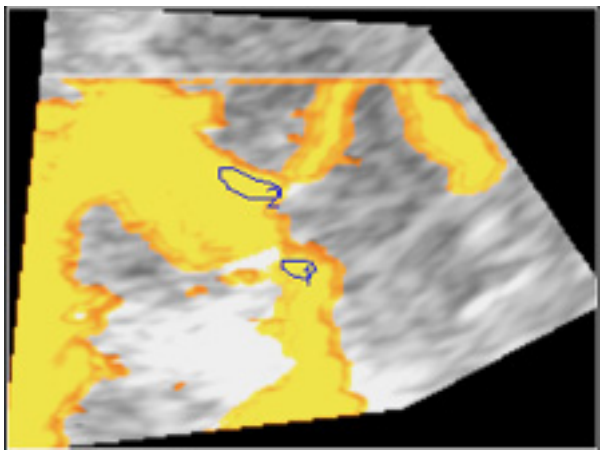


Fig. 1: Duplex image of a cTT examination

The upper circle marks the posterior cerebral artery, the lower one represents the vein of Galen.

The image has kindly been provided by Prof. Müllges, Würzburg University Hospital, Department of Neurology

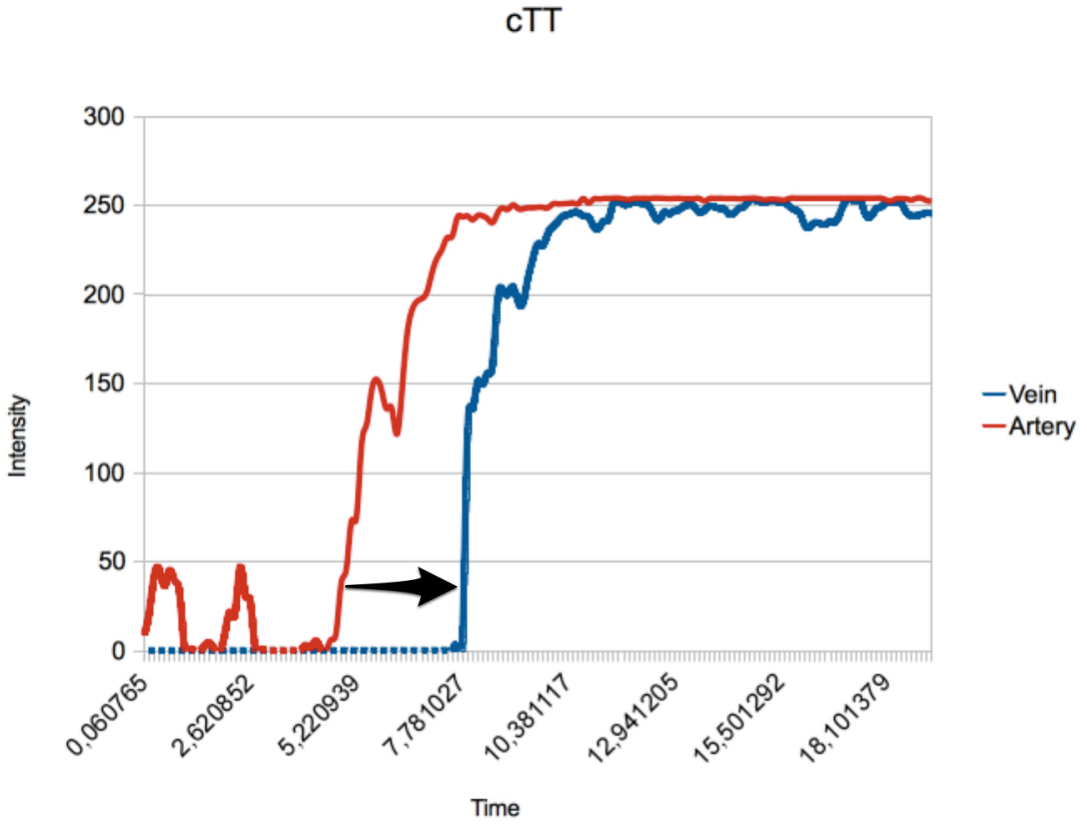


Fig. 2: Example diagram of measured cTT data

The arrow marks the measured transit time.

3.6 Neuropsychological testing

All neuropsychological tests were performed by the same examiner (BS) in the same way and order in every patient and in the same surroundings. MRI and cTT findings were not known to this investigator.

3.6.1 Mini-mental state-exam (MMSE)

MMSE is a well validated screening test for fast evaluation of basic cognitive functions such as orientation to time and place (10 points total), registration (repeating of three words immediately; 3 points), attention and calculation subtracting 7 five times in a row, starting at 100, or spell a five-letter word backwards; 5 points), recall and language (recall of the three words presented earlier, repeat a phrase, obey a written order, and follow a three-stage command; 9 points total) [25]. Within short time a score of up to 30 points is being determined. This score gives reliable hints towards the existence and severity of dementia [26]. A score below 25 out of 30 possible is widely accepted to indicate at least a mild form of cognitive impairment [27]. An exemplary test form is shown in the appendix (att. No. 1).

3.6.2 Hamburg-Wechsler intelligence test (HAWIE), subtest digit span

Digit span is a subtest of the internationally well-accepted HAWIE [28]. The full battery of HAWIE is one way to measure a subject's IQ. In this study, it was used as an item to asses short-time memory functions.

The test person is being read a sequence of digits between one and nine, starting with a sequence of three digits. After completely listening to the sample, the patient has to repeat the digits heard before. If he succeeds, the next sequence will be prolonged by one digit, ending at ten digits in a row.

If the patient fails to repeat a sequence correctly, a second sequence of the same length will be read to him. Should he succeed this time, the test continues in the usual way, otherwise the trial is over.

In a second task the patient is asked to repeat the digits read to him in reverse order. Starting at a sequence of two digits, it will be prolonged up to nine digits. The rules for falsely repeated sequences apply like in the first trial. In order to provide a maximum level of standardization, the sequences were presented via speakers by a computer program thus confronting each patient with the exact same voice, intonation and speed.

For every sequence which is being repeated correctly in the first attempt, two points are rewarded, one point is being rewarded for a correct solution in the second attempt.

The sum of all points in both the forward and reverse trial (max. 14 points each) will be transformed into a normalized score by a table of test results of an age-controlled standard population. The mean score to be expected after controlling for age is 10. Those tables exist for test persons from 16 to 79 years. Patients aged over 74 were compared to the table for the 74 to 79 years old. The data referred to origin from the latest manual available for the HAWIE [28].

3.6.3 Benton Visual Retention Test

This internationally well-accepted test looks into visuospatial perception and constructional skills [29]. The patient is shown a pattern consisting of up to three geometric forms for ten seconds. After that time, the pattern will be removed

and the patient is asked to draw the pattern he just saw as exactly as possible on a sheet of paper. He should consider the forms themselves as well as their size and topical relation to each other.

The test contains ten templates. For this study, the evaluation of the test was reduced to a simple discrimination between correct or false reproduction of each template resulting in a total score between zero and ten. The rules proposed by the test manual were followed in the evaluation process.

For this study the process of the test was additionally standardized by a computer-based presentation of the templates. Thus, examiner-related differences in the way or duration each template is shown could be minimized.

3.6.4 Test d2

d2 examines the ability of visual attention over a relatively long time (four minutes and 40 seconds). The patient is asked to cross out critical signs among a lot of similar but uncritical signs. The signs are arranged in 14 lines for every which of them the patient has 20 seconds to identify the relevant ones.

Several output values can be determined and standardized by corresponding tables from the test manual:

- Number of processed signs (GZ): This value only describes the patient's working speed. The number of processed signs, regardless if falsely or correctly, in every line is summed up.
- Number of errors (F): This value describes the number of errors made in each line up to the point, where the patient stopped processing. Omissions can be differentiated from confusions but for standardization both values are summed up.
- Over-all performance (GZ-F): The number of errors (F) is subtracted from the number of processed signs (GZ). As a result, a patient cannot achieve higher rankings in this test by increasing his working speed at the expense of diligence.
- Using a table with data from an age-controlled standard population standard values (SW) or percentile ranks (PR) respectively can be determined.

The comparison population used includes 3176 people tries to depict Germany's population as a whole [30].

3.6.5 Test of Attentional Performance (TAP, version 2.1, Fa. PSYTEST, Germany)

TAP is a fully computer-based regimen of tests scanning various qualities of attention [31]. Before each subtest, the patient is given profound explanations and the opportunity to practice the respective task.

In this study, three subtests out of the regimen were being used:

- Alertness:

  This subtest measures the reaction time the patient requires to answer a critical stimulus. Two different modes are presented.

  In the first mode, a critical stimulus (X) is shown at a previously known position on the screen. The patient has to react to that by pressing a button as quickly as possible.

  A second mode provides an acoustic warning signal before each

appearance of the critical stimulus. The time span between alert and stimulus varies randomly. Again, the stimulus is to be answered by pressing a button, but not so the alert.

Those two modes are supposed to examine both kinds of attention postulate in recent literature. For one, there is the so called intrinsic alertness, a state in which every wakeful person usually is. It represents the basic capability to respond to external stimuli without previous warning. On the other hand there is phasic alertness, a kind of focused alertness or arousal. It is predominant in situations where we expect something to happen and therefore are very vigilant. Of course, the first mode without an alert aims at intrinsic alertness, the second towards phasic alertness [32].

Each mode encompasses 20 critical stimuli and is run through by the patient twice, following a scheme of "ABBA" to minimize impacts of fatigue.

Automated output values for each condition (with or without alert) are mean, median, and standard deviation of reaction times. Apart from that the number of correct reactions, of omissions, outliers, and anticipations is put out. T-scores are given also automatically for medians and standard deviations of the reaction times.

- Go/Nogo:

  In this subtest the patient is required to react adequately to a critical stimulus whilst suppressing reactions to uncritical stimuli [31]. Skills of attention are required in this task as well as information processing and executive function.

  In random order one of the signs "+" or "x" is presented to the patient at a previously know position on the screen. He is to answer only signs of "x" by pressing a button and ignore the appearance of "+". Of the 40 stimuli shown to the patient, 20 are critical.

  Automated output values for this subtest are mean, median, and standard deviation of the reaction times as well as the number of correct responses, errors, and omissions.

  T-scores are given for the median and standard deviation of the reaction times and for the number of errors.

- Divided attention:

  The patient has to fulfill two tasks at the same time in this subtest which can be regarded as the hardest in this study setting. It examines skills of attention, information processing, executive function, and motor speed all in one. That is why, it is perfectly fit to assess deficits in patients with assumed VCI. The visual element is similar to Go/Nogo. The patient is shown one out of four symbols: "S", a mirror-inverted "S", "10", and "01". The order in which the different symbols appear on the screen is arbitrary. "10" and "01" are critical stimuli and to be answered by pressing a button whereas "S" and inverted "S" imply no reaction by the patient.

  A second, auditory task has to be processed at the same time. The patient is confronted with a periodic sequence of a high and a low tone. No reaction is required until the sequence disrupts randomly and two identical tones sound consecutively. This is considered the critical

stimulus and has to be answered by pushing a button.

The critical stimuli of both the visual and the auditive element bear n o relation to each other and have to be detected and answered independently.

Output values are the mean, median, and variance of the reaction times for the visual and the auditory element separately.

The number of errors and omissions is given out for both elements together.

T-values are available for medians and standard deviations of the reaction time and for the total number of errors and omissions respectively.

Furthermore, a category called “all erroneous reactions” was created, subsuming both errors and omissions.

3.7 Statistical analysis

The analysis of the data described in this paper was performed with the aid of IBM® SPSS® Statistics, version 19. Furthermore, all graphs were drawn by this software. Support and suggestions in order to identify the most suitable statistical algorithm for each given situation came from Jens-Holger Krannich, PhD, Comprehensive Heart Failure Center, University Hospital of Würzburg.

3.7.1 Descriptive statistics

All common descriptive parameters are given in the results section, i.e. number of participants, sex distribution, mean, median, and range of the participants' age.

3.7.2 Correlation between cTT and neuropsychological performance

Correlations between cTT and neuropsychological performance were determined by calculating Pearson's product-momentum correlation coefficient (PMCC) for all values which were interval-scaled (this applied to all measured values) and showed normal distribution. Correlations for non-normally distributed values were determined using Spearman's rank correlation. Both algorithms are widely used in scientific research. In order to be considered significant, a confidence interval of at least 95% (p=0.05) was required.

Normal distribution was tested for by Kolmogorov-Smirnov test. This test delivers stable and reliable results even for small samples.

3.7.3 Relation between neurological testing / cTT and the grade of WMH

The relation between neuropsychological testing and the grade of white-matter hyperintensities as well as the relation between cTT and neuropsychological findings was estimated by Kruskal-Wallis test. This test is an extension of the more common Mann-Whitney U test to three or more groups (in our case cTT on the one hand and four groups of different white-matter hyperintensities on the other). Just like Mann-Whitney U test, it is a non-parametric analysis of variance. Non-parametric testing was necessary because, clearly, grouping of patients for the grade of WML does only provide ordinal-scaled data. Furthermore, Kruskal-Wallis test allows you to work with results which are not necessarily normally distributed. This has to be assumed due to the low number of patients in each of the four WMH groups. The Null Hypothesis was shaped

as follows: “The distribution of cTT (s) / neuropsychological test is the same across the different grades of WMH.” Thus, rejection of the Null Hypothesis hints towards a significant relation between the respective two features. For the analysis containing cTT we just took the measured time in seconds. For the analysis of the test scores of neuropsychological test, we used the T-scores of all data where a comparative population was available. T-scores were used because they already include a valuation with respects to the expected performance among healthy individuals of the same age. Contrary to that, the sheer test scores only provide absolute figures which cannot be compared between among the study population.

