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Validation of brief cognitive tests in mild cognitive impairment, Alzheimer's disease and dementia with Lewy bodies.

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VALIDATION OF BRIEF COGNITIVE TESTS

in mild cognitive impairment, Alzheimer's disease and dementia with Lewy bodies

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Thesis at a glance

Paper	I	II	III	IV
Aim	To examine cube copying for evaluating AChEI treatment in AD.	To propose easy interpretations of brief cognitive tests for differentiating DLB from AD.	To compare the sensitivity of the MMSE and AQT for evaluating AChEI treatment in AD.	To compare the ability of brief cognitive tests and CSF biomarkers in predicting development of AD and dementia, in patients with MCI.
Method	85 patients with AD were evaluated before, and after 6 and 12 months of treatment. 56 healthy elderly subjects were evaluated over 3 years.	33 patients with DLB were matched with 66 patients with AD patients based on gender, MMSE score and age.	Changes in AQT and MMSE were measured during 2 months before treatment, and after 2 months of treatment in 75 patients with AD. Based on the changes before treatment, cut-offs to define treatment response were established.	99 patients with MCI were included. They were examined with the MMSE, clock drawing, AQT as well as the CSF biomarkers tau, P-tau and Aβ42. 53% progressed to dementia and 47% remained stable during a 5-year follow-up period.
Result	Cube copying deteriorated significantly before treatment in AD, but remained stable during 6 and 12 months of treatment. The healthy elderly remained stable in cube copying for 3 years.	The identified criteria were: 1) an MMSE orientation score $\times\,3 \geq$ total MMSE score; 2) a non-3-D cube drawing; 3) an impaired clock drawing. If $\geq$ two of these three were met, the sensitivity and specificity were 85% and 75%, respectively.	AQT, not MMSE, deteriorated significantly before treatment. Both tests improved after treatment, but AQT improved significantly more. With the AQT cut-off $\geq$16 sec and the MMSE cut-off $\geq$3 p, both falsely detected $\leq$5% as treatment responders before treatment. After treatment, AQT detected 34% as treatment responders and MMSE 17%.	Cognitive tests predicted 80% of the MCI-dementia correctly and CSF predicted 75% correctly. When specifically predicting MCI-AD, CSF classified 84% correctly and cognitive tests classified 81% correctly. No significant differences in prediction ability were found. The combination of both methods was significantly better than cognitive tests alone in predicting MCI-AD.
Conclusion	Cube copying can be useful for evaluating AChEI treatment in AD.	Easy interpretations of cognitive tests can be used to identify DLB and differentiate it from AD.	AQT is more sensitive than the MMSE in detecting treatment response in AD. AQT detected twice as many treatment responders as the MMSE.	Brief cognitive tests are just as accurate as CSF biomarkers in predicting dementia and AD in MCI patients. The combination of both methods provides significant added value when predicting AD.

Aβ42 = Amyloid-beta 1-42; AChEI = Acetylcholinesterase inhibitors; AD = Alzheimer's disease; CSF = Cerebrospinal fluid; DLB = Dementia with Lewy bodies; MCI = Mild cognitive impairment; MCI-AD/MCI-dementia = Patients with MCI who progress to AD/dementia; P-tau = Phosphorylated tau; RCI = Reliable Change Index.

List of original publications

I.   Palmqvist S, Hansson O, Minthon L, Londos E.
The usefulness of cube copying for evaluating treatment of Alzheimer's disease, *American Journal of Alzheimer's Disease and Other Dementias 2008; 23 (5): 439-446*.

II.   Palmqvist S, Hansson O, Minthon L, Londos E.
Practical suggestions on how to differentiate dementia with Lewy bodies from Alzheimer's disease with common cognitive tests, *International Journal of Geriatric Psychiatry 2009; 24 (12): 1405-1412*.

III.   Palmqvist S, Minthon L, Wattmo C, Londos E, Hansson O.
A Quick Test of cognitive speed is sensitive in detecting early treatment response in Alzheimer's disease, *Alzheimer's Research & Therapy 2010; 2 (5): 29*.

IV.   Palmqvist S, Hertze H, Minthon L, Wattmo C, Zetterberg H, Blennow K, Hansson O, Londos E.
Comparison of brief cognitive tests and CSF biomarkers in predicting Alzheimer's disease and dementia in patients with mild cognitive impairment: Five-year follow-up study, *Submitted to Journal of Alzheimer's Disease*.

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Abstract

Validation of brief cognitive tests
in mild cognitive impairment, Alzheimer's disease
and dementia with Lewy bodies

Background

It is estimated that 34 million people suffer from dementia, costing society US$422 billion each year. Alzheimer's disease (AD) is the most common dementia and the global prevalence is predicted to increase to over 100 million people by the year 2050, with the greatest increase in developing countries. Therefore, inexpensive and efficient instruments are required for investigation and evaluation.

Aim

To evaluate the brief cognitive tests cube copying, clock drawing, the Mini-Mental State Examination (MMSE) and A Quick Test of Cognitive Speed (AQT) in the early diagnosis, treatment evaluation and differential diagnosis of dementias.

Populations

  I.   85 patients with AD.
  II.   33 patients with dementia with Lewy bodies (DLB) and 66 with AD.
 III.   75 patients with AD.
 IV.   99 patients with mild cognitive impairment (MCI).

Findings

  I.   Cube copying was found useful for evaluating treatment with acetylcholinesterase inhibitors (AChEI) in patients with AD.
  II.   Easy and quick interpretations of the MMSE, clock drawing and cube copying differentiated patients with DLB from patients with AD.
 III.   AQT was twice as sensitive as the MMSE in detecting treatment response to AChEI in patients with AD.
 IV.   The MMSE, AQT and clock drawing were as accurate as cerebrospinal fluid biomarkers (tau, $A\beta42$ and P-tau) in predicting development of AD and dementia in mild cognitive impairment during an average of five years.

Conclusion

This thesis has improved the validity of brief cognitive tests and contributed with results that can be clinically relevant for evaluating treatment of AD, differentiating DLB from AD, and predicting development of AD and other dementias.

Sammanfattning

Användning och tolkning av enkla kognitiva tester
vid mild kognitiv svikt, Alzheimers sjukdom och Lewy body demens

Bakgrund

Uppskattningsvis har 34 miljoner människor världen över någon typ av demenssjukdom. Sjukdomarna leder till stort lidande för både patienter och anhöriga och beräknas kosta samhället 422 miljarder amerikanska dollar årligen. Den vanligaste demenssjukdomen är Alzheimers sjukdom och den utgör ca 60–70% av alla demenssjukdomar. Sjukdomarna blir allt vanligare och år 2050 beräknas över 100 miljoner människor vara drabbade av Alzheimers sjukdom. Främst kommer ökningen att ske i låginkomstländer. Det är därför viktigt att det finns billiga och enkla instrument för att tidigt kunna ställa diagnos och för att utvärdera behandling.

Syfte

Att utvärdera de enkla kognitiva testerna kubkopiering, klockritning, A Quick Test of Cognitive Speed (AQT) och Mini-Mental Test (MMT, på engelska kallat Mini-Mental State Examination, MMSE) vid tidig diagnostik, behandlingsutvärdering och differentialdiagnostik.

Patienter i artiklarna I - IV
- I. 85 patienter med Alzheimers sjukdom följdes före och efter behandling.
- II. 33 patienter med Lewy body demens jämfördes i kognitiv testning med 66 matchade patienter med Alzheimers sjukdom.
- III. 75 patienter med Alzheimers sjukdom följdes före och efter behandling.
- IV. 99 patienter med lindrig kognitiv svikt följdes under 5 år, varpå 52 patienter drabbades av olika demenssjukdomar medan 47 patienter inte försämrades.

Fynd
- I. Kubkopiering var användbart för att utvärdera läkemedelsbehandling med acetylkolinesterashämmare vid Alzheimer.
- II. Kubkopiering, MMSE och klockritning kunde skilja på sjukdomarna Lewy body demens och Alzheimer.
- III. Testet AQT var dubbelt så känsligt som MMSE för att utvärdera behandling med acetylkolinesterashämmare vid Alzheimers sjukdom.

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IV. Klockritning, MMSE och AQT är lika bra som analys av ryggmärgsvätska på att förutsäga vilka patienter med lindrig kognitiv svikt som senare kommer att utveckla Alzheimers sjukdom och andra demenssjukdomar.

Sammanfattning

Denna avhandling har bidragit med ny kunskap om hur enkla kognitiva tester kan tolkas och användas för att (1) utvärdera behandling vid Alzheimers sjukdom, (2) kunna skilja på Lewy body demens och Alzheimers sjukdom och (3) kunna förutsäga vilka patienter med lättare minnes- och tankeproblem som senare utvecklar Alzheimers sjukdom eller andra demenssjukdomar.

Abbreviations

2-D	Two-dimensional
3-D	Three-dimensional
AChEI	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADAS-cog	Alzheimer Disease Assessment Scale–cognitive subscale
ADL	Activities of daily living
AQT	A Quick Test of Cognitive Speed
AUC	Area under the curve
Aβ42	The 42-amino-acid isoform of amyloid-β1-42
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CGIC	Clinical Global Impression of Change
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computerized tomography
DLB	Dementia with Lewy bodies
FTD	Frontotemporal dementia
GDS	The Global Deterioration Scale (an assessment of dementia severity)
HD	Huntington's disease
IADL	Instrumental Activities of Daily Living
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
N	Number of patients/subjects
NICE	National Institute for Clinical Health and Excellence (in the UK)
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
P-tau	Phosphorylated tau
PD	Parkinson's disease
PDD	Parkinson's disease with dementia
PET	Positron emission tomography
PSMS	Physical Self-Maintenance Scale

PSP	Progressive supranuclear palsy
RCI	Reliable change index
	(test score changes of more than this index/CI states that a significant individual change has occurred)
RCT	Double-blind randomized placebo-controlled trial
REM-sleep	Rapid eye movement sleep
ROC	Receiver operating characteristic
r_p	Pearson correlation coefficient
r_s	Spearman correlation coefficient
SD	Standard deviation
SPECT	Single photon emission computerized tomography
tau	Total level of tau
VaD	Vascular dementia
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

1 Introduction to neurodegenerative diseases

1.1 Alzheimer's disease

One hundred and ten years ago, Alois Alzheimer met Auguste Deter, the first patient to be later diagnosed with Alzheimer's disease (AD). From this single case study, AD is now the most common dementia with an estimated prevalence of over 26 million people worldwide (Brookmeyer et al., 2007). Despite intense research for many decades, the cause of AD remains unknown. However, the pathological findings of aggregated beta-amyloid (plaque) and phosphorylated tau (tangles) are well established, and to a lesser extent the association with vascular pathology, mitochondrial dysfunction and inflammation (Santos et al., 2010, Sperling et al., 2011, Zotova et al., 2010). It is believed that the disease starts with a preclinical phase of perhaps a decade or two, where the pathology is evident but the individual is asymptomatic (Jack et al., 2010). The disease gradually progresses to mild cognitive impairment (MCI) and finally to functional impairment (dementia). There is no curative treatment, however, modifiable risk factors such as smoking, physical activity, social interaction, cognitive stimulation and diet have been identified (Flicker, 2010).

1.1.1 Neuropsychological prediction

Twamley et al. (2006) examined 73 studies of nondemented participants (no cognitive symptoms or MCI) who later developed AD. They found that attention was the most commonly affected domain (71% of the studies with attention tests found this), followed by impaired memory (50–57%), executive function (44%), processing speed (43%) and verbal ability (38%). In the Framingham cohort, Elias et al. (2000) found that abstract reasoning (similarities in WAIS) and retaining logical memory (delayed logical memory in WMS) were the best predictors of AD 10 to 22 years before diagnosis. However, at such early stages it is difficult to know whether these findings are risk factors for developing the disease or early symptoms of the disease.

In several longitudinal studies on MCI, tests of attention, processing speed, executive function and delayed word/paragraph recall were repeatedly the best predictors of AD (Blacker et al., 2007, Chen et al., 2000, Ewers et al., 2010, Fleisher et al., 2007, Tabert et al., 2006).

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1.1.2 Cognitive impairment

Memory and learning deficits are the hallmarks of Alzheimer's disease. In particular, the loss of memory of events (episodic memory) has been examined. It is affected early in the disease process and has been proposed as one of the biomarkers for diagnosing AD at the MCI stage (Dubois et al., 2007). The episodic memory deficits are caused by impaired encoding, storing (consolidating) and to a lesser degree retrieval of memory (Hannay et al., 2004, Twamley et al., 2006). This is illustrated in memory tests where cues are seldom of help for AD patients (Dierckx et al., 2007, Grober et al., 2010, Herlitz and Viitanen, 1991, Saka and Elibol, 2009). Semantic memory is also affected in AD (Chertkow et al., 2008), whereas procedural memory is preserved (Hirono et al., 1997).

Impairment in visual processing, both in object recognition and visuospatial ability, are seen in AD and the latter can be difficult to differ from constructional deficits in copying and drawing tests (Hannay et al., 2004). Different types of attention impairments are very common in AD, mostly in shifting or dividing attention and to a lesser extent focusing attention (Freed et al., 1989, Nebes and Brady, 1989, Oken et al., 1994, Baddeley et al., 2001). Executive dysfunction has traditionally been associated with subcortical and frontal diseases, however, it is also impaired early in AD (Hannay et al., 2004). Orientation to time and place is affected, as well as the ability to navigate in surroundings (Galasko et al., 1990, Possin, 2010, Small et al., 1997). Impairment in the ability to express and comprehend verbal content can sometimes be detected early in the disease stage with cognitive tests. However, it is often first clinically apparent at later stages (Hannay et al., 2004).

1.1.3 Treatment

There are currently four registered drugs for treating AD, the three acetylcholinesterase inhibitors (AChEI) donepezil, galantamine and rivastigmine, and the glutamate inhibitor memantine. A Cochrane report established that AChEI have positive effects on cognition, behavior and activities of daily living (ADL) based on 10 randomized, double-blind, placebo-controlled trials (RCTs) (Birks, 2006). AChEI are recommended for patients with mild to moderate dementia. No differences in efficacy are seen between the substances, but there is a lack of head-to-head studies. The treatment effect on a group level is quite modest and it has been proposed that the significant results seen in RCTs are mostly caused by a subgroup of patients with clinically important improvements (Qaseem et al., 2008). However, it can currently not be accurately predicted who will to respond the treatment.

The NICE guidelines state that the treatment should be reviewed after initiation and only continued if it is beneficial for global, cognitive, functional or behavioral symptoms (NICE, 2011). However, it is not specified how this beneficial

effect is established and there is no evidence for when to stop the treatment (NICE, 2011, Qaseem et al., 2008).

1.2 Dementia with Lewy bodies

Lewy bodies, the aggregation of the protein α-synuclein, were found by Fredric Lewy in 1912 in patients with Parkinson's disease (PD). The association of Lewy bodies with dementia was not made until the 1960's (Woodard, 1962). For decades the disease remained a pathological entity, until 1996 when the first clinical consensus criteria and the term dementia with Lewy bodies (DLB) were established (McKeith et al., 1996). DLB is the third most common dementia, constituting about 10–20% of postmortem cases and 0–30% of clinical cases (McKeith et al., 2004, Zaccai et al., 2005). Patients with DLB often suffer from hallucinations, parkinsonism, fluctuating alertness and REM sleep disorders (McKeith et al., 2005). These patients are more susceptible to neuroleptic reactions, respond better to AChEI treatment and have a worse quality of life compared with patients with AD (Bostrom et al., 2007, McKeith et al., 1992, Perry et al., 1991).

Cognitive impairment in DLB can be similar to that of AD, partly due to the overlap in pathologies. Domains that are more affected in DLB are attention, executive function and visuospatial ability (Metzler-Baddeley, 2007). Patients with DLB can have difficulties navigating themselves in the environment. However, this is not so much a problem of locating objects in reference to other objects or the environment, as it is a problem of locating objects in reference to themselves (Possin, 2010). That is, they have difficulties in arranging their body correctly, for example when sitting down in a chair or lying down on a bed.

The cognitive impairments of DLB are similar to Parkinson's disease with dementia (PDD) and the diagnoses are differentiated by the onset of parkinsonism. The disease is diagnosed as PDD if the patient has suffered from parkinsonism for more than a year before the onset of dementia, otherwise it is diagnosed as DLB (McKeith et al., 2005).

1.3 Other dementias

Vascular dementia (VaD) is the second most common form of dementia (Ott et al., 1995) and it can roughly be categorized as subcortical VaD or multi-infarct VaD (Erkinjuntti et al., 2000, Roman et al., 1993). The cognitive profile of VaD can vary greatly depending on the loci of the lesions. Patients with subcortical VaD often exhibits attention deficits and score low on tests of executive function (McPherson and Cummings, 1996). Memory disturbance is common and it is of-

ten caused by impaired retrieval rather than impaired encoding. Thus, patients with subcortical VaD tend to improve when cued on memory tests (Grober et al., 2008).

An uncommon dementia diagnosis is frontotemporal dementia (FTD). This entity consists of a behavioral variant (commonly known as frontal lobe dementia) and two variants with pronounced verbal impairment (semantic dementia and progressive nonfluent aphasia; Neary et al., 1998). Even more uncommon dementias are progressive supranuclear palsy (PSP), Huntington's disease (HD), multiple system atrophy (MSA), corticobasal degeneration and Creutzfeldt–Jacob disease.

2 Brief cognitive tests

This section is not intended for continuous reading, but rather as a small reference compendium for A Quick Test of Cognitive Speed (AQT), clock drawing, cube copying and the Mini-Mental State Examination (MMSE). To ease its use as a reference work, each test review follows a fixed format of *administration, scoring, reliability, demographic effects* etc. The literature review has primarily been focused on normative data and neurodegenerative diseases. The review has not been systematic for clock drawing and the MMSE, because of the amount of literature and lack of a specific aim. Cube copying and AQT have been reviewed more comprehensively, by systematically searching Medline, PsychINFO and Google Scholar. In addition to searching with the test names as keywords, the following terms were also used: "rapid automatic/automatized naming", "Alzheimer Quick Test", "Necker cube", "cube drawing" and "copy task".

2.1 A Quick Test of Cognitive Speed

The first version of AQT was created in 1969 by speech pathologist and assistant professor Elisabeth Wiig at the University of Michigan. One of her duties was to assess stroke patients with the Stroop test (Stroop, 1935). Unfortunately, some patients with left hemispheric strokes were easily able to name the colors in the Stroop without interference from the printed words. Consequently, the Stroop test was invalid for assessing cognitive impairment and guiding rehabilitation efforts in these patients. The answer was to develop a rapid naming test that assessed speed and executive function without requiring the patient to read. Such a test was constructed using familiar colors and geometric shapes. A pilot version was tested on several patients who produced normal Stroop results. Dr. Wiig and colleagues observed several features, among them, that they could monitor strokes that affected the left parietal lobe. In one patient, who suffered from repeated ischemic attacks, the naming time increased after each episode (Wiig, Elisabeth. Personal interview. 15 Apr. 2011).

During early development, the test had different names including the Wiig Color-Form Naming task, rapid automatized/automatic naming or RAN (which is the general term for that kind of test) and Alzheimer Quick Test (AQT) (Wiig, 2011). The current acronym AQT stands for A Quick Test of Cognitive Speed (Fig. 1).

The AQT color and form tasks measure perceptual processing speed (reaction, retrieval and response times) and AQT color-form measures processing speed, attention, set-shifting and working memory. The Stroop test uses a similar design, but with some important differences. The first Stroop task is similar to AQT color; however AQT and Stroop differ in the second and third tasks, which in Stroop requires word recognition, reading and inhibitory control.
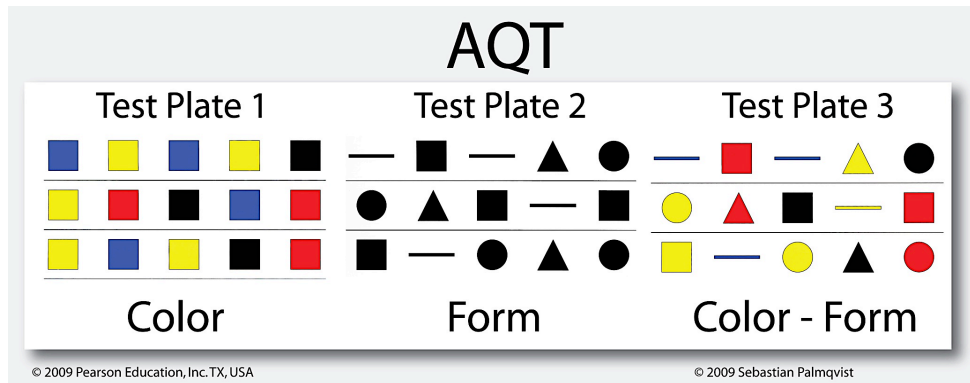
Figure 1. A sample of AQT. The complete test consists of 3 × 40 figures.

2.1.1 Administration

The most commonly used version of AQT consists of three tasks - color, form and color-form. The first task is color-naming (40 red, blue, green or yellow squares), the second task is form-naming (40 squares, circles, lines or triangles), and the last task is color- and form-naming (40 figures, see Fig. 1) (Wiig et al., 2002b). Other variants of AQT tasks include color-letters, color-animals and color-objects.

2.1.2 Scoring

The test score constitutes the number of seconds it takes to finish each task. The number of errors are also counted but not included in the score (Wiig et al., 2002b). The relevance of the errors is uncertain and no clear instructions in the manual specify how to interpret them. One study has found that the number of errors significantly differs between AD and healthy controls (Warkentin et al., 2008). Another study also found that the number of errors have diagnostic value, since they significantly contributed to differentiating subjective MCI from AD as well as subjective MCI from MCI (Backlund and Lindqvist, 2009). However, the overlaps in number of errors between patients and controls in these studies were quite large.

2.1.3   Reliability

The test-retest reliability was examined in a sample of 30 healthy adults by comparing scores at baseline and two weeks, which yielded the correlation coefficients 0.91 for color, 0.92 for form and 0.95 for color-form (Wiig et al., 2002b). A score of any given test always contains some amount of measurement error (no test is 100% reliable). The 90% confidence interval of the measurement error for AQT is ± 2 sec for color, ± 3 sec for form and ± 4 sec for color-form (Wiig et al., 2009). The calculations were based on 300 controls (ages 15-95 years) (Wiig et al., 2007). This means that there is a 90% probability that the "true" score of the subject is within the given ranges. It also means that in repeated administrations on healthy individuals the change should not be larger than the confidence intervals, otherwise a significant change of the individual AQT speed has occurred.

2.1.4   Demographic effects

Age

Two studies with healthy controls ranging from 15 to 94 years found that age accounts for 8–10% of the AQT variance and the effect of age was twice as large after 60 years compared to before 60 (Jacobson et al., 2004, Nielsen et al., 2007b). Another study with 300 healthy controls ranging from 15 to 95 years found that color-form task and color task scores each increased by 1 second per decade, and form task increased by 6 seconds per decade (Wiig et al., 2007). No such relationship has been found when examining AD patients (Wiig et al., 2010).

Education

Slower AQT times have been found in illiterates compared to literates, but no association with education has been found past the 9th grade (Jacobson et al., 2004, Nielsen and Wiig, 2006, Radford et al., 2007).

Gender

No association with gender has been found (Jacobson et al., 2004, Nielsen and Wiig, 2006, Wiig et al., 2002a).

Culture/Ethnicity/Language

AQT has been validated in American (including minorities), Spanish, Nordic, Arabic, West African and Greek populations, and does not seem to contain any culturally dependent questions (Bruna et al., 2007, Jacobson et al., 2004, Nielsen and Wiig, 2006, Radford et al., 2007, Warkentin et al., 2005, Wiig, 2006). There are also unpublished data referred to in Wiig et al. (2009) that supports this.

The naming time can vary depending on language, but AQT should be suitable worldwide as long as new normative scores are established for each language. If the geometric forms are not so common in some cultures, the variant with animals might work better. For bilingual subjects it is important that the dominant language is used since the nondominant language produces significantly slower results (Langdon et al., 2005).

2.1.5 Correlation with brain structures

An increase of blood flow in temporal, parietal and occipital areas, and a decrease in prefrontal areas have been measured in controls during color-form naming (Fig. 2) (Wiig et al., 2002a, Wiig et al., 2002b). In a study on 35 healthy elderly, there were significant correlations between slower AQT form and color-form speed, and EEG theta power in the left and right posterior quadrants of the brain ($r_s > 0.37 –$ 0.44), but not the anterior quadrants (Stomrud et al., 2010a). One study compared the cerebral blood flow of AD and healthy controls during AQT administration, and the AD patients showed a significant decrease in temporo-parietal areas and a significant increase in frontal areas compared to the healthy controls (Warkentin et al., 2008). This might be the effect of a compensatory mechanism and functional plasticity, which previously has been found in AD (Becker et al., 1996).

These studies indicate that AQT places demands on the bilateral posterior parts of the brain, not on the prefrontal cortex, in healthy individuals.
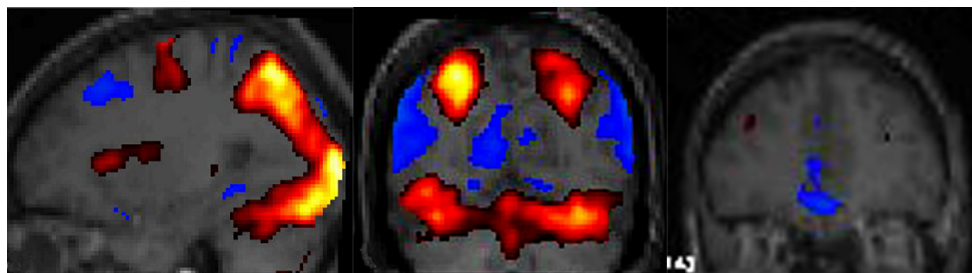
Figure 2. Functional MRI during AQT color-form in a healthy subject. Red/yellow indicates increased activity and blue indicates lower activity. Views from left o right: sagittal, coronary (posterior), coronary (frontal). *Source: Jonas Svensson, PhD. Printed with permission.*

2.1.6 Associations with other measures

In a population of 41 patients with either AD, affective disorders, or MCI, all three AQT measures correlated with WAIS-III (P IQ) at $r_p = –0.52$ to $–0.61$ (Nielsen et al., 2007b). Surprisingly, the attention and set-shifting test, Trail Making A + B, correlated significantly only with the AQT form task ($r_p = 0.52–0.56$), and similar-

ly with all measures of the Rey-Osterrieth Complex Figure Test (r_p = –0.43 to –0.60). No correlation was found with letter fluency.

Form and color-form, but not color, correlated highly with the MMSE (r_p = 0.70–0.72). The relationship was nonlinear in such a way that moderate MMSE scores correlated with AQT speed, but the AQT speed varied considerably among patients with maximum MMSE score (Nielsen et al., 2007b). It was suggested that AQT in comparison to the MMSE detects cognitive impairment in more mildly impaired patients.

One study has examined the relationship between depressive symptoms and AQT. In 372 patients diagnosed as subjective MCI, MCI or AD at a memory clinic, there was a small but significant association between color-form and the Cornell scale for depression (r_p = 0.21) (Backlund and Lindqvist, 2009). The same study also found a significant association with dementia severity (GDS) and color-form (r_s = 0.35).

A couple of studies have compared the relationship between AQT and Aβ42. The significant correlation coefficients have varied from –0.36 to –0.40 in AD patients (Wiig et al., 2010) to –0.54 in healthy elderly (Stomrud et al., 2010b). Results were not significant in a study of patients with subjective MCI, MCI or AD at a memory clinic (Backlund and Lindqvist, 2009). However, the latter study found a small, significant association with tau and phosphorylated tau (P-tau) (r_p = 0.16–0.17). Altogether these studies suggest that Aβ42 aggregation is involved in cognitive deficits that to some limited extend can be measured with AQT. In the study with only AD patients, this association could not be found for the MMSE (Wiig et al., 2010).

Table 1. Normative AQT color-form scores

Age Group	Mean	SD	Normal Range	Slower than normal	Atypical range
35–50 years	49.6	6.8	< 57 (**60**)	58–63	> 64 (**65**)
50–65 years	49.4	7.6	< 57 (**60**)	58–65	> 66 (**70**)
65–88 years	52.8	8.8	< 62 (**65**)	63–70	> 71 (**75**)

AQT scores are in seconds. Slower than normal: 1–2 SD; Atypical range: > 2 SD. Cutoff points are suggested to be rounded to the nearest 5 seconds for ease of reference, as shown in (**bold**). SD: standard deviation. *Printed with permission.*

2.1.7   Normative data

Normative data can be found in Jacobson et al. (2004), Wiig et al. (2002a) and Nielsen et al. (2007b), among others. In 2010 normative values of pooled data from the previous studies were announced (Table 1).