3.7.4 Proposal of a cutoff score for cTT

With all the data given it seemed possible to suggest a cutoff score for cTT, discriminating “normal” cTT from “prolonged” cTT dependent from the patients' performance in neuropsychological testing. Therefore patients were divided in two groups for each neuropsychological test previously proofed to be significantly correlated with cTT. The first group represents those patients with below-average performance in the respective test. “Below-average performance” was defined as a performance at least one standard deviation below average or a T-value of less than 41 compared to a standard test population, respectively. In the second group, patients with a test performance above this T-value were subsumed, ascribing to them “normal” test performance. By doing the math using various random cutoff scores and comparing the accuracy of each proposed cutoff score in terms of discriminating the two groups, a reasonable cutoff score could be found, eventually.

4. Results

4.1 Population

A total of 38 patients (28 male, 10 female) participated in the study after giving informed consent. The mean age was 73.8 years (median: 74.5), ranging from 57 to 91 years.

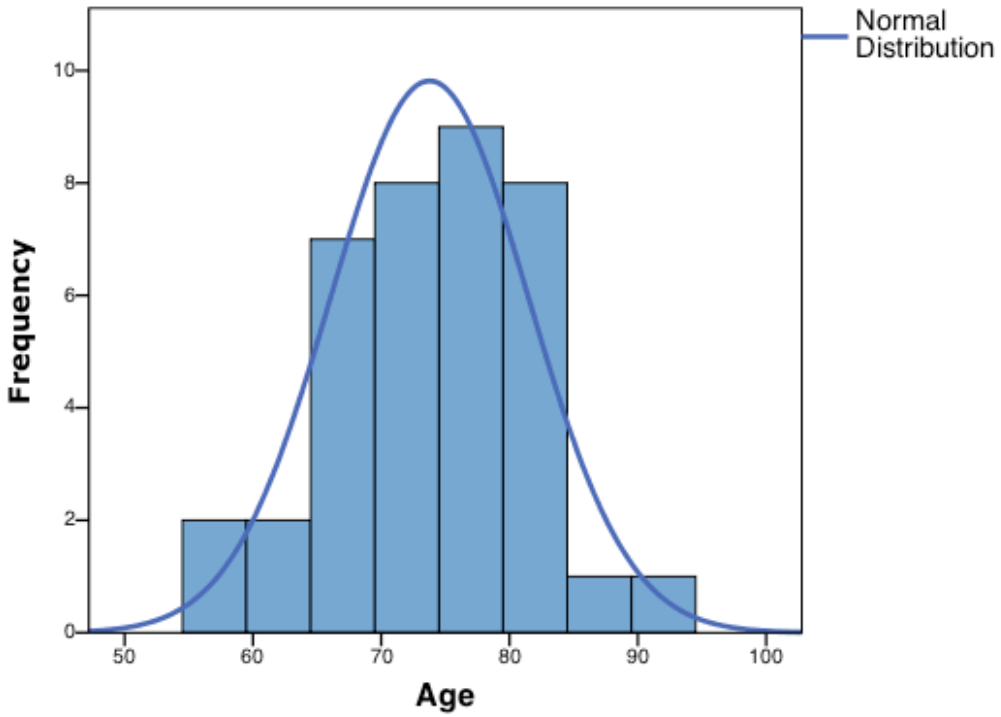


Fig. 3: Age distribution

4.2 MR imaging

MRI was performed in every patient. Each patient was assigned to an MRI group as depicted above. Results of the grouping are shown in the following table.

Group	Frequency	Percent
A	0	0
B	17	44.7
C	10	26.3
D	11	28.9
total	38	100

Table 1: Distribution of patients across MRI groups

4.3 cTT

In 36 patients, cTT was measured. In the remaining two patients the findings of cTT were not usable due to extremely prolonged wash-in time of the contrast agent.

The mean cTT was 6.25 s (median: 4.8; 1.15-25.9s; SD 5.12s).

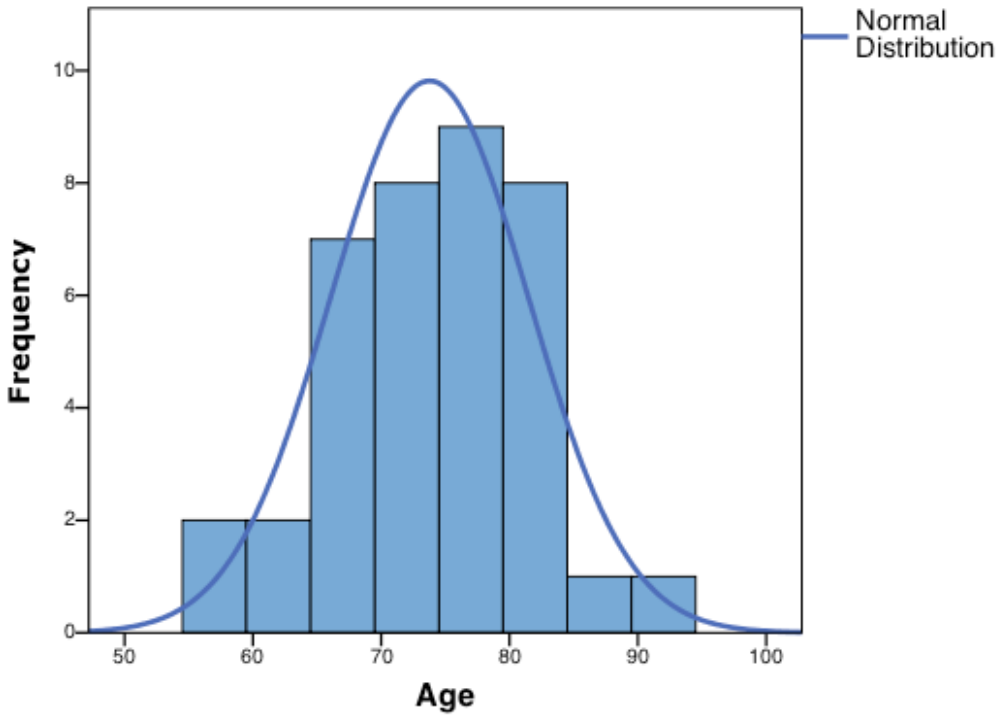


Fig. 3: Age distribution

4.2 MR imaging

MRI was performed in every patient. Each patient was assigned to an MRI group as depicted above. Results of the grouping are shown in the following table.

Group	Frequency	Percent
A	0	0
B	17	44.7
C	10	26.3
D	11	28.9
total	38	100

Table 1: Distribution of patients across MRI groups

4.3 cTT

In 36 patients, cTT was measured. In the remaining two patients the findings of cTT were not usable due to extremely prolonged wash-in time of the contrast agent.

The mean cTT was 6.25 s (median: 4.8; 1.15-25.9s; SD 5.12s).

4.4 Mini-Mental State Exam

MMSE could be performed in 35 patients. Three patients were not capable of understanding a majority of tasks. This let the interpretation seem to be prone to error. On the other hand, rewarding a score of zero would have underestimated their performance as well. Therefore, MMSE findings were not recorded for these patients.

The mean MMSE score was 27.9 (median: 29.0; 20 – 30; SD 2.3).

4.5 Hamburg-Wechsler Intelligence Test (HAWIE)

From this test, as depicted above, only the subtest digit span was performed. Basic point values as well as normalized values controlled for age went into further statistical review.

The mean basic point value was 10.9 (median: 11.0; 1 – 23; SD 3.7). The mean age-controlled score was 9.2 (median: 9.0; 2 – 18; SD 2.7).

4.6 Benton Visual Retention Test

One patient did not understand the instructions for the Benton test. Of the remaining 37 patients, the mean number of correct reproductions (out of ten possible) was 4.6 (median: 5.0; 0 – 9; SD 2.3).

4.7 Test d2

Due to impairment of vision, six patients were not able to perform this test. Results are given for GZ-F and its standard value (GZ-F-SW) as well.

The mean score for GZ-F was 310.3 (median: 309.5; 91 – 579; SD 111.2) and for its standardized value 96.3 (median: 97.0; 70 – 127; SD 14.0).

	N	range	min	max	mean	median	SD
age (years)	38	34	57	91	73.8	74.5	7.7
cTT (s)	36	24.8	1.2	25.9	6.3	4.8	5.1
MMSE score	35	10	20	30	28.0	29.0	5.1
basic score HAWIE	38	22	1.2	23	10.9	11.0	3.7
age-controlled score HAWIE	38	16	2	18	9.2	9.0	2.7
Benton correct reproductions	37	9	0	9	4.6	5.0	2.3
d2 (GZ-F)	32	488	91	579	310.3	309.5	111.2
d2 (GZ-F) *	32	57	70	127	96.3	97.0	14.0

Table 2: Descriptive statistics of test results (without TAP)

**= standard value*

4.8 TAP

4.8.1 Subtest "Alertness"

This subtest was performed by all 38 patients. Detailed results are shown in Tab. 3 below.

		N	range	min	max	mean	SD
1st round	correct reactions	38	0	20	20	20.0	0.0
	omissions	38	1	0	1	0.1	0.3
	outliers	38	2	0	2	0.6	0.6
	anticipations	38	0	0	0	0.0	0.0
	mean reaction time (ms)	38	446	217	663	366.7	113.1
	median reaction time (ms)	37	421	212	633	356.6	110.5
2nd round	correct reactions	38	0	20	20	20.0	0.0
	omissions	38	1	0	1	0.0	0.2
	outliers	38	1	0	1	0.5	0.5
	anticipations	38	5	0	5	1.0	1.3
	mean reaction time (ms)	38	414	224	638	348.2	101.8
	median reaction time (ms)	38	399	220	619	337.2	96.7
3rd round	correct reactions	38	1	19	20	20.0	0.2
	omissions	38	1	0	1	0.0	0.2
	outliers	38	2	0	2	0.7	0.5
	anticipations	38	6	0	6	0.8	1.4
	mean reaction time (ms)	38	388	222	610	340.6	102.1
	median reaction time (ms)	38	409	220	629	334.3	103.3
4th round	correct reactions	38	1	19	20	20.0	0.2
	omissions	38	6	0	6	0.3	1.1
	outliers	38	2	0	2	0.7	0.5
	anticipations	38	0	0	0	0.0	0.0
	mean reaction time (ms)	38	566	219	785	392.2	141.9

		N	range	min	max	mean	SD
	median reaction time (ms)	38	581	216	797	378.3	138.1
without alert	correct reactions	38	1	39	40	40.0	0.2
	omissions	38	7	0	7	0.4	1.3
	outliers	38	3	0	3	1.3	0.8
	anticipations	38	0	0	0	0.0	0.0
	mean reaction time (ms)	38	495	218	713	378.9	124.1
	median reaction time (ms)	38	474	215	689	365.4	117.9
with alert	correct reactions	38	1	39	40	40.0	0.2
	omissions	38	1	0	1	0.1	0.2
	outliers	38	3	0	3	1.2	0.7
	anticipations	38	8	0	8	1.8	2.4
	mean reaction time (ms)	38	398	226	624	344.0	98.9
	median reaction time (ms)	38	406	221	627	332.3	98.1

Table 3: Results of TAP subtest "Alertness"

4.8.2 Subtest “Divided Attention”

Of all patients, 35 underwent this test. Three patients were not able to mentally conceive the tasks they were set despite the detailed instructions given.

The underlying number (N) of patients for the median reaction time to auditive stimuli is only 31, because out of the 35 patients participating four did not react to a single auditive stimulus, thus the median reaction time being mathematically not determinable in these cases.

		N	range	min	max	mean	SD
auditive stimuli	correct reactions	35	20	0	20	14.4	6.8
	omissions	35	20	0	20	5.5	6.8
	outliers	35	1	0	1	0.3	0.5
	mean reaction time (ms)	35	1630	0	1630	709.2	337.0
	median reaction time (ms)	31	1187	385	1572	726.4	318.1

		N	range	min	max	mean	SD
visual stimuli	correct reactions	35	14	6	20	17.7	3.4
	omissions	35	14	0	14	2.3	3.4
	outliers	35	1	0	1	0.5	0.5
	mean reaction time (ms)	35	1388	480	1868	749.3	331.1
	median reaction time (ms)	35	1361	449	1810	729.1	309.0
total	errors	35	27	0	27	6.1	6.5
	omissions	35	28	0	28	7.8	8.7
	all erroneous reactions	35	33	0	33	14.0	10.2

Table 4: Results of TAP subtest "Divided Attention"

4.8.3 Subtest “Go/Nogo”

All patients underwent this subtest. The results are listed in the table below.

	N	range	min	max	mean	SD
correct reactions	38	14	6	20	18.7	3.0
errors	38	6	0	6	1.7	1.5
omissions	38	14	0	14	1.3	3.0
outliers	38	1	0	1	0.4	0.5
mean reaction time (ms)	38	1011	400	1411	597.2	201.9
median reaction time (ms)	38	899	393	1292	575.6	189.8

Table 5: Results of TAP subtest "Go/Nogo"

4.9 Further statistical analyses

4.9.1 Testing for normal distribution

Testing for normal distribution of all variables using the Kolmogorov-Smirnov test yielded the following results. A significance level of at least p=0.05 was considered not-normally distributed.

Variable		Significance	Normal distribution
cTT		0.174	yes
MMSE		0.074	yes
HAWIE basic score		0.654	yes
HAWIE age controlled score		0.453	yes
Benton test		0.488	yes
d2	GZ	0.734	yes
	F	0.487	yes
	GZ-F	0.912	yes
	KL	0.754	yes
	GZ*	0.623	yes
	GZ_PR	0.252	yes
	GZ-F*	0.819	yes
	GZ-F_PR	0.878	yes
	KL*	0.495	yes
	KL_PR	0.101	yes
Alertness	round 1, reaction time (mean)	0.165	yes
	round 1, reaction time (median)	0.277	yes
	round 1, reaction time (median, T-score)	0.701	yes
	round 2, reaction time (mean)	0.142	yes
	round 2, reaction time (median)	0.109	yes
	round 2, reaction time (median, T-score)	0.905	yes
	round 3, reaction time (mean)	0.059	yes
	round 3, reaction time (median)	0.073	yes
	round 3, reaction time (median, T-score)	0.901	yes
	round 4, reaction time (mean)	0.170	yes
	round 4, reaction time (median)	0.364	yes

Variable		Significance	Normal distribution
Alertness	round 4, reaction time (median, T-score)	0.143	yes
	without alert, reaction time (mean)	0.146	yes
	without alert, reaction time (median)	0.383	yes
	without alert, reaction time (median, T-score)	0.808	yes
	with alert, reaction time (mean)	0.249	yes
	with alert, reaction time (median)	0.205	yes
	with alert, reaction time (median, T-score)	0.971	yes
Divided Attention	auditive stimuli, correct reactions	0.065	yes
	auditive stimuli, omissions	0.070	yes
	auditive stimuli, reaction time (mean)	0.317	yes
	auditive stimuli, reaction time (median)	0.117	yes
	auditive stimuli, reaction time (median, T-score)	0.231	yes
	visual stimuli, reaction time (median, T-score)	0.160	yes
	total, errors	0.061	yes
	total, errors (T-score)	0.072	yes
	total, outliers	0.182	yes
	total, omissions (T-score)	0.093	yes
	total, all erroneous reactions	0.422	yes

Variable		Significance	Normal distribution
Go/Nogo	errors	0.286	yes
	reaction time (median, T-score)	0.803	yes

Table 6: Kolmogorov-Smirnov test for normal distribution

Normally distributed variables

**= standard value; PR= percentile rank*

Variable		Significance	Normal distribution
Alertness	round 1, correct reactions	n/a	no
	round 1, omissions	0.000	no
	round 1, outliers	0.002	no
	round 1, anticipations	n/a	no
	round 2, correct reactions	n/a	no
	round 2, omissions	0.000	no
	round 2, outliers	0.000	no
	round 2, anticipations	0.013	no
	round 3, correct reactions	0.000	no
	round 3, omissions	0.000	no
	round 3, outliers	0.000	no
	round 3, anticipations	0.000	no
	round 4, correct reactions	0.000	no
	round 4, omissions	0.000	no
	round 4, outliers	0.000	no
	round 4, anticipations	n/a	no
	without alert, correct reactions	0.000	no
	without alert, omissions	0.000	no
	without alert, outliers	0.000	no
	without alert, anticipations	n/a	no
	with alert, correct reactions	0.000	no

Variable		Significance	Normal distribution
Alertness	with alert, omissions	0.000	no
	with alert, outliers	0.000	no
	with alert, anticipations	0.000	no
Divided Attention	auditive stimuli, omissions	0.025	no
	auditive stimuli, outliers	0.000	no
	visual stimuli, correct reactions	0.003	no
	visual stimuli, omissions	0.003	no
	visual stimuli, omissions (T-score)	0.000	no
	visual stimuli, outliers	0.000	no
	visual stimuli, reaction time (mean)	0.028	no
	visual stimuli, reaction time (median)	0.020	no
Go/Nogo	correct reactions	0.000	no
	errors, T-score	0.015	no
	omissions	0.000	no
	omissions, T-score	0.000	no
	outliers	0.000	no
	reaction time (mean)	0.029	no
	reaction time (median)	0.011	no

Table 7: Kolmogorov-Smirnov test for normal distribution

Not normally distributed variables

Where a significance is not available, all values of the variable were identical and therefore considered not-normally distributed

This test was necessary to choose a fitting algorithm for further statistical analysis.

4.9.2 Correlation between cTT and neuropsychological findings

CTT turned out to be significantly correlated with a large number of neuropsychological tests. The following table no. 8 shows all significant correlations of cTT with neuropsychological tests using PMCC (meaning all values were normally distributed)

	Test	Correlation	Significance (2-tailed)	N
MMSE (score)		-0.356	0.042	33
d2	GZ	-0.441	0.013	31
	GZ-F	-0.435	0.014	31
	GZ*	-0.439	0.014	31
	GZ_PR	-0.444	0.012	31
	GZ-F*	-0.428	0.016	31
	GZ-F_PR	-0.450	0.011	31
Alertness	reaction time (mean) 1st round	0.436	0.008	36
	reaction time (median) 1st round	0.373	0.028	35
	omissions, 4th round	0.364	0.029	36
	reaction time (mean) 4th round	0.371	0.026	36
	reaction time (median) 4th round	0.341	0.042	36
	reaction time (mean) without alert	0.424	0.010	36
	reaction time (median) without alert	0.392	0.018	36
Divided Attention	reaction time (mean) auditive stimuli	0.480	0.005	33
	reaction time (median) auditive stimuli	0.591	0.001	29
	reaction time (median) t-value, auditive stimuli	-0.567	0.001	29
	reaction time (median) t-value, visual stimuli	-0.458	0.007	33
	errors, total	0.382	0.028	33
	all erroneous responses total	0.470	0.006	33

	Test	Correlation	Significance (2-tailed)	N
Go/Nogo	reaction time (median) T-score	-0.375	0.024	36

Table 8:
Significant correlations of cTT with neuropsychological test results (p=0.05)
Correlations significant within a confidence interval of 99% (p=0.01) are highlighted in blue.
PMCC
**= standard value; PR= percentile rank*

The next table no. 9 shows significant Spearman rank correlations as the respective values were not normally distributed.

	Test	Correlation	Significance (2-tailed)	N
Alertness	omissions, 4th round	0.337	0.044	36
	omissions, without alert	0.335	0.046	36
Divided Attention	correct reactions visual stimuli	-0.343	0.050	33
	omissions, visual stimuli	0.343	0.050	33
	omissions, T-score visual stimuli	-0.360	0.039	33
	outliers, visual stimuli	-0.396	0.022	33
	mean reaction time visual stimuli	-0.572	0.001	33
	median reaction time visual stimuli	0.556	0.001	33

Table 9:
Significant correlations of cTT with neuropsychological test results (p=0.05)
Correlations significant within a confidence interval of 99% (p=0.01) are highlighted in blue.
Spearman rank correlation

The following two tables show non-significant correlations using PMCC (tab. 10) or Spearman rank correlation (tab. 11).

	Test	Correlation	Significance (2-tailed)	N
	HAWIE basic score	-0.076	0.659	36
	HAWIE age controlled score	-0.046	0.789	36
	d2 F	-0.164	0.377	31
	Benton test	-0.272	0.114	35
Alertness	reaction time (median, T-score) 1st round	-0.276	0.103	36
	reaction time (mean) 2nd round	0.304	0.072	36
	reaction time (median) 2nd round	0.242	0.154	36
	reaction time (median, T-score) 2nd round	-0.183	0.286	36
	reaction time (mean) 3rd round	0.219	0.199	36
	reaction time (median) 3rd round	0.196	0.251	36
	reaction time (median, T-score) 3rd round	-0.085	0.622	36
	reaction time (median, T-score) 4th round	-0.201	0.240	36
	reaction time (median, T-score) without alert	-0.265	0.119	36
	reaction time (mean) with alert	0.280	0.098	36
	reaction time (median) with alert	0.263	0.121	36
	reaction time (median, T-score) with alert	-0.179	0.296	36

	Test	Correlation	Significance (2-tailed)	N
Divided Attention	correct reactions auditive stimuli	-0.188	0.294	33
	omissions, auditive stimuli	0.189	0.292	33
	errors, T-score, total	-0.143	0.427	33
	omissions, T-score, total	-0.306	0.083	33
Go/Nogo	errors	0.075	0.663	36

Table 10:
Non-significant correlations of cTT with neuropsychological test results (p=0.05)
PMCC

	Test	Correlation	Significance (2-tailed)	N
Alertness	correct reactions, 1st round	n/a	n/a	36
	omissions, 1st round	0.234	0.170	36
	outliers, 1st round	0.169	0.324	36
	anticipations, 1st round	n/a	n/a	36
	correct reactions 2nd round	n/a	n/a	36
	omissions, 2nd round	0.024	0.888	36
	outliers, 2nd round	0.024	0.889	36
	anticipations, 2nd round	-0.015	0.933	36
	correct reactions, 3rd round	0.155	0.368	36
	omissions, 3rd round	0.057	0.741	36
	outliers, 3rd round	0.089	0.605	36
	anticipations, 3rd round	0.198	0.248	36
	correct reactions, 4th round	-0.236	0.166	36
	outliers, 4th round	0.056	0.747	36
	anticipations, 4th round	n/a	n/a	36

	Test	Correlation	Significance (2-tailed)	N
Alertness	correct reactions without alert	-0.236	0.166	36
	outliers, without alert	-0.104	0.548	36
	anticipations, without alert	n/a	n/a	36
	correct reaction, with alert	0.155	0.368	36
	omissions, with alert	0.058	0.735	36
	outliers, with alert	-0.093	0.589	36
	anticipations, with alert	0.040	0.818	36
Divided Attention	omissions, auditive stimuli	0.117	0.518	33
	outliers, auditive stimuli	-0.062	0.730	33
Go/Nogo	correct reactions	-0.289	0.087	36
	errors, T-score	0.071	0.682	36
	omissions	0.289	0.087	36
	omissions, T-score	-0.294	0.082	36
	outliers	-0.120	0.487	36
	median reaction time	0.227	0.183	36
	median reaction time T-score	-0.222	0.192	36

Table 11:
Non-significant correlations of cTT with neuropsychological test results (p=0.05)
Spearman rank correlation
Correlations or significances which are not available result from all values for that variable being identical and therefore no rank correlation can be determined.

4.9.3 The relation between neuropsychological testing and the grade of white matter lesions

Kruskal-Wallis analysis of each T-score of the test results did not show significant differences in the distribution across the MRI groups. The exception were some categories within “Divided Attention": median reaction time to auditive stimuli, omissions of visual stimuli, and total number of omissions. However, when looking at pairwise comparison it turned out that only those patients with the largest extent of WMH (group D) could be significantly discriminated from the remaining patients. There was no significant difference in

the distribution between the other groups (those with lesser WMH). The following table gives an overview on the Kruskal-Wallis test results. The assumed Null Hypothesis (same distribution across MRI groups) was considered rejected at a significance level of p=0.05.

	Neuropsychological test	Significance for rejection of Null Hypothesis
	MMSE score	0.265
	HAWIE basic points	0.308
	HAWIE score points	0.379
	d2 GZ-F*	0.266
	Benton correct reproductions	0.059
Alertness	reaction time, median, T-score 1st round	0.708
	reaction time, median, T-score 2nd round	0.882
	reaction time, median, T-score 3rd round	0.932
	reaction time, median, T-score 4th round	0.959
	reaction time, median, T-score without alert	0.857
	reaction time, median, T-score with alert	0.822

	Neuropsychological test	Significance for rejection of Null Hypothesis
Divided Attention	omissions, T-score, auditive stimuli	0.077
	reaction time, median, T-score auditive stimuli	0.031
	omissions, T-score, visual stimuli	0.005
	reaction time, median, T-score visual stimuli	0.054
	errors, T-score, total	0.895
	omissions, T-score, total	0.011

Tab. 12: Kruskal-Wallis test for distribution of neuropsychological test performance across MRI groups

For test highlighted in blue, the Null Hypothesis is to be rejected and the distribution across the MRI groups can therefore be considered significantly different.

**= standard value*

4.9.4 The relation between cTT and the grade of white matter lesions

Kruskal-Wallis test showed that the Null Hypothesis could be rejected with a significance of p=0.012 when testing for all WMH groups at once. This means there is no significant difference in distribution of cTT over all three groups. When comparing pairwise, obviously WMH groups B and C do not differ significantly (p=1.000) as do not groups C and D (p=0.138). Solely groups B and C differ significantly in pairwise comparison (p=0.011).