2.1.8   Clinical findings

Several screening studies have been conducted, but AD is the only dementia that has been compared to controls. Slow naming times in AD patients were related to the pause time between the words, not the articulation time of the words (Warkentin et al., 2008). In screening studies, AQT have classified slightly more patients correctly than the MMSE (Nielsen et al., 2004, Warkentin, 2003, Warkentin et al., 2005). It is of note that the populations consisted of selected AD patients at a memory clinic or recruited healthy controls, which often poses no clinical difficulty in differentiating from each other. One study has however examined 204 patients at a memory clinic (Backlund and Lindqvist, 2009). After neuropsychiatric investigation, 58 patients received the diagnosis AD and 146 subjective MCI. Based on the cut-offs of the AQT manual, 97% of the patients with subjective MCI were classified correctly, as were 75% of the AD patients.

AQT has also been validated in a primary care setting with 29 healthy elderly and 52 consecutive patients with memory complaints that later were diagnosed with dementia (Segernäs-Kvitting et al., 2009). Studies comparing AQT, MMSE and Cognistat Cognitive Assessment reported that AQT had higher sensitivity than the other tests and higher specificity than the MMSE, but not the Cognistat.

In a comparison between 23 patients with dementia with Lewy bodies (DLB) matched with 18 AD patients based on the MMSE score, AQT color-form differentiated DLB from AD with a sensitivity of 78% and a specificity of 86% (cut-off > 100 sec) (Andersson et al., 2007), underscoring AQT's value in identifying this often missed dementia diagnosis.

Three studies have examined the use of AQT in therapy evaluation. Wiig et al. (2010) evaluated ADAS-cog, the MMSE and AQT at initiation of acetylcholinesterase inhibitor (AChEI) treatment, and 6 months later, in 60 AD patients. The MMSE, but not the ADAS-cog and AQT, decreased significantly (–1.45 points) during the treatment period. Since the study lacked a placebo group or pretreatment changes of the tests, this can be interpreted as either AQT being better at measuring the treatment effect or less sensitive in tracking cognitive decline compared to the MMSE. Reliability issues might also explain the result.

AQT has been used to evaluate memantine in DLB/PDD (Aarsland et al., 2009). In that RCT study, AQT form and the clinical global assessment CGIC, but not the MMSE, improved significantly after treatment compared to placebo. In another study, 15 patients with MCI conducted a goal-oriented rehabilitation pro-

gram (Londos et al., 2008). After 8 weeks of therapy, significant improvements in quality of life and AQT were seen, but not in Symbol Digit, WAIS III Digit Span or Rey-Osterrieth Complex Figure Test.

These treatment studies indicate that AQT can measure subtle cognitive changes and that these changes are clinically relevant for the patient, since the same changes were found in quality of life and clinical global assessments. However, this assumption needs further research.

2.1.9 Comments

In this chapter, most of the available AQT findings have been summarized. Compared to the MMSE and the clock drawing test, there are fewer published articles. Unfortunately, many of the AQT results have not been published in peer-reviewed journals, which should be accounted for when considering the findings. This applies to Backlund and Lindqvist (2009), Bruna et al. (2007), Jacobson and Wiig, (2005), Segernäs-Kvitting et al. (2009), Warkentin (2003), Warkentin et al. (2005), Wiig (2004, 2006), Wiig et al. (2009), Wiig et al. (2002b), Tufvesson et al. (2010).

The normative values presented in Table 1 have received some criticism from clinicians. It has been reported that some patients with clearly pathological scores are without clinical symptoms and perform normally on other cognitive tests. It is possible that the normative values of an aged group ranging from 65–88 years should instead be divided into two or three age groups, since this is the age span where the greatest decline in cognitive speed can be found. The pathological values in these seemingly normal patients might also reflect a preclinical cognitive impairment. Longitudinal follow-up of these patients is needed to investigate these hypotheses further.

Cortical function is what AQT is said to measure, specifically in the temporal-parietal regions. This is based on studies investigating blood flow and lesions in these areas. However, it has been suggested that AQT is also highly dependent on subcortical functions. This is supported by the abnormal naming speed in DLB (Andersson et al., 2007), and in subjects with arterial stiffness that presumably affects subcortical functioning (Tufvesson et al., 2010). It is further in agreement with the clinical findings of slowed cognition seen in patients with subcortical lesions. However, based on this assumption it seems that verbal fluency, which is very sensitive to subcortical diseases such as DLB (Gilman et al., 2005) and Parkinson's disease (Williams-Gray et al., 2006), should correlate with AQT, but it does not (Nielsen et al., 2007b). In one way this makes sense, since verbal fluency activates frontal regions (Brannen et al., 2001, Warkentin and Passant, 1993), which are deactivated during AQT performance (Wiig et al., 2002a, Wiig et al., 2002b). An alternative explanation to the AQT impairment of DLB might thus be that it is caused by the parietal dysfunction of DLB. To further investigate the

ability of AQT to assess subcortical or frontal lesions, it would be interesting to administer it to patients with FTD and subcortical VaD.

In conclusion, AQT is a quickly administered test that seems to be sensitive in screening cognitive impairment and tracking cognitive changes. There are studies validating it with brain imaging and other cognitive tests, as well as clinical and global assessments. AQT has no ceiling effect and no culturally dependent questions, which make it a promising test for the future. Assessment of cognitive speed complements many screening tests well, since the majority of tests only assess cognitive content. However, the cut-offs of AQT need to be further validated in consecutive populations at memory clinics and primary care units to warrant their generalizability.

2.2 Clock drawing

Figure 3. A clock drawing by a healthy 6-year old showing errors usually associated with left hemi-neglect. *Reprinted with the permission of Taylor & Francis.*

As children we spend years learning to grasp the concept of the clock. At the age of 7 or 8 years the typical child is able to tell time, but not until the age of 10 is it able to successfully draw a clock and set the time when asked (Fig. 3; Cohen et al., 2000). This simple task, taken for granted in youth, can become surprisingly difficult in old age or in the presence of cognitive impairment (Fig. 4).

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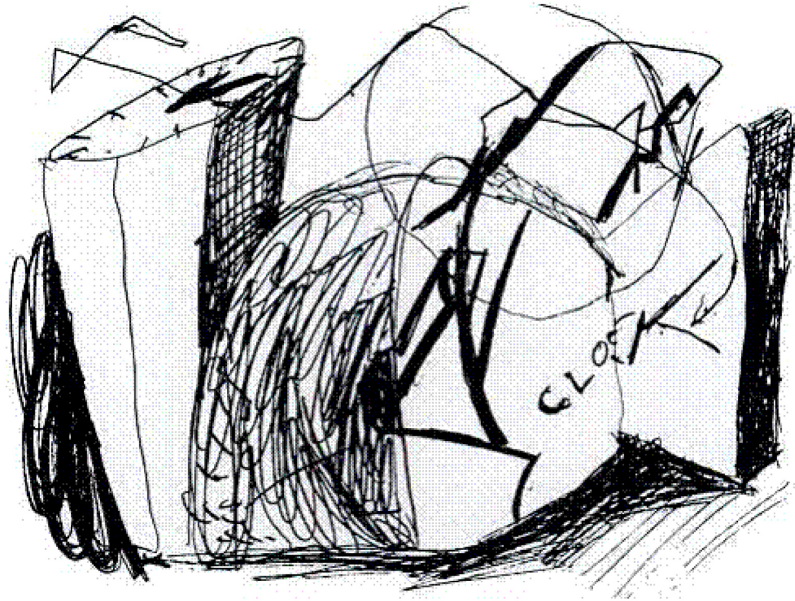
Figure 4. A patient with schizophrenia was asked to draw a clock and set the time to 11:10. Notice that the clock drawing ability is intact (upper left corner), but obviously the drawing shows other pathological attributes. *Reprinted with the permission of American Psychiatric Publishing.*

Clock drawing has been used by physicians in the examination of patients for more than a hundred years, and was perhaps first reported by S. J. Cole in 1905 in a case description of a 53-year-old "insane" woman in an asylum, probably suffering from Korsakoff's syndrome (Cole, 1905). He asked her to draw a clock, "out of her head". She managed only to draw a deformed circle with a square inside. Dr. Cole then tried a second type of administration in which he drew the circle and instructed her to indicate the positions of various hours. She then put different numbers in the clock, but they were completely disorganized. These two different ways of administering the clock test are still the two major variants used today.

Before the 1970's, only a handful of studies were reported on clock drawing. It was not until the 1980's that clock drawing research started to kick in. It is now one of the world's most widely used brief cognitive tests, especially in dementia assessments (Ismail et al., 2010, Reilly et al., 2004). Some of the reasons behind its success are the short administration time of less than two minutes, the requirement of only pen and paper, as well as its free use without any prohibiting copyrights.

Specifically which cognitive domains are being tapped during the clock drawing have been a subject of debate. Most important are semantic memory (knowledge of the word/concept "clock") as well as executive functions, visuo-construction and verbal comprehension (Freedman et al., 1994).

2.2.1 Administration

Some versions of the clock drawing test are administered on a piece of paper with a large pre-drawn circle on it, while an alternate approach requires the subject to draw freely, without a pre-drawn circle (see Pinto and Peters, 2009 for an over-view). The pre-drawn circle facilitates the assessment of numbers and the depiction of hands on the clock (Freedman et al., 1994). Free-drawn places higher demands on executive abilities.

During the course of drawing, micrographia can sometimes be observed, which will challenge assessment of clock drawing production (see Chapter 2.2.8–*Micrographia…*). In order to counteract micrographism, it has been suggested that the instruction "make it large" can be added, if a pre-drawn circle is not used (Strauss et al., 2006). In some versions clock drawing is complemented with clock copying, in which the patient is asked to copy a pre-drawn clock (Libon et al., 1993, 1996, Rouleau et al., 1992, Royall et al., 1998). The interpretation of copying versus drawing are explained in Chapter 2.2.8–*Drawing versus copying errors*.

Setting the Clock Time

Different time settings have been used, such as "1:45", (Royall et al., 1998), "2:45" (Sunderland et al., 1989) and "10:10" (Lin et al., 2003). There are even versions without any specified time setting (Watson et al., 1993, Wolf-Klein et al., 1989), but these have produced poorer sensitivity and specificity in dementia screening (Berger et al., 2008). The time setting "8:20" is thought to better measure parietal function (visuo-construction) and the most common time setting, "11:10", to better measure temporal function and executive skills (Freedman et al., 1994). However, it is unclear to exactly what extent the different time settings affect the outcome (Patocskai et al., 2011), and various approaches have different advantages (Freedman et al., 1994).

There are thus many different ways to administer the clock drawing test. My suggestion, modified from Strauss et al. (2006), is to use a pencil and a blank piece of paper, and ask the subject to "Please draw the face of a clock with all the numbers on it" and "Please set the time to 10 after 11". When giving the instructions, the word "hands" should not be used since this might give the subject a clue about what a clock contains.

2.2.2 Scoring

Since an early, simple 3-point scoring system was introduced (Goodglass and Kaplan, 1983), advanced scoring methods of 20 (Mendez et al., 1992) or even 25 points (Tuokko et al., 1992) have been developed. However, these more elaborate methods have not proved better than simpler ones (Pinto and Peters, 2009, van der Burg et al., 2004). Comparative studies have repeatedly shown that Shulman's 6-point method produces among the best sensitivities and specificities (Table 2). Other scoring methods with good sensitivity and specificity are the ones by Sunderland et al. (1989), Mendez et al. (1992), CERAD (Morris et al., 1988), Manos (1997), among others.

The current scoring version of Shulman (2000) uses a pre-drawn circle with time set to "11:10", and scores according to the following 6-point scale (0 to 5, worst to best):

5 = correctly drawn clock (numbers do not have to follow the circle perfectly, and very minor spacing errors can exist)

4 = minor visuospatial/organization errors (spacing of numbers less than about 30° off, placing of numbers outside the circle, micrographism, turns paper while drawing, draws lines/spokes to orient numbers)

3 = inaccurate denotation of 10 after 11 (writes "10" after the number 11, places minute hand on 10, does not draw hands)

2 = severe visuospatial errors of the numbers that make it impossible to correctly set the hands on 10 after 11 (omitted numbers, perseveration of numbers, reversed numbers, poor and uneven spacing between numbers)

1 = more severely disorganized clock than 2

0 = blank paper or nothing that could represent a clock

2.2.3 Reliability

Inter-rater reliabilities of different scoring methods are shown in Table 2. Test-retest reliabilities are mostly between 0.70–0.90. For an overview, see Shulman (2000) and Pinto and Peters (2009).

2.2.4 Demographic effects

Age

Age affects clock drawing (Kim and Chey, 2010, von Gunten et al., 2008) but this influence is reported to appear first after the age of 60 (Bozikas et al., 2008). See Table 3 for more on the effect of age.

Table 2. Comparative studies of different clock scoring methods

Scoring method	Sensitivity, Specificity	YI	Inter-rater reliability	Population	Reference
Shulman	93, 55	0.48	0.93		
Wolf-Klein	43, 86	0.29	0.93		
Sunderland	69, 58	0.27	0.85	72 with dementia 55 healthy elderly	Storey et al., 2001
Mendez	96, 26	0.22	0.93		
Watson	69, 44	0.13	0.81		
Shulman	96, 42	0.38	0.47	241 with dementia	van der Burg et al., 2004
CERAD	97, 32	0.29	0.75	232 healthy elderly	
Sunderland	85, 80	0.65			
Shulman	81, 79	0.60		79 with dementia 44 healthy elderly	Shramm et al., 2002
Manos Wolf-Klein	81, 75	0.56			
Watson	81, 73	0.54			
	56, 80	0.36			
Shulman	86, 96	0.82	0.91	28 with AD	Brodaty and Moore, 1997
Sunderland	79, 93	0.72	0.92	28 healthy elderly	
Wolf-Klein	79, 89	0.68	0.88		
Shulman	90, 56	0.46			
Manos	81, 60	0.41		334 with dementia 128 healthy elderly	Berger et al., 2008
Wolf-Klein	58, 81	0.39			
Lin	88, 49	0.37			
Watson	72, 64	0.36			
Mendez	91, 76	0.67			
Manos	81, 80	0.61			
CERAD	95, 64	0.59		129 with dementia 68 healthy elderly	Scanlan et al., 2002
Shulman	79, 80	0.59			
Sunderland	61, 88	0.49			
Wolf-Klein	42, 88	0.30			

YI: Youden Index (sensitivity + specificity – 1)

Culture/Ethnicity/Language

Clock drawing does not require well-developed language skills and should there-fore have a better specificity than the MMSE in situations with language difficul-ties (Shulman, 2000). The ethnic effects are reported as small (La Rue et al., 1999) or nonexistent (Marcopulos and McLain, 2003).