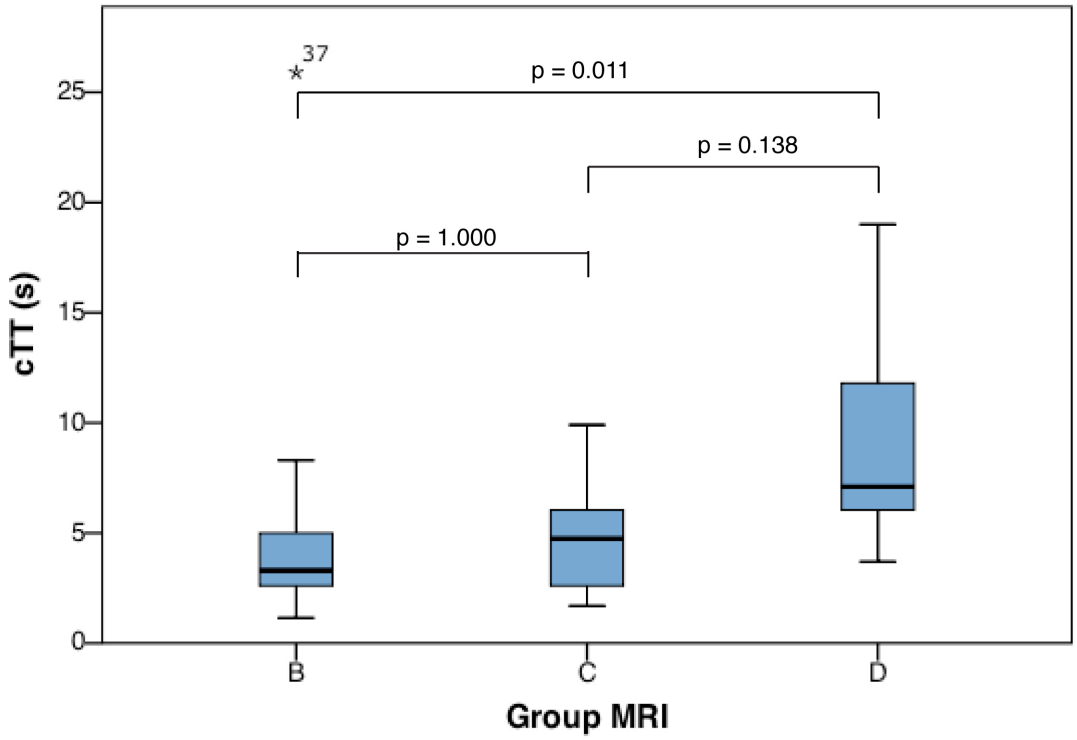


Fig. 4: Distribution of cTT across groups of MRI

MRI group	median cTT (s)
B	3.30
C	4.75
D	7.10

Tab. 13: median cTT in WMH groups

4.9.5 Determining a cutoff value for cTT

When comparing the median cTTs for both normal and below-average patients regarded in each test, a cTT of 5.5 seconds seemed reasonable to discriminate between the two groups. The considerations which led to this figure are explained in section 3.7.4. Again, Kruskal-Wallis-Test for independent samples was used to decide whether the affiliation with one cTT group or the other discriminates reliably between below-average and normal test performance. The Null Hypotheses were formulated according the following scheme: “The distribution of *test performance* is the same across the cTT groups.” Rejection of a Null Hypothesis was considered significant within a confidence interval of 95% (p=0.05).

When patients were grouped for cTT higher or lower than 5.5 seconds, one-way variance analysis (Kruskal-Wallis) shows that their performances in various tests differ significantly based upon the assignment to one group or the other.

Null Hypotheses (as explained in subsection 3.7) which could be rejected at a confidence interval of 95% (p=0.05) are highlighted in blue.

	Test considered in Null Hypothesis	Significance
MMSE		0.414
d2	GZ	0.017
	GZ-F	0.015
	GZ_SW	0.019
	GZ_PR	0.019
	GZ-F_SW	0.019
	GZ-F_PR	0.019
Alertness	mean reaction time - 1st round	0.143
	median reaction time - 1st round	0.209
	omissions - 4th round	0.125
	mean reaction time - 4th round	0.082
	median reaction time - 4th round	0.126
	omissions - without alert	0.087
	mean reaction time - without alert	0.104
	median reaction time - without alert	0.123
Divided Attention	mean reaction time - auditive stimuli	0.032
	median reaction time - auditive stimuli	0.004
	median reaction time T-score - auditive stimuli	0.004
	omissions - visual stimuli	0.016
	outliers - visual stimuli	0.518
	mean reaction time - visual stimuli	0.009
	median reaction - visual stimuli	0.015
	median reaction time T-score - visual stimuli	0.016
	errors - total	0.829
	all erroneous reactions	0.008

	Test considered in Null Hypothesis	Significance
Go/Nogo	median reaction time T-score	0.133

Tab. 14: Kruskal-Wallis test cTT across Neuropsychology

5. Discussion

The aim of this study was to evaluate the validity of cTT measurement and the presence of white-matter hyperintensities with respect to cognitive function in patients suffering from vascular cognitive impairment. Concrete questions were whether cTT is significantly correlated with cognitive performance, whether the extent of WMH shows similar relations, whether cTT is related with the extent of WMH, and if cTT might be a suitable procedure to easily yet reliably detect early stages of VCI.

Despite the small number of patients, a good distribution of age (s. fig. 2) could be obtained. Within this cohort it could be pointed out that cTT shows significant correlations with a patient's actual cognitive performance assessed in various neuropsychological tests. The correlations were especially strong in cognitive domains considered crucial in VCI. The extent of WMH did not or only little show comparable relations with cognitive performance. In conformity with that, cTT and the extent of WMH were not significantly correlated with each other.

Patients suffering from VaD or VCI in general show specific patterns of cognitive impairment. Not all domains of cognition are affected equally and, more importantly, the domains affected in general differ substantially from those affected in AD patients. Graham et. al [3] showed that in overall mildly demented patients those with AD show more severe impairment in tasks concerning episodic memory. Patients with VaD, on the other hand were more impaired in tasks of executive functions, attention and visuospatial/perceptual tasks, as well as semantic memory. In our study, we included no specific test for semantic memory. A more recent review states that “subcortical lesions are often associated with abnormalities of information processing speed [and] executive function...” [8]. O'Brien et. al. came to the conclusion, that “the characteristic neuropsychological profile (…) of subcortical ischemic vascular disease is believed to frequently include early impairment of attention and executive function, with slowing of motor performance and information processing. Episodic memory is believed to be relatively spared compared with that in AD” [4].

As varying the findings in recent literature may be in detail, two major differences between VCI and AD regarding the specifics of neuropsychological impairment seem to be undeniable: 1. A key feature of AD is an early and more severe loss of episodic memory, which does not or to a much lesser extent occur in VCI. 2. For VCI, deterioration in executive function and, less distinctively, attentional processes seems to be predominant.

5.1 Were the patients demented?

We applied a wide spectrum of neuropsychological tests in order to detect possible deficits in cognitive performance. A consensus paper on the neuropsychological assessment of patients after cardiac surgery [33] served as a guideline for the composition of the test battery. The tests chosen are altogether well-accepted procedures among neuropsychological professionals. The criterion which led to the selection of tests at hand was, aside from their being well-established, the endeavor to cover all relevant cognitive domains. As can be seen in tab.13 below, the tests selected assess a wide range of cognitive functions and should therefore be fit to detect most kinds of cognitive decline. Still, there is an emphasis on executive function, which was expected to be most affected. So several tests assessing this domain were chosen to make sure any possible impairment would be captured. Another important criterion when composing the test battery was the time limit. Most patients managed to perform all tasks within 30-45 minutes. A maximum of 60 minutes was not to be exceeded, as test results may have worsened due to fatigue.

Many of the test results can be compared to a large population of healthy individuals of around the same age. For the little remaining tests, no such comparative data were available. If and where a comparison population was available is depicted in section 3.6. Those data allow to determine whether study patients performed worse than one would expect. This would allow to diagnose them with dementia, assuming they did decline from a higher cognitive level. The varied tests conducted in this study and the main cognitive domain they are to represent are listed in the following table.

Test	Domain
MMSE	overall screening
HAWIE digit span	short-term memory
Benton visual retention	visuospatial perception constructional skills
d2	long-term attention
TAP Alertness	attention
TAP Divided Attention	executive function information processing motor speed
TAP Go/Nogo	attention executive function

Tab. 15: Conducted neuropsychological tests and their ascription to cognitive domains

As a cut-off for significant below-average performance we set a T-score of 40 or

less, i.e. more than one standard deviation below average performance. In a normally distributed population one would expect 15.89% of people to perform below average. The following table shows the percentage of patients that showed a T-score of 40 or less for each test that came with a healthy comparison population.

Test		Test performance	
		below-average (percentage of individuals)	**normal** (percentage of individuals)
d2 n=32	GZ_SW	28.9	55.3
	GZ-F_SW	23.7	60.5
Alertness n=38	median 1	55.3	42.1
	median 2	52.6	44.7
	median 3	55.3	42.1
	median 4	50.0	47.4
	median 1+4	55.3	42.1
	median 2+3	55.3	42.1
Divided Attention n=35	omiss. aud.	39.5	50.0
	median aud.	36.8	42.1
	omiss. vis.	89.5	0.0
	median vis.	50.0	39.5
	errors total	34.2	55.3
	omiss. total	47.4	42.1
Go/Nogo n=38	errors	10.5	86.8
	omissions	97.4	0.0
	reaction time (median)	60.5	39.5

GZ_SW: number of processed signs, standard value; **GZ-F_SW**: overall performance, standard value; **median 1**: median reaction time, 1st round; **median 2**: median reaction time, 2nd round; **median 3**: median reaction time, 3rd round; **median 4**: median reaction time, 4th round; **median 1+4**: median reaction time without alert (round 1 and 4); **median 2+3**: median reaction time with alert (rounds 2 and 3); **omiss.**: omissions; **aud.**: auditory task; **vis.**: visual task

Table 16: Test performances compared to a healthy comparative population
Below-average performance is defined as a performance at least one standard deviation (T-score<40) below average.
Percentages not adding up to 100% are caused by patients not performing the respective test.

Figures in the table quite clearly show that the percentage of patients performing below average is higher than expected in nearly every test. While for d2 the share of patients with low test performance is only little higher than one

standard deviation (i.e. 15.89%), which means long-term attention (the major domain of d2) was not severely affected across the study population. For all other items the difference becomes rather obvious. The exception to be made is the number of errors in the Go/Nogo test, where the patients at large performed even better than statistically expected. A reason for this circumstance might be that Go/Nogo is indeed to be considered a test with rather low requirements. As the given test population was mostly on a relatively high functional level, Go/Nogo might just not have challenged them enough.

For the remaining neuropsychological tests unfortunately no comparative data are available. But still, some interpretation of the results is possible:

For MMSE, the mean score was 27.9 (median: 29.0) out of 30. As depicted above, results between 27 and 30 score points are usually regarded as no hint towards a dementing process. This is consistent with recent considerations shown in the introduction that the traditional understanding of dementia (MMSE was first introduced in the 1970s) fails to embrace many patients with sub-demented conditions that are very likely to influence their every day activities.

We used one subtest out of the HAWIE battery (digit span). As a stand-alone item, it is not meant for the sake of diagnostic interpretation. Still, there are standardized scores that allow some evaluation. With an expected mean standardized score of 10, the study population performed nearly normally (mean: 9.2; median: 9.0). Taking into consideration that the used item examines memory function, there seems to be no indication of severe memory dysfunction.

Benton Visual Retention Test examines visuospatial perception and constructional skills. We only differentiated between correct and incorrect reproductions and there is no comparative data available, so the results have to be interpreted cautiously. Nevertheless, with a mean of 4.6 (median: 5.0) correct reproductions, only half of the items were drawn correctly. Even regarding the old age of most patients in the study, at least discrete deficits in this domain seem plausible.

In summary it can be said that the patient cohort was in fact demented to various degree as measured by their test performance. With respects to the scores in MMSE, which is often used for dementia screening, many of them would probably not have attracted attention on first sight. But in detailed neuropsychological testing distinct deficits become obvious in several cognitive domains. This becomes especially apparent where age-controlled comparative data are available as shown in the table above.

5.2 Do the patterns of cognitive impairment suit specific VCI deficits?

In order to decide whether cTT is a proper tool for the detection of (sub-)clinical VCI it has to be made sure that the study population actually presented with cognitive deficits one would expect in VCI patients. Those deficits are mainly found in the following cognitive domains, as pointed out earlier: Attentional processes, visuospatial perception, motor performance, executive function, and information processing. Memory, on the other hand is expected to be relatively spared. The previous paragraph pointed out, how the patients' performances in the various tests have to be estimated compared to a healthy population. When looking at the domains affected, a distinct pattern of impairment becomes obvious.

Though only slightly, the patients did show poor results in test d2, which combines a long-term attentional task (recognizing critical stimuli) with motor speed performance (crossing out critical signs as fast as possible). In the alertness from TAP, in each round more than half of the patients showed prolonged reaction times. This probably may be attributed to an actual deficit in attention or an impairment in motor speed, respectively.

In the subtest “Divided Attention" the patients were asked to react to two kinds of stimuli, auditory and visual, at the same time. Not only were the patients' reaction times prolonged for auditory and, even more, for visual stimuli, but they also omitted more critical stimuli than expected under each of the two conditions. In total, patients also made more errors (i.e. responding to a non-critical stimulus) and omitted more critical stimuli than the comparative population.

The results in the subtest “Go/Nogo" were normal with respect to the errors made. Yet, all patients made more omissions of critical stimuli than statistically expected. Unfortunately it turned out that the figures were basically unusable due to biases in the comparison population. More details on this matter are pointed out in section 5.3.

It has already been discussed earlier (previous page) that definite interpretations of the results of Benton Visual Retention Test are hard to give. However, assuming that a rate of only 50% of correct reproductions is rather low, this would document an impairment of visual perception and constructional skills.

Overall performance in MMSE was completely normal. This simply states that our patients were not severely affected yet. Interestingly enough, detailed examination by the other tests shows clear deficits nevertheless.

Recalling of numbers as a task of short-time memory did not show any abnormalities as well, indicating that this cognitive domain was, opposed to others, not impaired noticeably.

To sum up, the observed pattern of cognitive impairment in this patient series is remarkably close to what has been described as vascular dementia in recent literature. There were obvious deficits in the domains of attentional processes (Alertness, d2), visuospatial perception and constructional skills (Benton Test), motor performance (d2), executive function (Divided Attention, Go/Nogo), and information processing (Alertness, Divided Attention, Go/Nogo). No severe deficits were found in memory (recalling numbers). Thus, a majority of the patient cohort had signs of vascular dementia rather than AD.

5.3 On the relation between cTT and neuropsychological findings

As depicted earlier in this text (section 3.5), cTT is a reliable method to show and measure reduced cerebral blood flow indirectly via prolongation of the time a contrast agent needs to pass a predefined distance in the vascular system between a large artery and its draining vein. Given the suggestion that VCI originates mainly from small-vessel disease, cTT should also correlate with a patient's performance in neuropsychological testing, especially in those domains characteristic for VCI. For all correlation figures discussed in the following paragraphs, see Tab. 8-11.

In this study, a broad spectrum of cognitive domains was assessed in order to

correlate the respective test to cTT. Mini-mental State Exam was used as a general screening test for dementia. In this test, a large majority of patients performed normally (mean score 28.0 of 30). However, there is some scatter in the scores (20-30) and there is a weak, yet significant negative correlation between cTT and MMSE score ($r = -0.356$; $p = 0.042$). This suggests that also in patients who do not meet the criteria for dementia according to MMSE but show possible signs of beginning VCI, i.e. those with scores lower than 30 but higher than 25, cTT might be sensitive enough to show this development. Similar concerns derive from a recent publication, where MMSE was evaluated against a newer screening method, the Montreal Cognitive Assessment. Especially when it comes to executive function - a dominant domain in VCI - MMSE picked up significantly less cognitive abnormalities [34].

Memorizing of numbers as a subtest from the HAWIE assesses episodic short-term memory. No significant correlation of digit span with cTT was found for the age-controlled normalized score ($r = -0.046$; $p = 0.789$). This, for one, would again support findings of other studies ([2], [8]) where episodic memory has never been essentially impaired in VaD. Still, the relatively small number of patients in this study puts the interpretational value of this result into perspective.

The Benton Visual Retention test covers the visuospatial domain. Although some studies (e.g. [3]) claim this domain also to be characteristically affected in VCI, our study could at least not show any significant correlation with cTT ($r = -0.272$; $p = 0.114$). There are various reasons possibly explaining this: 1. We simplified the evaluation process of the Benton test to a correct/false decision for each test sheet. With these crude test results, which can therefore only range between 0 and 10, a highly sensitive assessment of the visuospatial domain might be impossible. 2. The resulting scores of this evaluation method cannot be standardized in any way. Moreover, the manual for the Benton test does not provide any normal scores gained from large healthy populations. 3. As a result of this, the results we found are hard to interpret. From a subjective point of view, one may claim that all patients in this study performed relatively poorly in this test (with a mean of 4.6 correct reproductions out of ten possible). Assuming a more or less constant poor baseline performance in all patients, finding a significant linear (or otherwise arithmetic) correlation is even harder. Given all this, visuospatial cognitive performance might indeed be affected. Larger study samples, more detailed evaluation of the test errors and a control group eventually may show a relation between cTT and Benton test performance in further studies.

Test d2 allows estimations of attentional processes over a relatively long time. Also, a component of executive function involvement can be claimed to be included in this test, as a patient has to decide whether each sign is critical or not. Moreover, also motor speed has its part, as the period of time available for each row of signs is limited. The share of patients scoring less than one standard deviation below the average performance of a comparative population is not much larger than one would expect by statistics (28.9 % for GZ_SW, 23.7% for GZ-F_SW; to be expected: 15.89%). Still, cTT prolongation shows a significant negative correlation with GZ-F-SW ($r = -0.428$; $p = 0.016$). This means that even in a cohort of patients with only slightly below-average performance in this test, cTT is prolonged in those with below-average

performance. Still, one restraint has to be mentioned. The main score for performance in the test d2, GZ-F, shows a rather wide range (91-579, median 309.5). This leads to the conclusion that, with this method alone, gaining hints whether one very patient is impaired in cognition might turn out hard. At least for the study cohort at hand, d2 might not be an ideal parameter assessing neuropsychological performance. Similar concerns will come up below when the applicability of MRI with the possibility of detecting WMH as a marker of cognitive decline is being questioned.

The subtest *Alertness* of *TAP* represents a classic attentional task. Neither with, nor without an alert before the critical stimulus did the patients produce many errors (omissions, outliers, or anticipations). An exception from that is the number of omissions in the 4th round (i.e. the 2nd round without alert) and in both rounds without alert combined (i.e. 2nd and 4th). Consequently, cTT shows significant correlations with the number of omissions in both rounds where no alert was presented before a critical stimulus ($r = 0.364$; $p = 0.029$ and $r = 0.346$; $p = 0.036$, respectively). It is arguable if this shows an actual relation or if the high number of omissions in the 4th round is more likely due to exhaustion effects and therefore leads to a slightly significant correlation for both rounds combined, as well. Looking at the reaction times patients needed to respond to a critical stimulus, it is remarkable that without as well as with precedent alert 55% of the patients showed a performance below average. This would well match with findings of other authors [8], stating that VCI can present with decreased processing speed. With reaction times without alert, cTT is significantly correlated (median: $r = 0.392$; $p = 0.018$, mean: $r = 0.424$; $p = 0.010$). Although the same percentage of patients performed below average with precedent alert, the correlation is not significant for this task (mean: $r = 0.280$; $p = 0.098$). This could be explained if assuming that the alert actually shortens the reaction time (and does not lead to an error of anticipation at the same time). In this case, reaction times obviously did not become short enough to improve the T-score to over 41 but still changed in a way which minimized the significancy of the Pearson correlation. If one considers reacting to a stimulus without an alert a more difficult task than doing the same with precedent alert (which seems reasonable in terms of reaction time, at least), increased significance of the correlation would also fit findings of Iemolo et. al. who state that “patients [with vascular cognitive impairment] may perform normally on simple tasks but reveal deficits as tasks increase in complexity” [1].

Go/Nogo is a test which focuses on examining executive function. Patients did not produce a high number of errors. In fact, 87% presented normal or above-average performance. Given the fact that Go/Nogo has to be considered a rather simple test and the patients participating in this study were, at least according to current diagnostic standards, not severely affected by their dementia, this is not surprising. The correlation with cTT is therefore not significant, either ($r = 0.075$; $p = 0.663$, for the correlation with the numbers of errors). The test results with respect to omissions led to some confusion. At first sight, all patients (97%) performed below average in this category. But when taking a look at the absolute figures, one was able to see, that even patients omitting not a single critical stimulus were ascribed a T-score of 39, thus classifying their result as "below-average". A phone call with the manufacturing company (Fa. PSYTEST, Germany) provided some better understanding: (1)

The output values in the SPSS file are misleading. Instead of a T-score of 39, the output of T>39 (or even T=50) would have been correct. (2) The reason for this phenomenon is the fact that across the comparison population, a large majority of candidates produced no omissions at all. Statistically, this leads to the impression of a below-average performance when omitting even only one critical stimulus. But apart from mathematical considerations this only makes the numbers unusable.

With this reservation one also has to judge the reaction times. 61% of patients performed below average regarding this criterion (T-score for median reaction time). The correlation between median reaction time (T-score) and cTT is therefore significant ($r = -0.375$; $p = 0.024$). Yet it stands to reason that also this characteristic of the test is skewed by an overall very good performance in the comparison population. As a conclusion, Go/Nogo has to be considered unfit for the needs of this study. Most likely the task is just too simple to make valid sense of the results one gains.

Divided Attention can be considered the most complex test for executive function and information processing in our test composition. When calculating PMCC for this test's parameters with cTT, results are as follows: highly significant correlations appeared for the median reaction time to auditive stimuli ($r = 0.591$; $p = 0.001$), as well as to its T-score ($r = -0.567$; $p = 0.001$), the median reaction time to visual stimuli ($r = 0.794$; $p = 0.000$) and its T-score ($r = -0.458$; $p = 0.007$), and the total number of erroneous reactions ($r = 0.470$; $p = 0.006$). Also significant are correlations with the number of omissions and outliers for visual stimuli ($r = -0.398$; $p = 0.022$ and $r = -0.372$; $p = 0.033$, respectively) and the number of errors for both conditions combined ($r = 0.382$; $p = 0.028$).

All this leads to the conclusion that cTT is in fact a valid [24] and easy to gain (measurement of cTT usually takes no longer than 15 minutes) parameter to quantify early vascular cognitive impairment. Even in a small study population, it presents highly significant correlations with patients' performance in neuropsychological testing. Moreover it is only significant for performance in those domains considered crucially affected in VCI and early in the course of VaD, whereas no such correlations were found for domains like episodic memory. This points towards both a high sensitivity and specificity of cTT for VCI. Certainly, further studies with larger samples and a matched control group of healthy patients will have to confirm those very assumptions. Yet, there are some limitations to the method. As it turned out, in two out of the examined 38 patients no usable cTT could be measured due to prolonged wash-in time of the contrast agent. Also, especially with increasing age of the patients, it becomes more difficult to find a sufficient temporal bone window as the bone tends to become less solid and thus scatters the ultrasound beam. There are no data so far on the frequency and importance of this phenomenon.

5.4 On the relation between cTT and the extent of WML

Several studies have stated a relation between the existence and severity of WML and the patients' clinical functioning [35],[15]. Obviously, the relation does not seem to be too strong, and it remains unclear which property of WML exactly is responsible for or correlated with cognitive decline. One study says it is more likely the volume of brain tissue affected by WMLs than their number

[36]. Another paper based on the same study population therefore stated that "WMH ... should ... be evaluated when assessing small vessel disease in relation to cognitive function."[37]. Latest results merge those two findings stating that there are critical areas of the brain where even small lesions can cause remarkable cognitive deficits [19]. As the focus of our study is on cTT in small-vessel disease, and cTT turned out to be a good marker for the severity of VCI, it seemed interesting to see, if and to what extent cTT prolongation correlates with the severity of WML. The results of Kruskal-Wallis analysis are depicted in Fig. 3 in chapter 4.9.4. The test was significant ($p = 0.012$), but only if the Null hypothesis assumes equal distribution of cTT across all three groups of WML load. As may be easily seen from the box-plot, there is no significant difference between group B and C ($p = 0.138$ in pairwise comparison). The significant difference therefore only exists between group D (severe WML) and the other groups. This might point towards an actually existing relation, which however cannot be stated on the basis of the data at hand. For one, the study population may be definitely too small for that purpose. Moreover, we did not include any patients that would fit the criteria for group A (no WML). On the other hand, there was no significant relation between the extent of WMH and patients' performance in neuropsychological testing (with few exceptions, thus most likely random). One way or the other, further studies without the restrictions mentioned will have to provide more reliable data to evaluate a possible quantitative relation between cTT and WML, also taking into consideration the latest findings on the importance of the location of the lesions.

5.5 On the clinical relevance of cTT in VCI: Proposal of a cutoff score

Given the strong correlations between neuropsychological testing and cTT, it seems reasonable to go one step further and try to transfer the findings into practical clinical methods. One attempt is to find a cutoff value for cTT which appears to reliably differentiate pathological prolongation from normal variations, based on the expected neuropsychological outcome. When proceeding as shown in chapter 4.9.5, a cTT of 5.5 seconds seems to fulfill this requirement. Non-parametric analysis of variance was performed for the two groups of cTT (below and above 5.5s) across all neuropsychological test which presented significant correlations with cTT before. Tab. 12 in chapter 4.9.5 summarizes the results. One can see that the test performance in test d2 is significantly different across the two groups. Because Kruskal-Wallis analysis does only state if the difference is significant but does not give the direction of the difference, this has to be tracked by looking at the corresponding box-plots. For each parameter of d2, as well as all the other parameters significant in Kruskal-Wallis analysis, patients with shorter cTT performed better in the respective neuropsychological test. No significant differences of cTT were found across the tests of TAP Alertness and Go/Nogo. For Divided Attention, however, each parameter except "outliers – visual stimuli" and "errors – total" presents a significant difference between the two groups of cTT. Having in mind that Divided Attention was the test in which patients showed below average performance most impressively, this gives a hint that the proposed cutoff of 5.5 seconds might indeed be of clinical relevance. What can be said for sure is that at least for test d2 and most parameters of Divided Attention, measuring cTT alone allows to reliably predict an impaired performance in neuropsychological

testing. Of course, as the initial aim of the study has never been to propose any cutoff score for cTT, the study design is not optimal for that purpose. Further investigations with a larger patient sample and a control group will have to make more precise statements about sensitivity and specificity of this method and maybe even adjust the exact cutoff score. Still, with the small sample of patients available in this study, it seems reasonable to propose the existence and clinical relevance of a cutoff score for cTT, thus suggesting that cTT is a valuable instrument to assess patients with possible or probable VCI.

6. Summary

Dementia, or any form of degenerative cognitive decline, is one of the major problems in present, and even more will be in future medicine. With Alzheimer's disease (AD) being the most prevalent, Vascular Dementia is the second most entity of dementing processes in the elderly. As diagnostic criteria are still imprecise and in many cases do not embrace early stages of the disease, recent studies have proposed more detailed classifications of the newly created condition Vascular Cognitive Impairment (VCI). Of all conditions subsumed under this term, subcortical small-vessel alterations are the most common cause for cognitive decline.

Frequently and predominantly affected cognitive domains in VCI are, among others, attention, visuospatial perception, information processing, and executive function. Episodic memory will remain spared in VCI for a long time.