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Depression

The effect of depressive symptoms has been debated, but it seems to have little or no impact on clock drawing (Bodner et al., 2004, Brodaty and Moore, 1997, Herrmann et al., 1998, Kirby et al., 2001, Lee and Lawlor, 1995, Manos, 1997). This can be practical in clinical situations, as depressive symptomatology in elderly might otherwise easily imitate the cognitive impairments of AD and other dementias.

Education

Numerous studies found that education correlated with clock drawing performance (Bozikas et al., 2008, La Rue et al., 1999, Ratcliff et al., 2003), while some studies did not show any correlation (Yamamoto et al., 2004, O'Rourke et al., 1997). One study found that, though the effect was small before the age of 70, education explained 10–40% of the score variance after 80 years of age (von Gunten et al., 2008). Illiterates tend to perform poorly and well-educated very well, leading one to consider that clock drawing has best discriminative value in populations with moderate education (6 to 9 school years) (Jitapunkul et al., 2000, Kim and Chey, 2010, Leung et al., 2005, von Gunten et al., 2008).

Gender

Studies reported that men perform slightly better than women on clock drawing, though noted that the differences were small and mostly due to confounding factors (La Rue et al., 1999, Ratcliff et al., 2003).

2.2.5 Correlation with brain structures

Clock drawing is sensitive to visuo-constructive impairment related to right or bilateral parietal lesions (Critchley, 1953), and is incorporated in a "parietal lobe battery" (Borod et al., 1980). However, impaired clock drawing is also associated with pathology in the left (Ueda et al., 2002) and right (Cahn-Weiner et al., 1999) temporal lobes in Alzheimer's disease (AD). Another study found that medial temporal lobe atrophy and periventricular white matter changes, but not deep white matter changes, contribute to clock drawing impairment (Kim et al., 2009). These findings suggest the importance of clock drawing with regards to memory and executive functioning. The latter is consistent with a SPECT study on dementia with Lewy bodies (DLB), which showed that clock drawing impairment was associated with reduced blood flow in fronto-subcortical networks (Nagahama et al., 2008). Both the relevance of visuospatial and memory/executive functioning were found in a PET study of 71 patients with AD, which concluded that clock drawing significantly correlates with glucose metabolism in the right parietal lobe and cingulate cortex (Lee et al., 2008).

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Tranel et al. (2008) reported a study that was perhaps the most extensive, including 117 patients with different focal lesions. Clock drawing impairment correlated with a variety of lesions in diverse regions of the brain, but foremost with the left inferior fronto-parietal region and the right parietal lobe. In this study, the classic relationship between parietal function and clock drawing was further explored. One might assume that parietal lesions caused visuospatial errors, but the parietal lesions in this sample caused a variety of different clock drawing errors. Surprisingly, only 50% of the patients with substantial right parietal lesions displayed clock drawing impairment. However, these results might be affected by brain plasticity occurring after incident lesions, since the population consisted of patients with chronic, not acute, lesions.

In summary, lesions from diverse regions (left and right temporal, parietal, frontal and subcortical) can cause clock drawing impairment. However, specific lesions should cause specific types of errors (see Chapter 2.2.8).

2.2.6 Associations with other measures

The clock drawing test has been examined for potential correlations with numerous other tests and scales. Clock drawing is moderately to highly correlated with tests of executive functioning (Libon et al., 1993, Royall et al., 1998, Suhr et al., 1998), visuo-construction (Libon et al., 1996, Libon et al., 1993, Suhr et al., 1998), temporal orientation (Suhr et al., 1998), semantic memory (Libon et al., 1996) and the MMSE ($r = 0.41–0.80$) (Adunsky et al., 2002, Heinik et al., 2004, Royall et al., 1999, Shulman, 2000). Low to moderate correlations have been found with general dementia ratings (Mendez et al., 1992, Shulman et al., 1993, Sunderland et al., 1989).

2.2.7 Normative data

Several studies have presented normative data, but the problem is that few follow the patients longitudinally to rule out incipient dementias. However, two studies followed the study participants for four years and excluded those who had a pathological decline in cognition (Crowe et al., 2010, Marcopulos and McLain, 2003; Table 3). Both studies showed that clock drawing errors are not unusual among healthy elderly. The types of errors that healthy elderly make are often similar to those made by AD patients (Kim and Chey, 2010), but it has been suggested that poor spatial planning might be the best discriminator between normal and pathological cognition (Tuokko et al., 1992). von Guten et al. (2008) examined 242 elderly and found that 25% made some kind of spatial errors of the numbers, 18% wrote the numbers counterclockwise and 10% did not place the minute hand on 2 when using the time set "11:10". It was very unusual for the healthy elderly to

write "10" after the number 11, to not sequence the numbers correctly or to perseverate.

Table 3. Normative data of clock drawing

Age (years)	Educational level					
	0–6 years				7–10 years	
	N	Mean	SD	N	Mean	SD
55–74	9	8.7	1.1	26	8.7	1.4
≥75	17	7.2	1.8	27	7.9	2.0

Scores are on a scale of 0 to 10 points (worst to best) according to Libon et al. (1993). Total number of subjects: 79 healthy elderly; SD: standard deviation; *Source: Marcopulos and McLain (2003). Reprinted with the permission of Elsevier Science*

2.2.8　Different types of errors

Stimulus-bound errors

One of the earliest errors in AD seems to be the misplacement of the minute hand (Fig. 5) (Leyhe et al., 2009). This is called a stimulus-bound error, since the subject processes the information more perceptually than semantically (hears "10", when asked to set the time to "11:10", and therefore draws one hand of the clock towards "10" instead of recoding the information and draw the hand towards 2) (Freedman et al., 1994). The error does not seem to be specific for any type of dementia (Lee et al., 2009), although more common in AD (Blair et al., 2006, Rouleau et al., 1992). In fact, misplacing of the hands can be seen in healthy elderly with a prevalence of 11–23% (Berger et al., 2008, Kim and Chey, 2010). A stimulus-bound error can also be that the patient hears "10 after 11" and therefore writes the number 10 after the number 11 (see Conceptual errors).

Conceptual errors

Conceptual error refers to impairment of the abstract knowledge of a clock. It can result in errors such as placing the hands randomly on the face of the clock, failing completely to draw numbers or hands, or writing "10" after the number 11 instead of drawing the hands. The latter error can also be categorized as a stimulus-bound error.

Conceptual errors are overrepresented in AD compared to Parkinson's disease with dementia (PDD), Huntington's disease and subcortical vascular dementia (VaD), and the most commonly observed error is writing "10" after the number 11 (Lee et al., 2009, Rouleau et al., 1992). Impaired time setting has also been related to lesions in the left inferior fronto-parietal region (Tranel et al., 2008). As

with stimulus-bound errors, these are also seen in healthy elderly, especially those with low education (Kim and Chey, 2010).
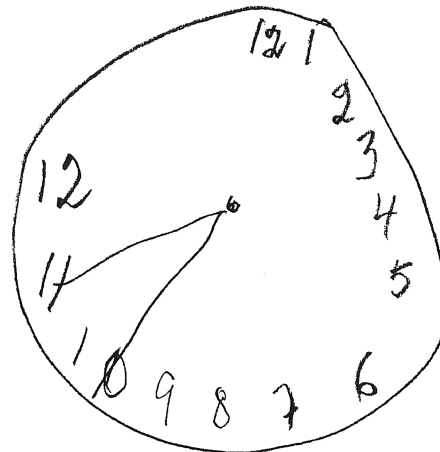
Figure 5. A drawing from a patient with AD, which shows stimulus-bound and spatial errors. P*rinted with permission from the patient and proxy.*

Spatial or planning errors

Spatial or planning deficits are defined as the inability to correctly place the numbers on the face of the clock. Examples of such errors include leaving a gap before 12, placing the numbers outside the circle and writing the numbers in reversed fashion. Except for a gap before 12 (Fig. 5), these errors are more common in PDD and subcortical VaD than in AD (Lee et al., 2009). In agreement with that finding, the errors are also typically seen in basal ganglia lesions (Tranel et al., 2008). It might be that subcortical lesions impair the planning and organization involved in clock drawing.

Perseveration errors

The most common variant of perseveration errors is perseveration of the number series, in which the subject fails to end the series at 12 and instead continues to write 13, 14, 15, 16 etc. Another, though quite unusual, error is drawing more than two hands (as seen scattered in Fig. 4). Perseverations errors are more common in PDD and subcortical vascular dementia than in AD (Lee et al., 2009).

Micrographia and other graphic errors

An abnormally small clock drawing (less than 3–4 cm in diameter) is often associated with lesions in the basal ganglia (Freedman et al., 1994). Other graphic errors

refer to different distortions of the clock face/circle (fragmented, oval, asymmetric etc.). The errors are related to dysexecutive functioning and are harder to detect with a pre-drawn circle (Libon et al., 1996). See also Chapter 2.3.9–*Micrographia*.

Drawing versus copying errors

Patients with AD tend to improve when asked to copy a pre-drawn clock after first trying to freely draw a clock, but such characteristic improvement was not seen when patients with VaD, DLB or Huntington's disease were examined (Cacho et al., 1999, Gnanalingham et al., 1996, Libon et al., 1996, Libon et al., 1993, Rouleau et al., 1992). These studies suggest that the free-draw condition places relatively greater demand on semantic memory and verbal comprehension, which are more impaired in AD. The copy condition places relatively greater demands on visuo-construction (Freedman et al., 1994).

2.2.9   Clinical findings

Dementia

Screening for dementia with clock drawing has been extensively reviewed (Freedman et al., 1994, Pinto and Peters, 2009, Shulman, 2000, Strauss et al., 2006). Beyond any doubt, clock drawing has an important place in dementia screening because many studies have shown that clock drawing is significantly impaired in AD, PDD, VaD, DLB, Huntington's disease, and to a lesser extent in fronto-temporal dementia (FTD) when compared to healthy elderly. Diagnostic accuracy improves when clock drawing is combined with the MMSE (Aprahamian et al., 2010, Cacho et al., 2010, Heinik and Shaikewitz, 2009, Shulman, 2000). Clock drawing has not proved as good as other screening tests such as the MMSE, Memory Impairment Screen (MIS), SKT (a short performance test) and verbal fluency (Beinhoff et al., 2005, Kirby et al., 2001, Nunes et al., 2008, Sager et al., 2006, Schramm et al., 2002).

Apart from dementia screening, clock drawing is also useful in predicting and tracking cognitive changes (Ferrucci et al., 1996, Lee et al., 2010, Shulman, 2000).

Differential diagnosis

The overlap between clock drawing scores of AD and VaD is large (Cosentino et al., 2004), but sometimes VaD produces poorer clock drawings (Heinik et al., 2002). AD and VaD appear to be dissociated by their respective qualitative errors and clock copying. AD errors tend to be be conceptual and stimulus-bound (Blair et al., 2006, Rouleau et al., 1992). Patients with VaD tend to more often exhibit graphic and planning difficulty and do not improve with the copy condition, as do AD (Kitabayashi et al., 2001, Libon et al., 1996, Libon et al., 1993). Similar dif-

ferences were seen when comparing AD with Huntington's disease (Rouleau et al., 1992). Graphical errors were not examined in DLB, but they did not improve with the copying condition (Gnanalingham et al., 1996). One study compared AD and FTD and found that FTD had better clock scores, but almost the same difficulty in avoiding graphic errors (Blair et al., 2006).

Mild cognitive impairment

Numerous studies found that clock drawing lacks sensitivity (20–67%), and shows good or only adequate specificity in differentiating mild cognitive impairment (MCI) from healthy elderly (Chiu et al., 2008, Connor et al., 2005, Lee et al., 1996, Powlishta et al., 2002, Seigerschmidt et al., 2002). Other studies have not found any significant difference between the groups (Beinhoff et al., 2005, Nunes et al., 2008, Sager et al., 2006). These studies examined clock drawing to find whether it could identify those at high risk for developing dementia. A more clinically relevant aim is to study the ability of clock drawing to predict the MCI patients who later develop dementia. Several studies have examined this and found no significant or poor predictive ability (Buchhave et al., 2008, Chen et al., 2001, Ehreke et al., 2011, Griffith et al., 2006, Jungwirth et al., 2009, Zanetti et al., 2006).

2.2.10 Comments

Clock drawing is an important tool in dementia screening and has achieved widespread popularity. It does, however, not have adequate psychometric properties to be administered alone to detect cognitive dysfunction and it benefits from being combined with another test such as the Mini-Mental Status Examination (MMSE). Clock drawing can give a certain indication of dementia severity and track cognitive changes. It should be assessed qualitatively, despite whatever quantitative "score" is obtained. Its value toward differentially diagnosing is limited but the addition of the copy task as well as qualitative assessment improves its usefulness in that respect. It is however of note that clock drawing provides poorer differential diagnosis compared to for example the MMSE (Ala et al., 2002, Brandt et al., 1988).

Clock drawing should not be used alone to identify MCI or to predict a development of dementia in MCI patients. Its value in diagnosing mild dementia, particularly in highly educated populations is also questionable. However, its cheap and quick administration as well as its relatively high sensitivity and specificity, make it a great complement to other screening tests.