The diagnosis of dementia / cognitive impairment is presently often made in late stages of the disease, when therapeutical options are poor. Thus, early detection of changes of the subcortical small vessels is desirable, when there is still time to identify and aggressively treat risk factors and underlying conditions like diabetes, hyper- or hypotension, and hyperlipidemia. This study aimed to evaluate whether cTT correlates to cognitive dysfunction, i.e. if cTT is fit as an early diagnostic tool for VCI. The study cohort included 38 patients from the Neurological Clinic of the Würzburg University hospital admitted due to diagnoses other than dementia or stroke.

In general, mainly three diagnostic tools come to mind: Neuropsychological tests, neuroimaging (e.g. magnetic-resonance tomography), and measuring cerebral arterio-venous transit time (cTT). Therefore, we set up a broad battery of neuropsychological tests covering all major domains of cognitive function and assessed the patients with alterations in MRI typical for VCI (i.e. white matter hyperintensities, WMH). In summary it can be said, that we examined a population mildly affected by cognitive impairment who showed patterns of dysfunction characteristic for a vascular etiology. Assessment of patients by our test battery was more sensitive than the still commonly used MMSE. The most sensitive tests to detect VCI were "Divided Attention", "d2", and to some extent "Alertness".

Statistical analyses showed that several scores within each test characteristic for VCI were correlated significantly with cTT ($p=0.05$); some correlations, mainly those of Divided Attention were even highly significant ($p=0.01$). This strongly suggests that cTT is indeed a valuable tool to easily asses the extent of cognitive impairment caused by small vessel disease and thus is even more feasible than the test battery in terms of early detection of VCI.

In further statistical analysis we had a look for a possible influence of WMH on cTT prolongation. Figures showed that cTT tended to be prolonged in patients with a greater extent of WMH, whereas there was no significant overall correlation between cTT and the extent of WMH.

With all the findings given so far, in a last step we tried to propose a cutoff value for cTT separating normal from below-average test performance. A cutoff of 5.5 seconds turned out to meet this requirement best. It significantly discriminated the two groups (cTT higher or lower than 5.5 sec) with respect to some of their test scores. However, it was not possible to integrate the test performances of all the relevant tests. Keeping in mind that the proposal of such a cutoff has never been the primary aim of the study and more participants are certainly needed to further elucidate, it is left to further studies to answer this question.

What this study was able to show is the following: First, patients with signs of small-vessel lesions in MRI show distinct patterns of cognitive impairment which differ clearly from those expected in AD patients and are in line with other authors as typical findings for VCI. Secondly, the extent of cognitive dysfunction correlates strongly with the prolongation of cTT. Thirdly, a strong relation between the extent of WMH and the patients' test performances could not be shown. This may be because our MRI subgroups were too small, or rather because the location of the respective lesion was not taken into consideration.

As a result of this study it turned out that cTT is certainly capable of fulfilling the task to easily and effectively detect and evaluate possible microvascular lesions of the brain with respect to the actual clinical relevance for the patient. When compared to the other proposed diagnostic tools, neuropsychological testing and MRI, the advantages of cTT are obvious: its measurement is a low-cost and quick procedure which would spare both patients and examiners a long neuropsychological exam or complement it. cTT is safe to assess as the only possible risks derive from the use of the contrast agent, which are rare and easily manageable. It has also proven to be more accurate in showing the extent of cognitive impairment than MRI. Finally, it is widely available. The only prerequisite is an ultrasound machine capable of transcranial color-coded duplex sonography. No cost-intensive procedures like MRI are needed. So, with neuropsychological testing remaining the gold standard, cTT here proved to be a reliable alternative which is more time- and cost-effective than MRI.

Zusammenfassung

Demenzen und alle anderen Formen kongnitiver Leistungseinschränkungen gehören heute zu den bedeutendsten medizinischen Herausforderungen und werden in der Zukunft noch weiter an Bedeutung gewinnen. Die häufigste der Demenzerkrankungen bei älteren Patienten ist die Alzheimer-Krankheit, gefolgt von den vaskulären Demenzen. Da die Diagnosekriterien in vielen Fällen noch unpräzise sind und vor allem frühe Stadien der Erkrankung nicht erfassen, wurden in der neueren Literatur detailliertere Untergruppen der neu eingeführten Entität „vaskuläre kognitive Funktionsstörung“ (vascular cognitive impairment, VCI) etabliert. Subkortikale Veränderungen an den kleinsten Gefäßen stellen unter allen Pathologien, die unter diesem Begriff subsumiert sind, die häufigste Ursache für kognitive Leistungseinschränkungen dar.

Häufig und bevorzugt betroffene kognitive Domänen des VCI sind unter

anderem Aufmerksamkeit, räumliche Wahrnehmung, Informationsverarbeitung und Exekutivfunktion. Das episodische Gedächtnis bleibt fürgewöhnlich lange intakt.

Die Diagnose Demenz bzw. VCI wird oft erst in späten Stadien der Krankheit gestellt, wenn die therapeutischen Mittel bereits stark begrenzt sind. Deshalb wäre eine Möglichkeit zur frühen Entdeckung subkortikaler Gefäßveränderungen wünschenswert in einem Stadium der Krankheit, in dem es noch möglich ist, Risikofaktoren wie Diabetes mellitus, arterielle Hyper- und Hypotonie und Fettstoffwechselstörungen auszumachen und konseqeuent zu behandeln. Das Ziel dieser Studie war es zu untersuchen, ob cTT mit dem Ausmaß kognitiver Dysfunktion korreliert, ob also cTT als frühes diagnostisches Verfahren für vaskuläre demenzielle Prozesse geeignet ist. Die Studienpopulation umfasste 38 Patienten aus der Klinik und Poliklinik für Neurologie der Universität Würzburg. Die ausgewählten Patienten befanden sich nicht auf Grund von Schlaganfällen oder Demenz in stationärer Behandlung.

Generell stehen drei wesentliche diagnostische Verfahren für vaskuläre Demenzen zur Verfügung: neuropsychologische Tests, bildgebende Verfahren (z.B. Magnetresonanztomographie) und das Messen der zerebralen arteriovenösen Transitzeit (cTT). Daher wurde für diese Studie eine umfangreiche Batterie neuropsychologischer Tests zusammengestellt, die alle wesentlichen kognitiven Domänen untersucht. Mit Hilfe dieser Batterie wurden Patienten untersucht, die für die vaskulären Demenz typische Veränderungen im MRT zeigten (Hyperintensitäten der weißen Hirnsubstanz, WMH). Es zeigte sich, dass die von uns untersuchte Population insgesamt von leichten kognitiven Funktionseinschränkungen betroffen war und das Muster der befallenen Domänen gut mit einer vaskulären Ätiologie vereinbar ist. Die Untersuchung der Patienten mittels der von uns zusammengestellten Testbatterie war dabei sensitiver als der nach wie vor weit verbreitete Mini-Mental-Status-Test (MMST). Die sensitivsten Tests zum Erkennen vaskulärer Demenz waren Geteilte Aufmerksamkeit, d2 und zu einem gewissen Grad Alertness.

Die statistische Auswertung zeigte, dass verschiedene Parameter jedes Tests einer charakteristischen Domäne signifikante Korrelationen mit der Verlängerung der cTT aufwies ($p=0,05$). Vor allem beim Test Geteilte Aufmerksamkeit waren einige Korrelationen sogar hoch signifikant ($p=0,01$). Diese Ergebnisse weisen darauf hin, dass die cTT tatsächlich ein geeignetes Instrument ist, das Ausmaß vaskulär bedingter kognitiver Dysfunktion zu erfassen und dabei auch praktikabler ist als eine umfangreiche Testbatterie in Bezug auf die Früherkennung von VCI.

In weiteren statistischen Untersuchungen untersuchten wir einen möglichen Einfluss von WMH auf die Verlängerung der cTT. Die Ergebnisse zeigten, dass die cTT tendenziell verlängert ist bei Patienten mit größerem Ausmaß von Marklagerschädigungen, wobei keine generelle signifikante Korrelation zwischen der cTT und dem Ausmaß der Marklagerschädigungen bestand.

Mit allen diesen Erkenntnissen versuchten wir in einem letzten Schritt, einen möglichen Grnazwert für die cTT zu finden, der „normale“ von unterdurchschnittlichen Testleistungen zu trennen in der Lage ist. Diese Anforderung erfüllte am besten Wert von 5,5 Sekunden für die cTT. Nach dieser

Maßgabe gebildete Gruppen (cTT größer oder kleiner als 5,5 Sekunden) unterschieden sich in einigen Testergebnissen signifikant voneineander. Jedoch war es nicht möglich, eine sichere Differenzierung anhand des cTT-Grenzwertes für alle relevanten neuropsychologischen Tests zu erreichen. Da das Finden eines solchen Grenzwertes nie ein Ziel dieser Studie war und sicherlich mehr Studienteilnehmer für diesen Zweck erforderlich sind, wird es die Aufgabe weiterer Untersuchungen sein, diese Frage zu beforschen.

Die vorliegende Studie konnte folgendes zeigen: 1. Bei Patienten mit magnetresonanztomografischen Zeichen der Marklagerschädigung finden sich spezifische Muster der kognitiven Dysfunktion, die sich deutlich von denen unterscheiden, die man z.B. bei der Alzheimer-Demenz erwarten würde. Diese Muster stimmen dabei mit denen überein, die auch von anderen Autoren in neueren Untersuchungen beobachtet werden konnten. 2. Das Ausmaß der kognitiven Dysfunktion korreliert gut mit der Verländerung der cTT. 3. Eine eindeutige Korrelation zwischen dem Ausmaß der Marklagerschädigung und der cTT konnte nicht beobachtet werden. Dies kann daran liegen, dass die gebildeten MRT-Untergruppen jeweils zu wenige Individuen umfassten oder dass der Ort der jeweiligen Läsionen nicht berücksichtigt wurde.

Ein Ergebnis dieser Studie ist, dass die cTT sicherlich in der Lage ist, einfach und zuverlässig mögliche mikrovaskuläre Schädigungen des Gehirns auch im Hinblick auf ihre tatsächliche klinische Relevanz zu entdecken. Im Vergleich mit anderen Diagnoseverfahren (Testpsychologie und MRT) sind die Vorteile der cTT offensichtlich: die Messung ist ein kostengünstiges und schnelles Verfahren, das sowohl Patienten als auch Untersuchern eine langwierige neuropsychologische Untersuchung erspart. Die Messung der cTT ist ein sicheres Verfahren, da die wenigen aus der Anwendung des Kontrastmittels sich ergebenden Risiken selten und gegebenenfalls leicht behandelbar sind. Zudem erwies sich die cTT als präziser bei der Aufgabe, das Ausmaß kognitiver Dysfunktion zu messen, als es die MRT vermochte. Zuletzt ist die cTT auch flächendeckend verfügbar. Die einzige Voraussetzung ist ein Duplex-fähiges Ultraschallgerät. Kostenintesive Untersuchungen wie die MRT können vermieden werden.

Wenn auch die Testpsychologie der Goldstandard bleiben wird, erwies sich die cTT als zuverlässige Alternative die im Vergleich zur MRT sowohl Zeit als auch Kosten spart.

7. Bibliography

1. Iemolo, F., et al., *Pathophysiology of vascular dementia.* Immun Ageing, 2009. **6**: p. 13.
2. Villardita, C., *Alzheimer's disease compared with cerebrovascular dementia. Neuropsychological similarities and differences.* Acta Neurol Scand, 1993. **87**(4): p. 299-308.
3. Graham, N.L., T. Emery, and J.R. Hodges, *Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia.* J Neurol Neurosurg Psychiatry, 2004. **75**(1): p. 61-71.
4. O'Brien, J.T., et al., *Vascular cognitive impairment.* Lancet Neurol, 2003. **2**(2): p. 89-98.
5. World Health, O., *ICD-10 : international statistical classification of diseases and related health problems / World Health Organization* 2004, Geneva :: World Health Organization.
6. Wetterling, T., R.D. Kanitz, and K.J. Borgis, *The ICD-10 criteria for vascular dementia.* Dementia, 1994. **5**(3-4): p. 185-8.
7. Bowler, J.V. and V. Hachinski, *Vascular cognitive impairment: a new approach to vascular dementia.* Baillieres Clin Neurol, 1995. **4**(2): p. 357-76.
8. Moorhouse, P. and K. Rockwood, *Vascular cognitive impairment: current concepts and clinical developments.* Lancet Neurol, 2008. **7**(3): p. 246-55.
9. Lim, A., et al., *Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series.* J Am Geriatr Soc, 1999. **47**(5): p. 564-9.
10. Jellinger, K.A. and J. Attems, *Is there pure vascular dementia in old age?* J Neurol Sci, 2010. **299**(1-2): p. 150-4.
11. Rockwood, K., et al., *Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging.* Neurology, 2000. **54**(2): p. 447-51.
12. Lobo, A., et al., *Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group.* Neurology, 2000. **54**(11 Suppl 5): p. S4-9.
13. Melzer, D., M. Ely, and C. Brayne, *Cognitive impairment in elderly people: population based estimate of the future in England, Scotland, and Wales.* BMJ, 1997. **315**(7106): p. 462.
14. Pantoni, L. and J.H. Garcia, *Pathogenesis of leukoaraiosis: a review.* Stroke, 1997. **28**(3): p. 652-9.
15. Pantoni, L., A. Poggesi, and D. Inzitari, *The relation between white- matter lesions and cognition.* Curr Opin Neurol, 2007. **20**(4): p. 390-7.
16. Ott, A., et al., *Diabetes mellitus and the risk of dementia: The Rotterdam Study.* Neurology, 1999. **53**(9): p. 1937-42.
17. Leblanc, G.G., et al., *Genetics of vascular cognitive impairment: the opportunity and the challenges.* Stroke, 2006. **37**(1): p. 248-55.
18. Jellinger, K.A., *Understanding the pathology of vascular cognitive*

impairment. J Neurol Sci, 2005. **229-230**: p. 57-63.

19. Duering, M., et al., *Strategic role of frontal white matter tracts in vascular cognitive impairment: a voxel-based lesion-symptom mapping study in CADASIL.* Brain, 2011. **134**(Pt 8): p. 2366-75.
20. Middleton, L.E. and K. Yaffe, *Promising strategies for the prevention of dementia.* Arch Neurol, 2009. **66**(10): p. 1210-5.
21. Qiu, C., B. Winblad, and L. Fratiglioni, *The age-dependent relation of blood pressure to cognitive function and dementia.* Lancet Neurol, 2005. **4**(8): p. 487-99.
22. Puls, I., et al., *Diagnostic impact of cerebral transit time in the identification of microangiopathy in dementia: A transcranial ultrasound study.* Stroke, 1999. **30**(11): p. 2291-5.
23. Breteler, M.M., et al., *Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging. The Rotterdam Study.* Stroke, 1994. **25**(6): p. 1109-15.
24. Puls, I., et al., *Cerebral arteriovenous transit time (CTT): a sonographic assessment of cerebral microcirculation using ultrasound contrast agents.* Ultrasound Med Biol, 1999. **25**(4): p. 503-7.
25. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res, 1975. **12**(3): p. 189-98.
26. Holsinger, T., et al., *Does this patient have dementia?* JAMA, 2007. **297**(21): p. 2391-404.
27. Mungas, D., *In-office mental status testing: a practical guide.* Geriatrics, 1991. **46**(7): p. 54-8, 63, 66.
28. Tewes, U., *Hamburg-Wechsel-Intelligenztest für Erwachsene, Revision 1991; Handbuch und Testanweisung,* 1994, Verlag Hans Huber
29. Benton Sivan, A. and O. Spreen, *Der Benton-Test*
    Handbuch. 7., vollst. überarbeitete Auflage ed1996.
30. Brickenkamp, R., *Test d2*
    Aufmerksamkeits-Belastungstest
    Manual. 9., überarbeitete und neu normierte Auflage ed2002, Göttingen Bern Toronto Seattle: Hogrefe Verlag für Psychologie.
31. Zimmermann, P. and B. Fimm, *TAP*
    Testbatterie zur Aufmerksamkeitsprüfung
    Version 2.1
    Teil 1, 2007.
32. Sturm, W. and K. Willmes, *On the functional neuroanatomy of intrinsic and phasic alertness.* Neuroimage, 2001. **14**(1 Pt 2): p. S76-84.
33. Murkin, J.M., et al., *Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery.* Ann Thorac Surg, 1995. **59**(5): p. 1289-95.
34. Pendlebury, S.T., et al., *Underestimation of cognitive impairment by Mini- Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study.* Stroke, 2010. **41**(6): p. 1290-3.

35. Pantoni, L., et al., *Role of white matter lesions in cognitive impairment of vascular origin.* Alzheimer Dis Assoc Disord, 1999. **13 Suppl 3**: p. S49-54.
36. van Straaten, E.C., et al., *Impact of white matter hyperintensities scoring method on correlations with clinical data: the LADIS study.* Stroke, 2006. **37**(3): p. 836-40.
37. van der Flier, W.M., et al., *Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study.* Stroke, 2005. **36**(10): p. 2116-20.

8. Appendix

Att. 1: Test form Mini-Mental State Exam

www.pflegedienst-aml.de/media/mmst-test.pdf

Mini-Mental Status-Test (MMST)

....

Name und Vorname des Patienten *Datum*

1. Orientierung

In welchem Jahr leben wir? ☐
Welche Jahreszeit ist jetzt? ☐
Welches Datum haben wir heute? ☐
Welchen Monat haben wir? ☐
In welchem Bundesland sind wir hier? ☐
In welchem Land? ☐
In welcher Ortschaft? ☐
Wo sind wir (in welcher Praxis / Altenheim)? ☐
Auf welchen Stockwerk? ☐

2. Merkfähigkeit

Fragen Sie den Patienten, ob Sie sein Gedächtnis prüfen dürfen. Nennen Sie dann drei verschiedenartige Dinge klar und langsam (ca 1 pro sec) “Zitrone, Schlüssel, Ball”. Nachdem Sie allle drei Worte ausgesprochen haben, soll der Patient sie wiederholen. Die erste Wiederholung bestimmt die Wertung (vergeben Sie für jedes wiederholte Wort einen Punkt), doch wiederholen Sie den Versuch, bis der Patient alle drei Wörter nachsprechen kann. Maximal gibt es 5 Versuche. Wenn ein Patient nicht alle drei Wörter lernt, kann das Erinnern nicht sinnvoll geprüft werden.

Punkte 0-3 ☐

3. Aufmerksamkeit und Rechnen

Bitten Sie den Patienten, bei 100 beginnend in 7er Schritten rückwärts zu zählen. Halten Sie nach 5 Substraktionen (93, 86, 79, 72, 65) an und zählen Sie die in der richtigen Reihenfolge gegebenen Antworten. Bitten Sie daraufhin das Wort “Preis” rückwärts zu buchstabieren. Die Wertung entspricht der Anzahl von Buchstaben in der richtigen Reihenfolge (z.B. SIERP=5, SIREP=3). Die höhere der beiden Wertungen wird gezählt.

Punkte 0-5 ☐

4.Erinnern

Fragen Sie den Patienten, ob er die Wörter noch weiß, die er vorhin auswendig lernen sollte. Geben Sie einen Punkt für jedes richtige Wort.

Punkte 0-3 ☐

5. Benennen

Zeigen Sie dem Patienten eine Armbanduhr und fragen Sie ihn was das ist. Wiederholen Sie die Aufgabe mit einem Bleistift. Geben Sie einen Punkt für jeden erfüllten Aufgabenteil.

Punkte 0-3 ☐

6. Wiederholen

Bitten Sie den Patienten, den Ausdruck “ Kein Wenn und Aber” nachzusprechen. Nur ein Versuch ist erlaubt.

Punkte 0-1 ☐

7. Dreiteiliger Befehl

Lassen Sie den Patienten den folgenden Befehl ausführen. “ Nehmen Sie ein Blatt in die Hand, falten Sie es in der Mitte und legen Sie es auf den Boden.” Geben Sie einen richtigen Punkt für jeden richtig ausgeführten Befehl.

Punkte 0-3 ☐

8. Reagieren

Schreiben Sie auf ein weißes Blatt in grossen Buchstaben: “Schließen Sie die Augen”. Der Patient soll den Text lesen und ausführen. Geben Sie einen Punkt, wenn der Patient die Augen schließt.

Punkte 0-1 ☐

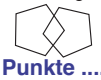
9. Schreiben

Geben Sie dem Patienten ein weißes Blatt, auf dem er für Sie einen Satz schreiben soll. Diktieren Sie den Satz nicht, er soll spontan geschrieben werden. Der Satz muß ein Subjekt und ein Verb enthalten und einen Sinn ergeben. Konkrete Grammatik und Interpunktion werden nicht verlangt.

Punkte 0-1 ☐

10. Abzeichnen

Zeichnen Sie auf ein weißes Blatt zwei sich überschneidene Fünfecke und bitten Sie den Patienten, die Figur genau abzuzeichnen. Alle 10 Ecken müßen vorhanden sein und 2 müßen sich überschneiden, um als ein Punkt zu zählen. Zittern und Verdrehen der Figur sind nicht wesentlich.

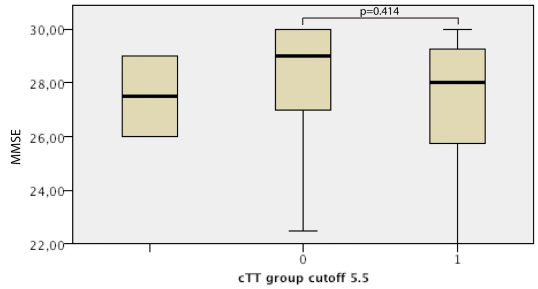


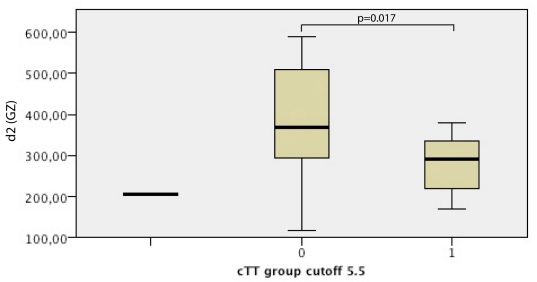
Punkte 0-1 ☐

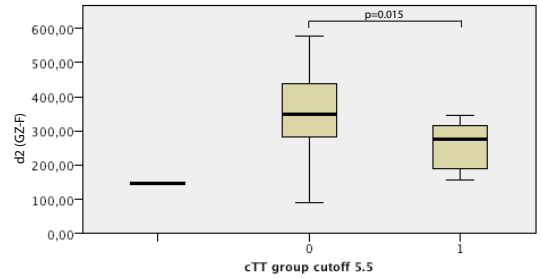
Summe der Punkte ..... ☐

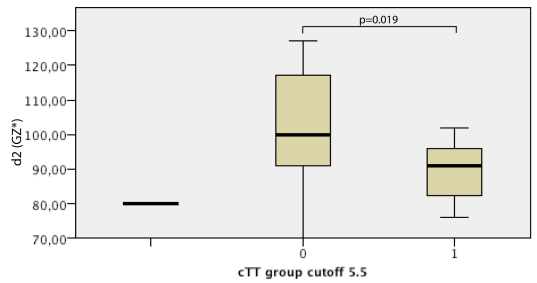
Att. 2: neuropsychological tests across cutoff groups cTT (Kruskal-Wallis)