2.3 Cube copying

When looking at the world around us, photons are hitting the retina through which electrical signals enter the brain. The signals are carried through the optic nerve and optic tract, to the primary visual cortex in the occipital lobe. There, a rudimentary image is formed without any additional information about what is seen. The image is further processed in the occipital lobe and divided into the ventral stream projecting to the temporal lobe and the dorsal stream projecting to the parietal lobe. Features such as simple shapes, orientation and color first emerge when the image is processed through the ventral stream. As the stream continues to the temporal lobe, the extracted information gets increasingly complex with processing of items such as human faces. The ventral stream recognizes "what" we see. The dorsal stream on the other hand recognizes "where" things appear. Information processed here gives the image a location in space, motion and depth. These two processes described here are called the visual bottom-up system. The top-down system refers to executive processes that interact with the image formed by the bottom-up system. This includes organizing complex visual information, shifting visual attention, inhibiting and selecting visual information, planning how to use the information etc (Possin, 2010). The brain areas mostly involved in the top-down system are the lateral prefrontal cortex, the parietal lobes and frontal-striatal circuits (Kastner and Ungerleider, 2000, Miller and Cohen, 2001).
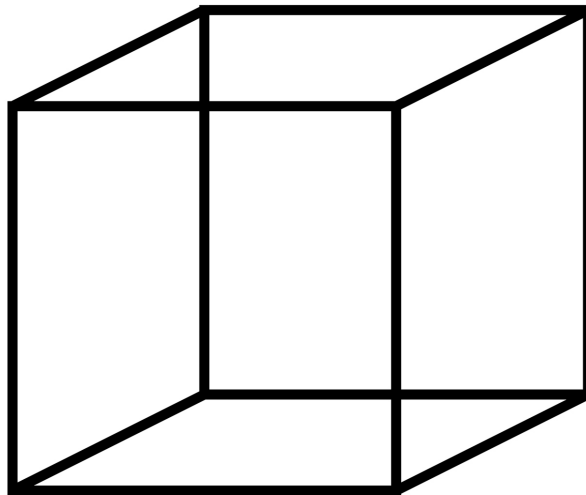
Figure 6. The Necker cube.

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When looking at Figure 6, a three-dimensional (3-D) figure emerges from a two-dimensional (2-D) image. It can be perceived as a cube with the front side either facing upwards or downwards. While looking at it, bottom-up processes are mostly used. The figure is called the Necker cube and was first described in 1832 by Louis Albert Necker (1832). It is an example of an ambiguous figure, where the viewer can perceive the figure in different ways. Researchers have been discussing how the brain interprets ambiguous figures for 180 years and there has been much focus why the perspective of an ambiguous image suddenly reverses (Long and Toppino, 2004). In a simplified way, two processes are thought to be involved in cube copying. First, the visuospatial part as previously described where the subject tries to perceive the figure. Second, a constructional praxis process is enacted that involves the copying of the cube. This is why cube copying and other similar tasks are often described as visuo-constructive tests.

Cube copying can be used as a test by itself, but is often integrated as part of a more extensive test or test battery. Some examples of tests containing cube copying tasks are the Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-cog), the Montreal Cognitive Assessment (MOCA), the Cognitive Assessment Battery (CAB), the Rivermead Perceptual Battery, the Rowland Universal Dementia Assessment Scale (RUDAS) and the Addenbrooke's Cognitive Examination (ACE).

2.3.1 Administration

The test is administrated by asking the subject to copy the figure (Fig. 6). The words "as exactly as possible" can also be added to limit careless mistakes. Preferably, the word "cube" should not be used since this might trigger the subject to draw a cube from his or her mind instead of copying the figure. Asking a patient to draw a cube has less clinical value since the majority of healthy elderly fail this, unlike when asked to copy a cube (Gaestel et al., 2006). Also, different brain areas become activated when drawing than when copying (Ferber et al., 2007).

There are two major versions of the figure, the one shown in Figure 6 and a cube with an opaque front side. The latter is not an ambiguous figure and only contains 9 lines, which probably makes it easier to copy.

2.3.2 Scoring

There is no consensus regarding the scoring method. Many different systems have been created and most of them have only been used in one or a couple of studies. Below are listed some of the scoring methods:

- Maeshima et al. (1997) used a quantitative method where the number of correct connections was counted (defined as three lines meeting less than 3 mm away from each other), which yields a score of 8 points in a perfect

cube. A second score was then created by evaluating the number of "plane errors" (a plane constituting of two parallel lines). Errors were scored for each omitted or skewed line (with a maximum of 12 errors if the patient did not draw anything). However, Maeshima did not specify a degree of the angle to define nonparallel lines. This caused a later study to modify the version and only count lines as parallel if the lines diverged less than 10° from each other (Buchhave et al., 2008). They also calculated connection errors in order to combine the two measures into a combined score within a range of 0–20 points.

- The evaluation of 3-D features in the drawing has been used as a part of several scoring methods, but it has also been used as an independent method. The perception of 3-D, or its absence, in a drawing might seem subjective, but it can actually be predicted quite well. Hochberg et al. (1960) found that the perception of 3-D was more obvious the more angles a figure has, the more asymmetrical the angles are and the more intersecting lines there are.

- Rosen et al. (1984) developed a scoring method where the subject can score between 0 and 6 points. The following has to be fulfilled to receive 6 points: a 3-D perspective, 12 lines, correct orientation of the front face, no incorrect lines, parallel lines (< 20°) and a proper connection of lines. Paganini-Hill and Clark (2000) later modified this version slightly and changed the definition of parallel to < 10°.

- More & Wyke (1984) used a combined quantitative and qualitative method. First, the number of correct lines was counted, then the number of tries, the size and any additional incorrect lines were evaluated. Lastly, it was observed whether or not the patients used a piecemeal approach (see Chapter 2.3.9–*Piecemeal approach*).

- Shimada et al. (2006) described 8 different patterns a cube copying could have, each pattern being slightly more correct. In this qualitative method, pattern 0–2 constituted 2-D drawings and pattern 3–7 were increasingly successful 3-D drawings.

- The consortium to establish a registry for Alzheimer's disease (CERAD) used a scale in which the subject could receive 4 points if the following was fulfilled: a 3-D perspective, the front face correctly oriented, the internal lines correctly drawn and parallel opposite sides (< 10°) (Ericsson et al., 1996, Morris et al., 1988).

- Other scoring methods have also been developed, including: Gaestel et al. (2006), Seki et al. (2000) and Fontan-Scheitler et al. (2009).

2.3.3 Reliability

Different reliability modalities for the scoring methods have been very poorly described (i.e. test-retest, inter-rater, intra-rater etc.) Only one study was found to report a reliability value. Buchhave et al. (2008) showed an inter-rater reliability of $r_p = 0.96$, when using the modified Maeshima score.

2.3.4 Demographic effects

Education

Many studies have shown a significant association between cube copying and education (Ardila et al., 1989, Ericsson et al., 1996, Gaestel et al., 2006, Paganini-Hill and Clark, 2000, Shimada et al., 2006). In 858 healthy elderly, Gaestel et al. (2006) found that there was a 4–5 times increased risk of making errors on cube copying for those with 6–9 years of education compared to those with more than 9 years of education. Those with only 0–5 years of education had 19–24 times higher risk of making errors compared to the latter group.

Depression

There are contradictory results as to whether different depression scales are associated with cube copying performance. Small effects of depression were seen in healthy individuals (Gaestel et al., 2006), but not in neurodegenerative diseases (Maeshima et al., 1997, Maeshima et al., 2004).

Age

Several studies have reported a significant negative association with age, but the results do not confirm whether this effect is smaller or larger than that of education (Ardila et al., 1989, Ericsson et al., 1996, Gaestel et al., 2006, Paganini-Hill and Clark, 2000). One study has shown that it seems to be specifically the ability to perceive and draw 3-D, not 2-D, figures that is impaired in elderly compared with younger individual (Plude et al., 1986).

Gender

Cube copying has also shown a significant gender association, with a slightly better performance among men (Ardila et al., 1989, Gaestel et al., 2006, Paganini-Hill and Clark, 2000).

It is worth noting that the association with all the discussed demographic variables is questionable when looking at patients with dementias, MCI or brain lesions (Buchhave et al., 2008, Maeshima et al., 2004, Seki et al., 2000). This is probably because the cognitive impairment associated with such medical conditions has greater impact on cube copying, independent of demographic variables.

2.3.5 Correlation with brain structures

While looking at a Necker cube, the occipital lobe, the parietal lobes and the pre-motor cortex are activated (Inui et al., 2000, Schoth et al., 2007). The premotor activation might be involved in shifts of attention (top-down system) (Rosen et al., 1999), as these subjects were instructed to reverse the cube perspective, or were looking at a computerized rotating Necker cube. The actual brain region activated in the spontaneous change of perspective is thought to be located in the inferior part of the right parietal lobe (Britz et al., 2009). The right anterior superior temporal sulcus is, on the other hand, thought to be involved in the stabilization of the perspective (perceptual memory) when the attention is drawn away from the cube (e.g. to copy it on a piece of paper) (Shen et al., 2009).

Earlier it was thought that impaired ability to copy figures was caused by lesions in the right hemisphere (Arrigoni and Derenzi, 1964), but it was later found that lesions in either hemisphere could cause the impairment (Arena and Gainotti, 1978). This is in agreement with a study on MCI, which found that impaired cube copying was significantly associated with a decreased blood flow in both parietal lobes (Buchhave et al., 2008). Several studies have shown that even if lesions on either side of the brain can result in visuo-constructive impairment, the type of errors in the drawings tend to differ depending on which side of the brain is damaged (Gainotti and Tiacci, 1970, Griffiths and Cook, 1986, Villa et al., 1986). The authors suggest that right-hemisphere lesions cause visuospatial deficiencies resulting in impaired spatial relationships and neglect. Left-sided lesions, on the other hand, might interfere with the constructional part of the task, leading to impaired programming and planning of action.

2.3.6 Associations with other measures

Maeshima et al. (1997) examined 40 patients with PD and found correlations of r_s = 0.37–0.43 with WAIS-R, and the strongest correlation was found with Block Design. Poor ADL function was also associated with low cube score.

Cube copying score has shown low to moderate correlation with the MMSE in MCI and various dementias (r_s = 0.30–0.50) (Buchhave et al., 2008, Maeshima et al., 2004). The highest correlations have been found with Raven's Colored Progressive Matrices (r_s= 0.61–0.65) in a population of various dementias (Maeshima et al., 2004). The association with dementia severity (measured with CDR) is lower (r_s = –0.21) (Ericsson et al., 1996).

2.3.7 Normative data

Gaestel et al. (2006) examined 858 healthy elderly in a population-based cohort and found that 82% did not make any kind of cube error. Only 1.9% of the cohort developed dementia within 5 years. Ericsson et al. (1996) studied 444 healthy

elderly and found that 24%–42% (depending on age group) received the highest cube score according to the CERAD method (which has high demands for a perfect cube). None of these studies provided standard deviations of the cube score to calculate appropriate cut-off values.

Shimada et al. (2006) studied randomly selected elderly and found that only 20% among the healthiest (CDR=0; N=98) copied a cube perfectly, but 95% were at least able to make a 3-D copy. Paganini-Hill and Clark (2000) provided mean and SD cube scores in of a cohort of 1,733 elderly. If a −1.5 SD is used to calculate a cut-off, then a score of at least 4 of 6 points on the modified Rosen scale indicates a normal value. For younger men and older women this might have to be adjusted 1 point up and down, respectively. A shortcoming of this cohort was that a follow-up was not incorporated into the study design, thereby enabling one to rule out possible incipient dementia by later established morbidity.

2.3.8 Clinical findings

Several studies have shown that cube copying is significantly impaired in AD, DLB, PD, VaD and unspecified dementia when compared to healthy elderly (Ericsson et al., 1996, Gaestel et al., 2006, Maeshima et al., 1997, Maeshima et al., 2004, Moore and Wyke, 1984, Shimada et al., 2006). Although none of the studies provide sensitivity and specificity values, these would probably be poor due to the overlap between patients and healthy controls.

Not surprisingly, hemi-neglect also affects cube copying and one study found that neglect severity correlates significantly with the number of correct vertices on the left side of the drawing (r = −0.44), but not on the right side (Seki et al., 2000).

Cube copying seems to be less affected by frontal lesions. One study showed that 17 patients with frontotemporal dementia (FTD) performed significantly better than AD, VaD and DLB, and no significant difference was found compared to healthy elderly (Maeshima et al., 2004).

One study has specifically examined cube copying as a potential predictor of MCI progression to AD (Buchhave et al., 2008). The modified Maeshima score predicted development of AD with an area under the curve (AUC) of 0.64 (p < 0.01) in 147 patients with MCI who were followed longitudinally for more than 4 years. Although the AUC was quite modest, it was still better than that of the clock drawing test (AUC 0.59; non-significant) and the MMSE (AUC 0.60; p = 0.03). The annual incidence of AD was 18% for patients with a cube copying score of < 13 of 20 points, compared to 8% for those with scores of ≥ 13 points.

A retrospective study compared 17 AD patients with urinary incontinence with 17 AD patients without urinary incontinence, matched on MMSE score, gender and age. It showed that cube copying was significantly more impaired in those with urinary continence. In the same paper this finding was verified in a prospec-

tive study (Davidson et al., 1991). The underlying mechanism is not clear, but the authors suggested a cortical mechanism of incontinence.

It has also been suggested that cube copying can be of some guidance when evaluating if a patient has the capacity to drive a car. Thirty-seven drivers who had their drivers license suspended performed significantly worse on cube copying compared to 37 matched control drivers (Johansson et al., 1996). This knowledge is often applied clinically, since many neuropsychological batteries that evaluate driving ability contain a cube copying task or similar tests.

2.3.9 Different types of errors

There are many different types of cube copying errors. Some of them have been categorized and analyzed. The errors explained below are not specific to cube copying, but can be seen in many drawing and copying tasks.
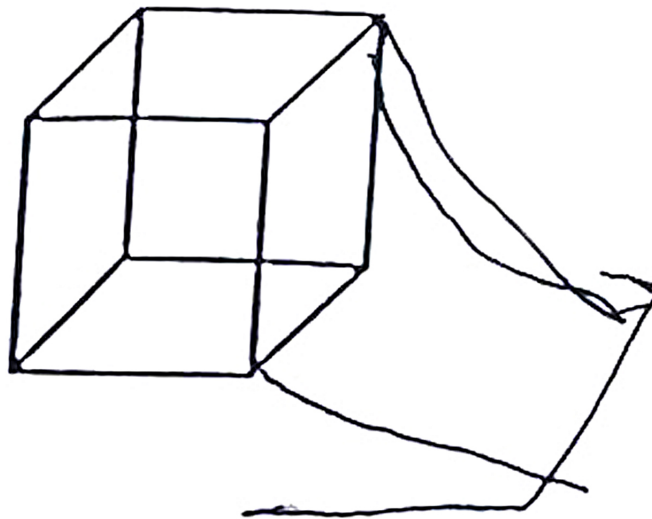
Figure 7: Closing-in phenomenon. The original cube on the left side, and the patient's attempt on the right side. *Reprinted with permission from the patient and proxy.*

Closing-in

Closing-in is an error in which the patient cannot draw a cube that stands alone, but instead the patient's drawing overlaps with the original cube (Fig. 7). This phenomenon was first described in 1935 by Mayer-Gross (1935) as a "fear of empty space". Since this, perhaps, primitive explanation, three main hypotheses have been put forth. The earliest suggests that it might be related to primitive responses such as the sucking and grasping reflex, which can be seen in dementia

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(Ajuriaguerra et al., 1960). Another explanation is that the phenomenon occurs as a compensation of impaired visuospatial ability and visuospatial working memory (Lee et al., 2004). Lastly, the "attraction" hypothesis proposes that the hand is involuntarily drawn towards the locus of the visual attention (i.e. the original cube), which would suggest an executive dysfunction (McIntosh et al., 2008). The three hypotheses have been tested in a recent study, which favored the visuospatial theory (Serra et al., 2010).