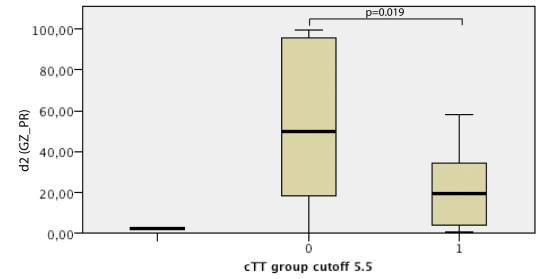
as mentioned in section 5.5

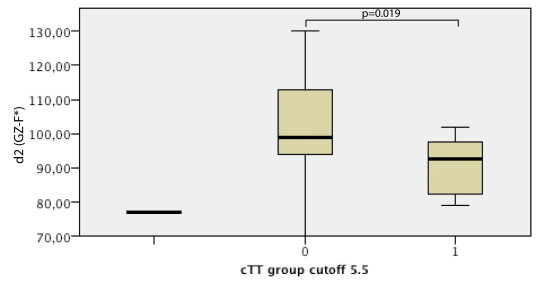


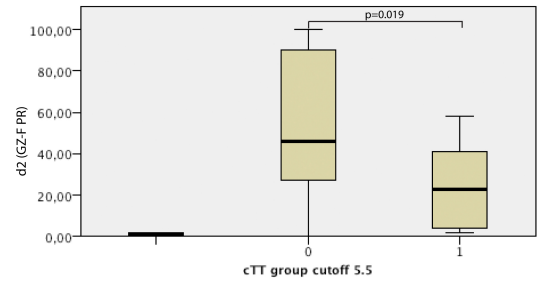


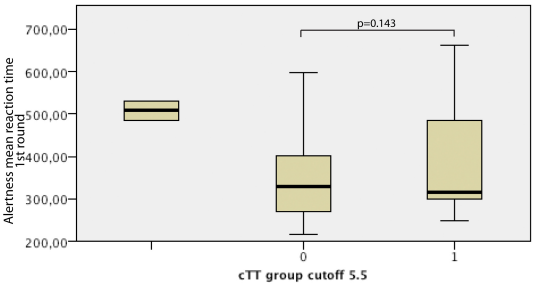


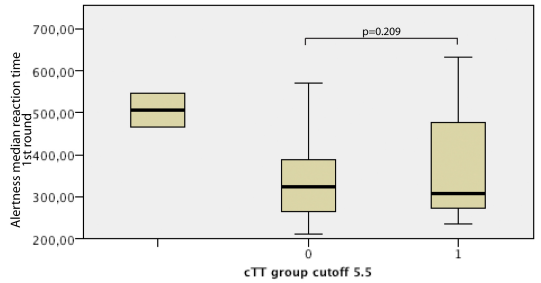


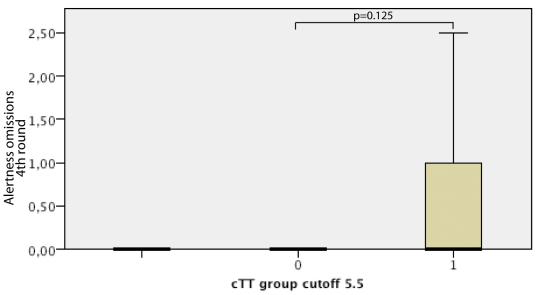






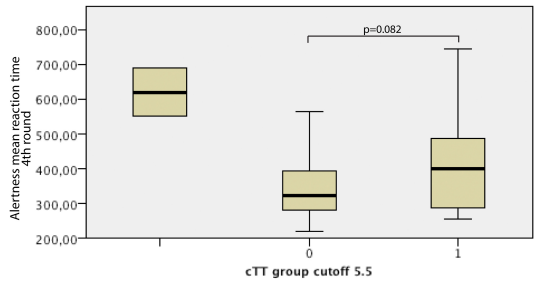


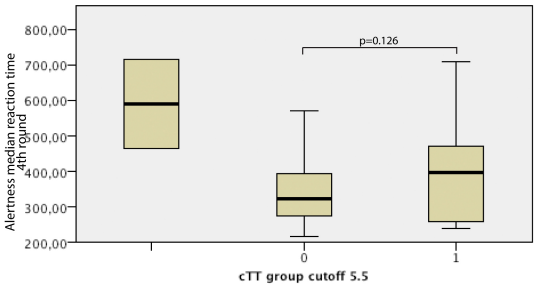


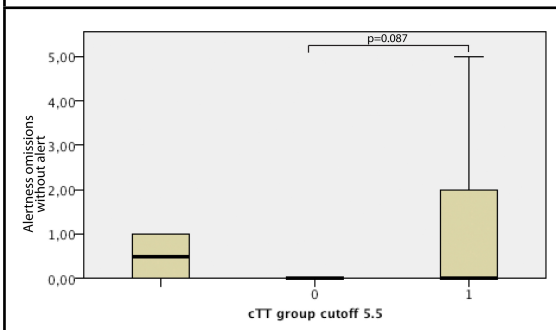


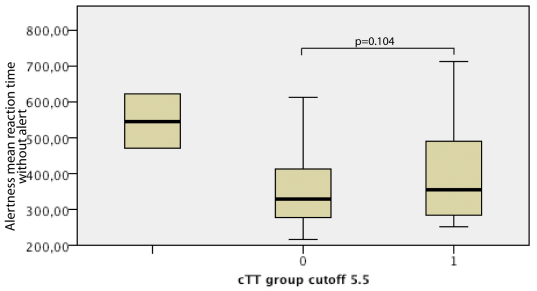
Att. 2: neuropsychological tests across cutoff groups cTT (Kruskal-Wallis)

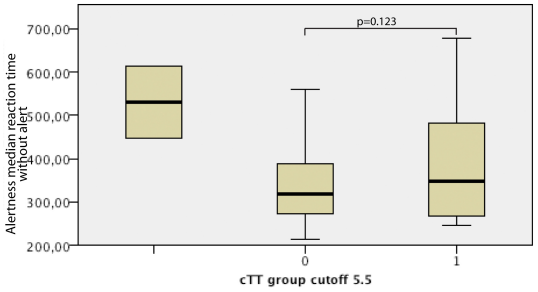
as mentioned in section 5.5

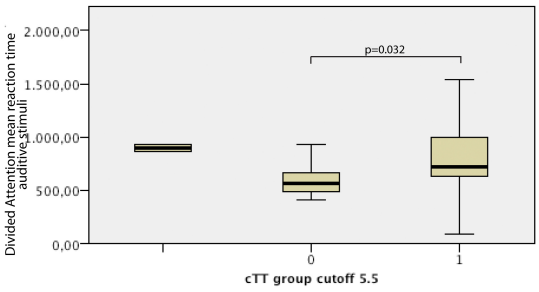


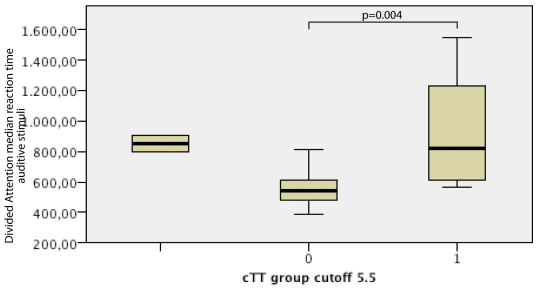


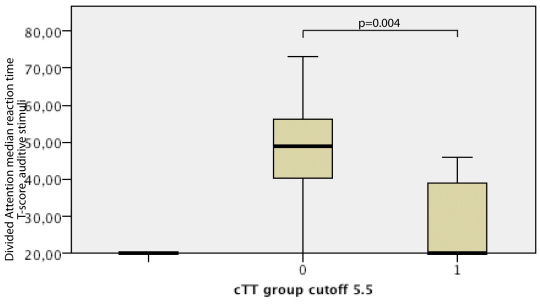


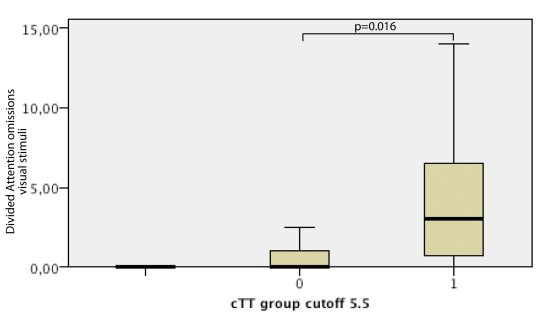


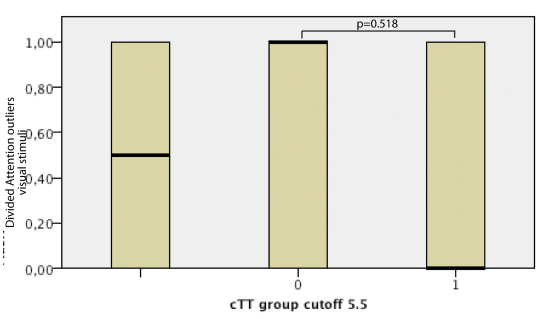






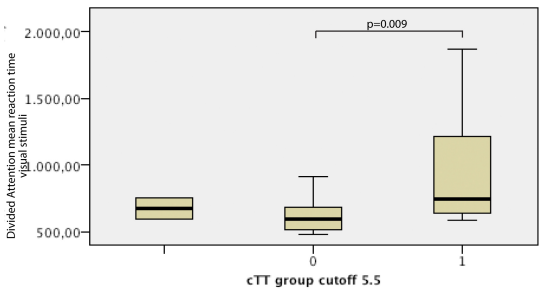


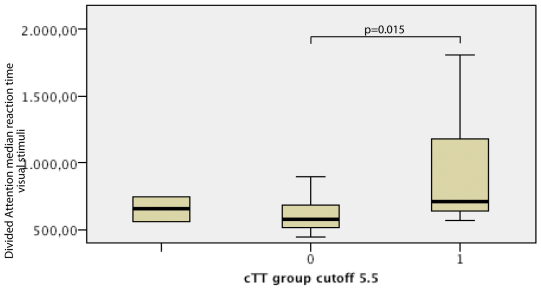


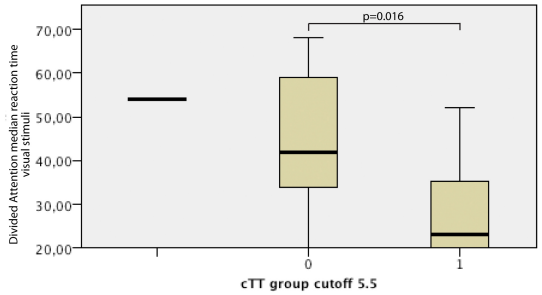


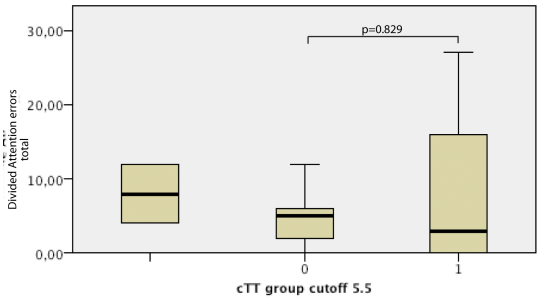
Att. 2: neuropsychological tests across cutoff groups cTT (Kruskal-Wallis)

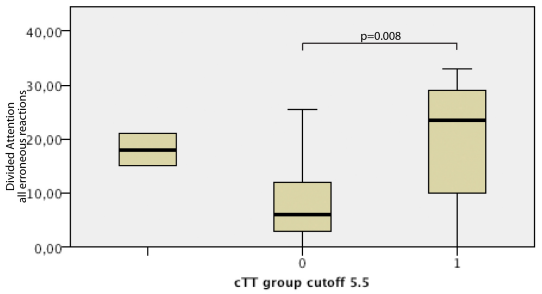
as mentioned in section 5.5

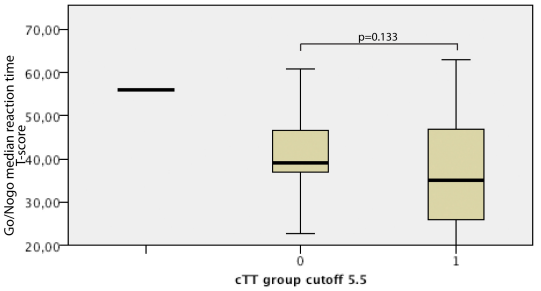












Danksagung

Mein besonderer Dank gilt Herrn Prof. Wolfgang Müllges für die stets fürsorgliche Betreuung dieser Doktorarbeit, seine zahllosen hilfreichen Anmerkungen und Ideen und den sehr kollegialen persönlichen Kontakt.

Des weiteren möchte ich Herrn Dr. Jens-Holger Krannich danken, der mir zur praktischen Durchführung der Testpsychologie sowie zur statistischen Auswertung der Daten nützliche Hilfestellungen gegeben hat.

Lebenslauf

Benedikt Schmid
geb. 12. März 1986

Sept. 1992- Juli 1996	Besuch der Grundschule in Aschheim
Sept. 1996- Juni 2005	Besuch des Franz-Marc-Gymnasiums in Markt Schwaben
Juli 2005- März 2006	Ausbildung zum Rettungssanitäter Zivildienst beim Bayerischen Roten Kreuz in München Tätigkeit im Rettungsdienst
April 2006- Mai 2012	Studium der Humanmedizin an der Julius-Maximilians-Universität Würzburg

Würzburg, 26. Juli 2012

	Test	Correlation	Significance (2-tailed)	N
MMSE (score)		-0.356	0.042	33
d2	GZ	-0.441	0.013	31
	GZ-F	-0.435	0.014	31
	GZ*	-0.439	0.014	31
	GZ_PR	-0.444	0.012	31
	GZ-F*	-0.428	0.016	31
	GZ-F_PR	-0.450	0.011	31
Alertness	reaction time (mean) 1st round	0.436	0.008	36
	reaction time (median) 1st round	0.373	0.028	35
	omissions, 4th round	0.364	0.029	36
	reaction time (mean) 4th round	0.371	0.026	36
	reaction time (median) 4th round	0.341	0.042	36
	reaction time (mean) without alert	0.424	0.010	36
	reaction time (median) without alert	0.392	0.018	36
Divided Attention	reaction time (mean) auditive stimuli	0.480	0.005	33
	reaction time (median) auditive stimuli	0.591	0.001	29
	reaction time (median) t-value, auditive stimuli	-0.567	0.001	29
	reaction time (median) t-value, visual stimuli	-0.458	0.007	33
	errors, total	0.382	0.028	33
	all erroneous responses total	0.470	0.006	33

	Test	Correlation	Significance (2-tailed)	N
Go/Nogo	reaction time (median) T-score	-0.375	0.024	36

Table 8:
Significant correlations of cTT with neuropsychological test results (p=0.05)
Correlations significant within a confidence interval of 99% (p=0.01) are highlighted in blue.
PMCC
**= standard value; PR= percentile rank*

The next table no. 9 shows significant Spearman rank correlations as the respective values were not normally distributed.

	Test	Correlation	Significance (2-tailed)	N
Alertness	omissions, 4th round	0.337	0.044	36
	omissions, without alert	0.335	0.046	36
Divided Attention	correct reactions visual stimuli	-0.343	0.050	33
	omissions, visual stimuli	0.343	0.050	33
	omissions, T-score visual stimuli	-0.360	0.039	33
	outliers, visual stimuli	-0.396	0.022	33
	mean reaction time visual stimuli	-0.572	0.001	33
	median reaction time visual stimuli	0.556	0.001	33

Table 9:
Significant correlations of cTT with neuropsychological test results (p=0.05)
Correlations significant within a confidence interval of 99% (p=0.01) are highlighted in blue.
Spearman rank correlation

The following two tables show non-significant correlations using PMCC (tab. 10) or Spearman rank correlation (tab. 11).

	Neuropsychological test	Significance for rejection of Null Hypothesis
Divided Attention	omissions, T-score, auditive stimuli	0.077
	reaction time, median, T-score auditive stimuli	0.031
	omissions, T-score, visual stimuli	0.005
	reaction time, median, T-score visual stimuli	0.054
	errors, T-score, total	0.895
	omissions, T-score, total	0.011

Tab. 12: Kruskal-Wallis test for distribution of neuropsychological test performance across MRI groups

For test highlighted in blue, the Null Hypothesis is to be rejected and the distribution across the MRI groups can therefore be considered significantly different.

**= standard value*

4.9.4 The relation between cTT and the grade of white matter lesions

Kruskal-Wallis test showed that the Null Hypothesis could be rejected with a significance of p=0.012 when testing for all WMH groups at once. This means there is no significant difference in distribution of cTT over all three groups. When comparing pairwise, obviously WMH groups B and C do not differ significantly (p=1.000) as do not groups C and D (p=0.138). Solely groups B and C differ significantly in pairwise comparison (p=0.011).

Att. 2: neuropsychological tests across cutoff groups cTT (Kruskal-Wallis)

as mentioned in section 5.5