Closing-in has mostly been studied in AD populations and the prevalence is believed to be approximately 10–25% at memory clinics, depending on the definition of closing-in (Ambron et al., 2009, Serra et al., 2010). It has been suggested as a marker for dementia (Gainotti et al., 1992) and shows higher specificity for AD compared to subcortical VaD (Kwak, 2004). It should, however, be noted that it can occur in many conditions and is also common in children (Gainotti, 1972).

Micrographia

The term is most often used for a small handwriting size, but it can also be defined as a pathologically small drawing compared to the original figure or the intended space for the drawing. Micrographia has mostly been described in subcortical diseases such as Parkinson's disease (Kim et al., 2005), Huntington's disease (Iwasaki et al., 1999) and progressive supranuclear palsy (PSP) (Sakai et al., 2002), but it can also be seen clinically in AD and VaD. Micrographia is often associated with lesions in the basal ganglia (Blahak et al., 2011).

Piecemeal approach

This term is used to describe a fragmented quality of drawing or copying in which the subject uses a lot of lines, often incorrectly, to complete the figure (Seki et al., 2000). It was described as early as 1905 even though the word piecemeal was not used (Cole, 1905). It can be seen in brain damage with multiple etiologies (Trojano et al., 1993). It has been associated with right-hemispheric damage (Fischer and Loring, 2004) and hemi-neglect (Gainotti and Tiacci, 1970), but the association with hemi-neglect could not be verified in a later study (Seki et al., 2000). It was, instead, suggested to be related to global cognitive dysfunction.

2.3.10 Comments

No review paper has yet been published on cube copying and several important areas need further research despite its long-term and widespread use. The lack of a consensus scoring method and reliability evaluation is one of the first areas that need to be addressed. Cut-offs need to be established and tested in different settings. Even though there are no specified cut-offs, certain suggestions for how to interpret cube copying can be made based on the studies with normative data. Only a minority of healthy elderly produces perfect cube copying, but almost every-

one succeeds in making a 3-D cube drawing. The majority seems to, at most, omit one or two lines, make a few connections that do not quite meet, or make slight errors in perspective when trying to draw parallel lines. More errors, or even lack of 3-D, might thus be interpreted as a pathological sign.

Despite the gaps in knowledge, cube copying is a useful and simple screening test of visuo-construction. It assesses too few cognitive domains to be used on its own. Cube copying should instead be used as a complement to other brief screening tests that lack visuospatial assessment or assess it poorly, like the Mini-Mental State Examination (MMSE).

2.4 The Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) may have had an inauspicious beginning but is today one of the most popular cognitive screening instruments available. In 1975, Susan Folstein was a psychiatry resident at a geriatric psychiatric unit where Marshal Folstein was a junior attending physician. At rounds, Marshal Folstein often asked Susan Folstein to report the cognitive status of the patients, only to find she had forgotten to ask questions that would elicit this information. They agreed that Marshal Folstein would write down all the questions so she would not miss anything. This was the starting point of the Mini-Mental State (MMS), subsequently named the Mini-Mental State Examination (MMSE) (Folstein, Marshal F. Interview by PAR inc. 6 Aug. 2010).

The MMSE included tasks familiar to physicians of that time, but also included new ones (Strauss et al., 2006). It was called "mini" since it only examined cognition and not mood. Its authors suggested that it should be used to separate "patients with cognitive disturbance from those without such disturbance" and to "follow the changes in cognitive state when and if patients recover". Furthermore, they pointed out that it was not intended as a diagnostic test (Folstein et al., 1975).

Who could have predicted that this quite simple paper would be cited over 22,000 times during the following 36 years? The MMSE now exists in over 100 translations (Auer et al., 2000), making it the world's most widely used cognitive screening test (Ismail et al., 2010, Malloy et al., 1997). It has often become the criterion standard of cognitive assessment and sometimes the significance of the results are over-interpreted. For example, in some units it decides which patients are suitable for Alzheimer's disease (AD) treatment, driving a car and making informed consent. All this is very far from the original idea of the simple cognitive screening test proposed by the authors.

What the MMSE measures is debated, though it is often referred to as a test of global cognition. Without a specified rational, the original paper organized specific tasks into two sections, seven parts in total. The first section included orienta-

tion, memory and attention, while the second section included naming, following commands, writing a sentence and copying pentagons (Folstein et al., 1975). Through factor analysis, Jones & Gallo (2000) argued that "concentration," (serial 7s/WORLD), "language and praxis" (naming, following commands, construction), "orientation" (time and place orientation), "memory" (delayed recall) and "attention" (registration) are the cognitive abilities being tapped. Banos & Franklin (2002) found similar factors, but contradictory papers have been published (Braekhus et al., 1992, Fillenbaum et al., 1987, Tinklenberg et al., 1990, Zillmer et al., 1990).

2.4.1 Administration

The MMSE takes about 5–10 minutes to administer and sometimes a couple of more minutes in subjects with cognitive impairment. Since it has been used freely for more than 30 years there are many different versions with a general lack of standardization. One of the tasks that most commonly differs between versions is the attention task. Some versions have utilized backward spelling of WORLD, while others have used serial 7s instead. Still, others use different combinations of the two (Tombaugh and McIntyre, 1992). Unfortunately, WORLD and serial 7s correlate weakly ($r = 0.39$; $p < 0.05$) (Holzer et al., 1984). Ganguli et al. (1990) found that WORLD produced higher scores indicating that it is an easier task than serial 7s. In a study of 833 community-dwelling subjects, serial 7s produced the highest variability in the sample and the highest alpha coefficient compared to both WORLD and a combination of WORLD and serial 7s (Espino et al., 2004). This is in agreement with how the Folsteins themselves viewed it: "We regret that we ever included the option of spelling WORLD backwards; we never use WORLD" (Strobel and Engedal, 2008).

The MMSE exists in many modified versions and test batteries, for example the Addenbrooke's Cognitive Examination (ACE) (Mathuranath et al., 2000), the Modified Mini-Mental State (3MS) (Teng and Chui, 1987), the Cognitive Abilities Screening instrument (CASI) (Teng et al., 1994), the CERAD battery (Morris et al., 1988) and the Severe Mini-Mental State Examination (SMMSE) (Harrell et al., 2000). There are also special versions for hearing- and vision-impaired individuals, but further studies are needed to warrant their validity (Busse et al., 2002, Uhlmann et al., 1989).

2.4.2 Scoring

Scoring is quite complex and differs between versions. The manual should therefore be consulted.

2.4.3   Reliability

Most studies report good test-retest reliability (r = 0.80–0.95) in different populations with one month between test-retest (Tombaugh and McIntyre, 1992). In some cohorts with healthy controls the reliability is very low, probably due to ceiling effects (Tombaugh and McIntyre, 1992).

A practice effect was obtained for up to two weeks when retesting AD patients (Doraiswamy and Kaiser, 2000), but no significant effect was found at an interval of three months (Helkala et al., 2002). However, in healthy subjects a practice effect was noticeable after 3 months (Helkala et al., 2002). Interestingly, in addition to a natural practice effect, Keating (1987) found that some patients study the questions just before the next administration to improve the score.

Inter-rater reliability varies substantially depending on version. It was initially reported to be unacceptably low (Strauss et al., 2006), but it was improved to acceptable or good reliability in more standardized versions where the instructions and scoring were better specified (Malloy et al., 1997, Strobel and Engedal, 2008).

2.4.4   Demographic effects

Age

A clear effect of age has been found (Tombaugh and McIntyre, 1992). See also Table 4.

Culture/Ethnicity/Language

Several studies found that African Americans and Hispanic Americans on average score lower on the MMSE than European Americans (Anthony et al., 1982, Escobar et al., 1986, Espino et al., 2001, Mulgrew et al., 1999). This effect was also evident when stratifying the scores according to education level (George et al., 1991). Authors have commented that specific questions such as orientation to time and place, following commands and repeating a sentence appeared to be more affected by ethnicity (Morales et al., 2006, Parker and Philp, 2004).

Education

As shown in Table 4, subjects with high education score higher on the MMSE. The effect is more prominent than that of ethnicity, gender and socioeconomic status (Bird et al., 1987, Brayne and Calloway, 1990, Fillenbaum et al., 1988, Uhlmann and Larson, 1991). Indeed, Tombaugh & McIntyre (1992) suggested that the MMSE should not be administered to subjects with less than 8 years of education. It is of note that the effect of age and education can be difficult to interpret, since low education and old age are known risk factors of dementia. It is therefore possible that in a community-dwelling sample like that in Table 4, the groups with

older and less educated subjects have an overrepresentation of mild cognitive impairment (MCI) and mild, not yet detected, dementias that affect the MMSE score.

Gender

Women tend to be better at the language tasks and spelling "WORLD" backwards, but worse on serial 7s (Jones and Gallo, 2002). Overall though, no relevant gender bias was found in a study of 20,000 community-dwelling subjects (George et al., 1991).

2.4.5 Correlation with brain structures

In a neuropathological study, the MMSE score was highly predicted by neurofibrillary tangles in the hippocampus and entorhinal cortex, and to a lesser degree by amyloid in the entorhinal cortex (Giannakopoulos et al., 2003). This was in agreement with a large postmortem study of a cohort of 334 subjects, which found that neurofibrillary tangles in the medial temporal lobes are significantly associated with MMSE score in mild to moderate cognitive impairment (scores of 20–28 points) (Nelson et al., 2010). With greater cognitive impairment (0–19 points), MMSE scores are highly correlated with tangles throughout the neocortex.

In a study of 150 patients with either MCI or AD, MMSE correlated with plaque and tangle counts in all examined regions (hippocampus, entorhinal cortex, frontal-parietal and temporal cortices) (Sabbagh et al., 2010). Two studies found in vivo correlations between MMSE score and medial temporal atrophy, but not atrophy elsewhere (Aylward et al., 1996, Bigler et al., 2002). A SPECT study found that decreased blood flow in bilateral parietal areas is associated with a lower MMSE score (DeKosky et al., 1990).

In conclusion, these studies suggest that general brain pathology can affect the MMSE score, but the foremost associations are between the MMSE and temporal areas and to a lesser extent parietal areas. This also reflects the proposed cognitive domains of the MMSE. Orientation, delayed recall and verbal ability are mostly associated with temporal regions, while calculation and visuo-construction are mostly associated with parietal regions (Banich, 2004).

2.4.6 Associations with other measures

There are hundreds of studies that have examined the relationship between MMSE and various tests and scales. Since the MMSE covers a quite broad area of functions, it shows significant correlations with many tests. For an overview see Tombaugh & McIntyre (1992) and Strauss et al. (2006). Overall, the specific tasks of the MMSE (orientation, memory etc.) show modest correlations with neuropsychological tests of the corresponding cognitive domains (Benedict and Brandt,

1992, Giordani et al., 1990, Mitrushina and Satz, 1994). The tasks should therefore be interpreted cautiously as measures of specific cognitive functions.

The MMSE has shown correlations of 0.40–0.75 with different dementia scales (Tombaugh and McIntyre, 1992). Unfortunately, this has led to the MMSE being wrongly used an instrument to assess dementia severity in many settings.

2.4.7   Normative data

Crum et al. (1993) have published a large normative study of 18,056 community-dwelling adults using data stratified by age and educational level (Table 4). Later, Iverson et al. (1998) suggested criterion cut-offs based on these groups (Table 4). The data in Table 4 must be interpreted cautiously since the subjects were neither examined to rule out mild dementia nor followed longitudinally to rule out incipient dementias (see Chapter 2.4.4 – *Education*).

Table 4. Normative MMSE scores of community-dwelling subjects

Educational level		Age (years)					
		60-64	65-69	70-74	75-79	80-84	≥85
5 to 8 years	N	310	633	533	437	241	134
	Mean	26	26	26	25	25	23
	SD	2.3	1.7	1.8	2.1	1.9	3.3
	Cut-off	≤22	≤23	≤23	≤21	≤21	≤17
9 to 12 years	N	626	814	550	315	163	99
	Mean	28	28	27	27	25	26
	SD	1.7	1.4	1.6	1.5	2.3	2.0
	Cut-off	≤25	≤25	≤24	≤24	≤21	≤22
College or more	N	270	358	255	181	96	52
	Mean	29	29	28	28	27	27
	SD	1.3	1.0	1.6	1.6	0.9	1.3
	Cut-off	≤26	≤27	≤25	≤25	≤25	≤24

MMSE scores from 0 to 30 points (worst to best). Data from the Epidemiologic Catchment Area household surveys (USA, 1980 to 1984) by age and education level (Crum et al., 1993). Only certain age groups and education levels are shown here. Abnormal cut-offs are from Iverson (1998). Cutoffs are greater than 1.64 SD below mean scores. N: Number of subjects; SD: standard deviation.

Changes in MMSE score

A 3- or 4-point change is considered sufficient to claim as an individually significant change according to the reliable change index (RCI) of the MMSE, i. e. an actual change that is not caused by measurement errors or practice effects (Tombaugh, 2005). This is based on findings of the amount of variance in scores obtained by 232 healthy elderly. For more elaborate RCIs based on age, education and initial MMSE score, see Tombaugh (2005). Others have found the RCI to be 2–3 points (Eslinger et al., 2003, Iverson, 1998). It is of note that a RCI should be interpreted cautiously since it is dependent both on how standardized the administration and scoring of the MMSE was and how cognitively stable the control population was.

2.4.8 Clinical findings

Dementia screening

Screening for cognitive impairment has been extensively investigated. Generally, the MMSE is best suited for identifying moderate to severe dementia. It has poor sensitivity in mild dementia, MCI, focal brain lesions (especially on the right side) and various disorders with executive, visuospatial and processing speed impairment (Fischer et al., 2004, Strauss et al., 2006, Tombaugh and McIntyre, 1992).

The conventional cut-off score of the MMSE is less than 24 points, which in the original article classified 100% of the patients correctly (Tombaugh and McIntyre, 1992). It is however worth mentioning that Folstein et al. (1975) examined two dementia populations with mean MMSE scores of 12.2 and 9.7 points, respectively. In later studies, these cut-offs produced good specificity, but quite low sensitivities of 63–69% (Feher et al., 1992, Galasko et al., 1990, Kay et al., 1985, Kukull et al., 1994).

The sensitivity of the different MMSE tasks varies (Braekhus et al., 1992). Small et al. (2000) found that delayed recall is the most sensitive for AD and Galasko et al. (1990) found that orientation to place and delayed recall are just as good as using the total MMSE score. Orientation to time has also proved sensitive to AD (Fillenbaum et al., 1994, Galasko et al., 1990). The different language tasks have shown the least sensitivity to cognitive impairment, and are more weakly correlated with corresponding verbal neuropsychological tests (Feher et al., 1992).

Mild cognitive impairment

In studies with MCI patients, the MMSE can often predict the outcome significantly, but not as well as tests of delayed recall and (speed dependent) executive function (Chen et al., 2000, Small et al., 2000, Tierney et al., 2003, Tierney et al., 2010, Tierney et al., 1996).

Measuring changes in MMSE score

A change of 1 point from 26 to 25 points is not the same as a change from 6 to 5 points, neither is a change from 24 to 23 points in one patient necessarily the same as 24 to 23 points in another patient due to varying difficulties of the tasks (Mungas and Reed, 2000, Salmon et al., 1990, Tombaugh and McIntyre, 1992). At high and low end, MMSE scores do not seem to reflect cognitive changes very well. It is instead preferred to use a more extensive cognitive battery to detect change in milder cognitive impairment, and to use activities of daily living (ADL) scales where severe cognitive impairment is present.

Pooled data from 3,492 untreated AD patients showed that the average MMSE decline was 3.3 points per year (95% CI: 2.9–3.7; Han et al., 2000), but intra-individual variance is high. Indeed, some patients remain stable or even improve during one year (Clark et al., 1999).

Much discussion has ensued regarding the interpretation of change in MMSE scores, for example, what amount of change in points is clinically relevant over time. Clark et al. (1999) suggested at least a decline of 4 points and Doody et al. (2001) 5 points or more. Burback et al. (1999) asked 162 specialists what change in MMSE represented to them a clinically meaningful change and found the mean score to be 3.7 points (95% CI: 3.5–4.0). The American College of Physicians and the American Academy of Family Physicians suggest a change of at least 3 points (Qaseem et al., 2008).

Comparison with other screening instruments

Several reviews have refrained from recommending the MMSE for screening in primary care (Brodaty et al., 2006, Lorentz et al., 2002, Milne et al., 2008). Instead they have proposed brief tests such as the General Practitioner Assessment of Cognition (GPCOG), the Memory Impairment Screen (MIS) and the Mini-Cognitive assessment instrument (Mini-Cog). These are all faster to administer and produce similar or better sensitivity and specificity. The disadvantage is of course that fewer people are familiar with their administration and normative data.

A fairly new screening test is the Montreal Cognitive Assessment (MoCA), which takes a few minutes longer than the MMSE to administer (Nasreddine et al., 2005). MoCA has been extensively compared to the MMSE in various settings and populations. It shows a higher sensitivity and an equal or lower specificity, and is most useful in MCI, mild dementia and disorders with executive impairment such as Parkinson's disease (PD) (Olson et al., 2011, Godefroy et al., 2011, Damian et al., 2011, Dalrymple-Alford et al., 2010, Olson et al., 2010, Dong et al., 2010, Mickes et al., 2010, Pendlebury et al., 2010, Gagnon et al., 2010, Fujiwara et al., 2010, Hoops et al., 2009, Nazem et al., 2009, Smith et al., 2007).

Differential diagnosis

A couple of studies have examined the utility of MMSE tasks to aid in differentiating disorders that have different cognitive profiles. Jefferson et al. (2002) compared vascular dementia (VaD), AD and PD with dementia (PDD) matched on MMSE score, and found that AD scored significantly lower on orientation to time and delayed recall than VaD and PDD. Patients with VaD and PDD on the other hand scored significantly lower on pentagon copying, sentence writing, serial 7s/WORLD and registration. Ala et al. (2002) found that patients with dementia with Lewy bodies (DLB) produced lower scores on serial 7s and pentagon copying compared to patients with AD. Similar results were found when comparing AD and Huntington's disease (HD) (Brandt et al., 1988). Patients with AD scored lower on orientation and delayed recall while HD patients scored lower on serial 7s and sentence writing.

The percent of correctly classified patients in the two latter studies was around 80%, but would likely be much lower in settings with a variety of disorders or a different prevalence of the diseases (Larner, 2003). However, the results show that AD, with its temporal pathology, tends to have lower scores on tasks of memory and orientation. Subcortical diseases, such as DLB, HD and subcortical VaD tend to be more impaired on tasks of attention and construction.

2.4.9   Comments

The MMSE is still the world's most frequently used screening test for cognitive impairment, even though there are brief tests tapping a broader range of cognitive functions and showing a higher sensitivity and specificity. One of the reasons might be that there is no other test that so many practitioners are familiar with. This not only makes it a useful cognitive assessment tool, but its results are easily reported among colleagues and across clinical settings.

The MMSE should be regarded as a minimal cognitive assessment, keeping in mind that some cognitive domains such as visuospatial ability, delayed recall, abstract thinking, processing speed and executive functions may be inadequately measured. This is probably why the MMSE has low sensitivity in MCI and mild dementia. In these cases, other tests are preferably added to better cover all domains. The administration and scoring of the MMSE lacks standardization in many versions, which makes the score interpretation difficult especially when evaluating repeated measures. Demographic data affects MMSE scores and one should, therefore, consider age, education and language ability when assessing the score (Malloy et al., 1997). However, evidence varies for how this affects test sensitivity and specificity (Strauss et al., 2006, Tombaugh and McIntyre, 1992).

Patient characteristics and behavior are important to consider in addition to the MMSE score. First, one should assess the test situation for behavior that could affect the score negatively, and which other influences on process that do perhaps

not show up in the score. Was the patient cooperative and alert? Was there observation of poor planning or impatience, despite no lowering of the score? Was the patient extraordinarily slow? How the subject arrived at individual errors should also be considered. For example, the qualitative error is very different if the patient wrongly guesses that the present year is 2010 or 1959. One should also investigate which parts the patient fails on, since this information might aid in the diagnostic differentiation of AD from subcortical dementias. Patients with AD tend to be more impaired in orientation and delayed recall, while subcortical dementias are more impaired on visuo-construction and attention.

If one considers the quantitative and qualitative aspects of the MMSE as well as its limitations, it can be a very valuable instrument of cognitive assessment.

3 Aims of the thesis

The general aim of this thesis was to propose new interpretations and fields of application for brief cognitive tests in mild cognitive impairment (MCI), Alzheimer's disease (AD) and dementia with Lewy bodies (DLB).

3.1 Paper I

To examine the ability of cube copying to evaluate acetylcholinesterase inhibitor (AChEI) treatment in AD. The aim was also to examine two different cube-scoring methods: assessment of three-dimensionality and a thorough quantitative assessment.

3.2 Paper II

To propose an algorithm, based on easy interpretations of brief cognitive tests, to differentiate DLB from AD.

3.3 Paper III

To compare the sensitivity of A Quick Test of Cognitive Speed (AQT) with the Mini-Mental State Examination (MMSE) in identifying treatment response to AChEI in AD.

3.4 Paper IV

To compare the ability of brief cognitive tests and analysis of cerebrospinal fluid in predicting the development of AD and dementia in patients with MCI.

4 Material and methods

Table 5. Populations in papers I–IV

Paper	Diagnosis	Number of patients	Sample from study
I	AD	85	SATS
	Healthy elderly	56	NoMAS
II	DLB	33	DLB follow-up study
	AD	66	MAS
III	AD	75	SATS
IV	MCI[1]	99	MCI study

[1] The follow-up diagnoses were stable MCI, AD, VaD, DLB, PSP and semantic dementia.

4.1 Studies

The subjects in all papers underwent a thorough examination by physicians working at the Neuropsychiatric clinic, Skåne University Hospital, Malmö, Sweden. The physicians were experienced in dementia disorders and cognitive impairment. The examination consisted of structured medical history, physical, psychiatric and neurological examination, cognitive testing and CT or MRI of the brain. The patients and/or proxy gave their informed consent to participate in the studies. All patients (except the healthy controls) were referred to the clinic as part of clinical routine. The different populations and studies are specified in table 5.

4.1.1 The Swedish Alzheimer Treatment Study (SATS)

SATS is a follow-up program for open-label acetylcholinesterase inhibitor (AChEI) treatment in Alzheimer's disease (AD), which started in 1997. Ten centers in Sweden participated in the program, but only patients from the Neuropsychiatric clinic in Malmö were examined (papers I and III). The inclusion criteria were: 1) diagnosis of probable AD according to NINCDS-ADRDA (McKhann et al., 1984) and 2) living at home (mild to moderate dementia). Exclusion criteria were: 1) ongoing AChEI treatment or 2) contraindications to AChEIs.

The first patients received donepezil treatment, which was initiated at baseline. Later, when rivastigmine and galantamine came on the market the physicians could choose the treatment they found most suitable. The patients were assessed

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with cognitive testing as well as global and ADL scales at baseline, 2 months (no ADL assessment), 6 months and semi-annually until the last visit at 36 months. This study has been described in more detail by Wallin (2008).

4.1.2   The Normal Material Study (NoMaS)

NoMAS consists of healthy elderly who were recruited through advertisement or contacted as non-blood relatives of patients visiting the Neuropsychiatric clinic. The inclusion criteria were: 1) no complaints of memory loss; 2) intact ADL; 3) normal results on cognitive testing. The exclusion criteria were: 1) advanced pathology on CT of the brain; 2) active mental or physical disease that probably affected the cognitive status; 3) fulfillment of MCI or any type of dementia diagnosis. The patients were assessed at baseline, 3 years and 4.5 years. In total there were 62 subjects. This population has been described in more detail by Stomrud (2009).

4.1.3   The Malmö Alzheimer Study (MAS)

This cross-sectional study included patients who were investigated between 1999 and 2003. The inclusion criteria were: 1) diagnosis of probable AD (McKhann et al., 1984); 2) investigation with cognitive tests, CT of the brain and cerebrospinal fluid (CSF) and 3) living at home (mild to moderate dementia). The exclusion criterion was advanced vascular pathology on CT.

Although data was only collected at baseline, the patients were followed longitudinally to ensure the diagnosis of AD. The initial population consisted of 260 patients, but after later reviewing the diagnoses, only 218 patients remained. More information about this study has been published by Nielsen et al. (2007a).

4.1.4   The dementia with Lewy bodies follow-up study (DLB follow-up study)

This study included patients who were referred to the clinic between 1997 and 2004 and diagnosed with probable DLB according to the older consensus criteria (McKeith et al., 1996). They were followed longitudinally to ensure the diagnosis. After exclusion of other diagnoses, 50 patients remained.

4.1.5   The mild cognitive impairment study (MCI study)

Patients who fulfilled the Petersen criteria for MCI at the initial visit were included (Petersen, 2004). The inclusion criteria were thus: 1) memory complaints of the patient, but preferably also acknowledged by an informant; 2) objective memory impairment in relation to age and education, as assessed by the physician; 3) a relatively preserved general cognition based on the physicians structured inter-

view; 4) an MMSE score of at least 24 points; 5) intact or very slightly impaired activities of daily living (ADL) and 6) no dementia (according to the DSM-IIIR criteria (American Psychiatric Association, 1987)). The exclusion criteria were: subdural hematoma, major depression, current alcohol abuse, brain tumor, CNS infection, schizophrenia or other distinct disease that was a probable cause of the MCI. Patients with signs of white matter changes, silent infarctions, low plasma concentrations of B12 or folate and mild to moderate depressive symptom were not excluded. Although these findings can cause MCI, they are often found without any cognitive impairment.

These criteria generated a cohort of 171 patients who were followed longitudinally with repeated clinical visits. At follow-up visits they either showed no deterioration in cognition or ADL (stable MCI) or they fulfilled the criteria of dementia (American Psychiatric Association, 1987). The different dementias were diagnosed as: probable AD (McKhann et al., 1984); vascular dementia (VaD) (either subcortical VaD (Erkinjuntti et al., 2000) or probable VaD (Roman et al., 1993)); probable DLB (McKeith et al. 2005); progressive supranuclear palsy (PSP) (WHO, 1992) and semantic dementia (Neary et al., 1998). A consensus group of physicians determined the diagnoses. This group was blinded to the cognitive tests and cerebrospinal fluid (CSF) data from the initial visit. CSF was analyzed in 159 patients who have been described more thoroughly by Hertze et al. (2010).

4.2 Patient samples in the papers

For an overview of the populations, see Table 5.

4.2.1 Paper I

Patients fulfilling the following criteria were included: 1) participant of SATS in Malmö; 2) treated with donepezil; 3) cube drawings from baseline and from the 6 or the 12 months visit. This generated a sample of 85 AD patients. Compared to those only fulfilling criteria 1 and 2 (35 patients), the 85 included patients had significantly better MMSE scores, but no differences were found in age or gender.

Healthy elderly from NoMAS with cube drawings from baseline and the 3 years visit were also included (56 patients).

4.2.2 Paper II

Patients with DLB who had performed at least two of the following tests were included: the MMSE (33 patients); clock drawing (30 patients) and cube copying (31 patients). A total of 33 patients were included. Thirty of them had performed

the cognitive testing at the same occasion and three had done it within two and a half months. The earliest data of the patients was collected. Each patient with DLB was matched to two patients with AD from MAS according to: 1) Gender; 2) MMSE score and 3) age. Due to the gender differences between AD and DLB, the gender match was unsuccessful and 39% DLB women and 62% AD women were included.

4.2.3   Paper III

Patients fulfilling the following criteria were included: 1) Participant of SATS in Malmö; 2) MMSE and AQT color-form scores from baseline, the 2 months visit, and from a visit 1–6 months before baseline and 3) MMSE score of at least 13 points and AQT color-form score of at most 190 seconds. This generated a population of 75 AD patients.

4.2.4   Paper IV

Patients from the MCI study with CSF data (tau, Aβ42 and P-tau) and scores of the MMSE, clock drawing and AQT were included (99 patients). These did not differ from the rest of the study population (72 patients) regarding MMSE score, age, presence of APOE ε4 allele or gender.

4.3 Measures

The different measures of the papers are shown in table 6.

Table 6. Measures and main statistics in papers I–IV

Paper	Cognitive tests	Other measures	Main statistics
I	Cube copying MMSE	CGIC IADL PSMS	McNemar test Spearman correlation Wilcoxon paired test
II	Clock drawing Cube copying MMSE		Mann-Whitney U test ROC curve analysis
III	AQT MMSE		McNemar test Paired t test Reliable Change Index
IV	AQT Clock drawing MMSE	Aβ42 P-tau Tau	Logistic regression ROC curve analysis

4.3.1   Cognitive tests

The cognitive tests have been described in greater detail in Chapter 2. Only specific considerations will be presented here.

Cube copying

Cube copying was assessed in two ways. First, it was scored according to the method of Maeshima et al. (2004). Since the authors did not specify a degree of angle to define parallel planes, all lines in the drawing that represented a line in the original cube was counted. Second, the three-dimensional features of the cube drawings were also assessed, i. e. if the drawing looked like a 3-D figure or not. The 3-D assessment was used in papers I and II, while the cube score was used in paper I.

The Mini-Mental State Examination (MMSE)

The MMSE was used in all papers. It was administered and scored according to standardized guidelines at the Neuropsychiatric clinic. The administration and scoring of the attention part of the MMSE have changed over the years. In paper I, both serial 7s and spelling WORLD backwards were administered and the one with the highest score was included in the total MMSE score. Serial 7s was used in papers II and IV, but if the patient could not perform the task, WORLD was instead used. In paper III, three simple arithmetic tasks were tested on the patient. If the patient succeeded with the arithmetic tasks, serial 7s was used. Spelling WORLD backwards was used only if the patient did not succeed with the arithmetic tasks. Once it had been determined if WORLD or serial 7s should be used, the administration for that patient was never changed.

Clock drawing

Clock drawing was used in papers II and IV. The test was administered on a blank piece of paper and the time setting "11:10" was used. It was scored according to Shulman (Shulman, 2000, Shulman et al., 1993). In paper II the score was dichotomized at the cut-off less than 5 points and in paper IV at less than 4 points.

AQT

AQT was administered and scored according to the manual (Wiig et al., 2002b). All three parts (color, form, color-form) were administered, but only color-form was analyzed. AQT was used in papers III and IV.

4.3.2 Other measures

Clinical Global Impression of Change (CGIC)

CGIC is the generic term for scales that first assess the global condition of a patient at baseline and thereafter assess the change compared to baseline (Schneider and Olin, 1996). In paper I, only the baseline value was used, which states the condition of the patient from 1 (normal) to 7 (most severe dementia). This was based on the physician's overall judgment of the patient's clinical impression (interview of the patient and proxy, cognitive testing and ADL scales). The clinical global impression is perhaps the most relevant evaluation instrument, but unfortunately it is quite subjective and the test-retest reliability is low (r_s = 0.44–0.59) (Knopman et al., 1994).

Instrumental Activities of Daily Living (IADL)

IADL is a scale, which rates activities that involve different objects (Lawton and Brody, 1969). The scale was used in paper I and include the following eight items: preparation of food, managing different ways of transportation, finances and medication, shopping, telephoning, doing laundry and housekeeping. Some of the items may not be applicable for some patients (e.g. an elderly man who never in his life did laundry). Therefore a ratio from 0 (best) to 1 (worst) was calculated (the patients total score divided by the maximum score of the applicable items).

Physical Self-Maintenance Scale (PSMS)

In contrast to IADL, PSMS assesses the basic functions feeding, dressing, grooming, physical ambulation, bathing as well as urinary and feces continence (Lawton and Brody, 1969). These are rated from a scale of 6 (best) to 30 points (worst). PSMS was used in paper I.

Figure 8. Lumbar puncture performed by a physician at the Neuropsychiatric clinic, Malmö, Skåne University Hospital, Sweden. © Sebastian Palmqvist 2008

Cerebrospinal fluid (CSF) analysis

The CSF was collected a couple of weeks after the cognitive testing (Fig. 8). It was stored in polypropylene tubes at -80°C and analyzed after the clinical follow-up. The measured substances were the total amount of tau (tau), tau phosphory-lated at Thr181 (P-tau) and the 42-amino-acid isoform of amyloid-β1-42 (Aβ42). This was done using the Luminex xMAP technology (Olsson et al., 2005). The procedures of the Alzheimer's Association Flow Chart for lumbar puncture were followed (Blennow et al., 2010). CSF analysis was used in paper IV.

4.4 Statistical analysis

4.4.1 General statistics

An overview of the main analysis methods in the papers is shown in Table 6. The Mann-Whitney *U* test was used to compare different measures and demographic variables (all papers). If the variables were dichotomized or categorical, the χ^2 test was used (papers I, II and IV). The McNemar test was used to analyze the related categorical variables "change in 3-D ability" (paper I) and "treatment responders" (paper III). Changes over time in different measures were compared with the Wilcoxon matched-pairs signed rank test (papers I and III). The exception was the test changes expressed as percentages (paper III), which were compared with the paired *t* test. Linear relations were examined with Spearman correlation in papers I and IV, and Pearson correlation in paper III. Sensitivity and specificity was calculated using ROC curve analysis (papers II and IV).

The SPSS software was mainly used (versions 12, 14, 17 and 19). MedCalc (version 9 and 11) was used for Receiver Operator Characteristic (ROC) curve analysis and comparison of area under the curves (AUCs).

4.4.2 Reliable Change Index (RCI)

There are different methods of calculating a RCI. The one used in paper III is described in the supplement to paper III. The most common use of a RCI is to establish a 90% CI of test changes seen in a healthy, stable population (Tombaugh, 2005). The changes that are seen in such a population are due to measurement errors, practice effects etc. The established RCI can then be used to assess if the score change of a subject is within the normal variation or if there is significant change in cognition (or whatever the test measures). However, in paper III the RCI was instead used to establish normal variations of the MMSE and AQT in untreated AD patients. The RCI was then used to measure significant individual changes after treatment. I propose that the RCI method can have advantages when compar-

ing tests of treatment evaluation in AD, compared to using the Wilcoxon matched-pairs signed rank test or the paired *t* test.

Probably only a minority or perhaps about 50% of AD patients improve when treated with AChEI. If the treatment is evaluated with a cognitive test that is unreliable and neither measures cognitive decline nor positive treatment effect well (test A), the mean score change of the population will be 0 points after the treatment. If one instead evaluates the treatment with a reliable test that measures cognitive decline and treatment effect well (test B), some patients will improve due to treatment effect and some will decline due to lack of treatment effect. The mean change for test B will also be 0 points and no differences can be found between the tests. However, if a RCI is established based on the natural variability of the score change when no treatment is given, the differences between test performances of A and B can easily be found after treatment.

4.4.3   Logistic regression analysis and comparison of AUCs

Logistic regression analysis was used in paper IV to predict follow-up diagnoses. The covariates were entered using the backward LR method. The limit to be entered in the model was set to $p = 0.05$ and the limit of removal was set to $p = 0.051$. To compare the different models, the probabilities of each model were saved as a new variable (a value between 0 and 1 for each individual). These probability variables were then used to plot ROC curves and the AUCs of the different models were compared using a method by DeLong et al. (1988).

5 Main features

5.1 Paper I

Treatment of Alzheimer's disease (AD) with acetylcholinesterase inhibitors (AChEI) can improve visuospatial ability, among other cognitive domains (Behl et al., 2006, Thiyagesh et al., 2010). This is poorly measured with the most common evaluation test, the Mini-Mental State Examination (MMSE). A better way to assess visuospatial ability is to ask the patient to copy a cube. Although the cube-copying test has been around for decades, its ability to evaluate AD treatment has not been examined. We therefore assessed cube drawings in 85 patients with AD at baseline and after 6 and 12 months of treatment. Cube drawings before baseline were assessed to examine change in cube copying without treatment. Cube drawings from 56 healthy elderly people were also assessed. The cube scoring method of Maeshima et al. (2004) was used, as well as assessment of three-dimensionality (3-D; i.e. if the cube drawings exhibited 3-D features or not). The validity of cube copying was further examined by correlating the cube score with other scales. The changes in MMSE scores before and after treatment were also evaluated.

Results

1. The cube score correlated significantly with activities of daily living (ADL) scales (r_s = –0.13 to –0.36), the MMSE (r_s = 0.24 to 0.43) and the global dementia rating CGIC (r_s = –0.44)
2. In the healthy untreated elderly, cube copying and MMSE scores were unchanged over 3 years.
3. Before treatment of the AD patients, the MMSE and cube score as well as the percentage of successful 3-D drawings deteriorated significantly.
4. During treatment of the AD patients, the MMSE score remained stable for 6 months. However, it had deteriorated significantly after 12 months compared with baseline. The cube score and percentage of correct 3-D drawings remained stable after 6 and 12 months.

Comments

This study provides preliminary evidence that cube copying can be used to evaluate AChEI treatment in AD. Due to its narrow cognitive span, it should not be used alone but preferably in combination with tests such as the MMSE, which measures visuospatial ability poorly. Many cube-scoring methods are too complicated to be suitable in clinical situations. This study found that the simple assess-

ment of whether 3-D features exist or not in a drawing can be of use when evaluating cube drawings.

One can only speculate about the reasons why the MMSE deteriorated significantly after 12 months of treatment, whereas cube copying did not. Cube copying may measure those cognitive abilities more affected by treatment with AChEI, or the MMSE is better at tracking cognitive decline. It could also be an issue involving the reliability of either test.

In addition to the results published in the article, we also examined how well changes in cube score (more than 1 point) agreed with clinicians' qualitative judgment of whether drawings had improved, stabilized or deteriorated. Agreement between the qualitative assessment and cube score was moderate ($\kappa = 0.49$–0.58). A clinician's judgment is likely to be better than a 3-D assessment to track changes in cube copying and can, to some extent, be used to approximate changes in cube score.

5.2 Paper II

Dementia with Lewy bodies (DLB) is the second most common form of dementia and constitutes 0–30% of clinical dementia diagnoses (Zaccai et al., 2005) and 10–20% of neuropathological dementia cases (McKeith et al., 2004). Despite its relatively high prevalence, DLB is unfamiliar to most clinicians and many symptoms of DLB are similar to those for AD. The consensus criteria for DLB are complex (McKeith et al., 2005) and not examined in every patient with cognitive impairment. These factors often result in DLB being underdiagnosed. This can have serious consequences because patients with DLB often are very sensitive to neuroleptics and require different medical care than patients with AD (McKeith et al., 2005).

Differences in neuropsychological profiles have been identified between patients with AD and DLB (Collerton et al., 2003, Metzler-Baddeley, 2007). Most of these were established with tests not commonly used and with statistical methods that are difficult to translate into clinical practice. Therefore, the aim of the present study was to establish easy interpretations of brief cognitive tests for identifying DLB and differentiating it from AD. The clock drawing test, the cube-copying test and the different parts of the MMSE were examined in 33 patients with DLB and 66 patients with AD matched for gender, MMSE score and age.

Results

1. The mean MMSE score in both groups was 23 points. Compared with patients with AD, patients with DLB produced significantly worse results for clock drawing (p < 0.001), cube copying (p < 0.001), MMSE at-

tention (p = 0.03) and MMSE visuo-construction (copying pentagons) (p=0.02) and better for MMSE orientation (p < 0.001).

2. The following easily identified criteria were established to differentiate DLB from AD: (1) MMSE orientation × 3 ≥ total MMSE score; (2) unsuccessful clock drawing; (3) cube drawing without 3-D features.

3. If (1) and (2) were met in patients with MMSE scores of 21–27 points, the sensitivity and specificity were 93% and 70%, respectively, to separate DLB from AD. If at least two of the three criteria were met, the sensitivity was 85% and the specificity 75% to separate DLB from AD regardless of MMSE score.

Comments

These findings are in agreement with previous neuropsychological results in AD and DLB (Collerton et al., 2003, Connor et al., 1998, Hanyu et al., 2006, Metzler-Baddeley, 2007, Shimomura et al., 1998). The proposed algorithms cannot be used diagnostically, but instead as reminders that the clinical criteria for DLB should be examined more thoroughly in some patients.

Twenty-nine percent of the DLB patients' cube drawings lacked 3-D features. However, only 2% of cube drawings by patients with AD lacked 3-D features. The lack of 3-D has poor sensitivity but very high specificity that can be useful at early stages of the diseases.

The optimal cut-offs in the present study were established in the same population that they were tested in, which makes the generalizability uncertain. However, we recently tested the criterion "MMSE orientation × 3 ≥ total MMSE score" on an additional 87 patients with DLB and found that 90% fulfilled this criterion regardless of their total MMSE score. Surprisingly, this criterion was better in the new population than the original population. However, the algorithms still require testing in another population, preferably a consecutive population at a memory clinic.

5.3 Paper III

The recommended treatment for mild and moderate AD is AChEI. This treatment has been shown to have significant effects on cognition in many randomized controlled trials (Birks, 2006). Attention has been proposed as the cognitive function that improves most (Foldi et al., 2005, Vellas et al., 2005). However, the treatment is quite expensive, not all the patients experience positive effects and some adverse events such as nausea, vomiting and diarrhea have been reported (Birks, 2006). To enhance the efficacy of AChEI it would be beneficial to identify those

who respond positively to the treatment, which is also recommended according to the NICE guidelines (NICE, 2011).

One test that has promising psychometric characteristics is A Quick Test of Cognitive Speed (AQT). AQT exhibits no cultural or gender bias, no ceiling or practice effects, it takes 3–5 minutes to administer and places demands on attention, among other cognitive domains. Only the color-form task of AQT was analyzed in this study. The MMSE is the most common and recommended evaluation test and it was therefore used for comparison (NICE, 2007).

Test changes 2 months after AChEI treatment, and during an average period of 2 months before treatment, were examined in 75 patients with mild to moderate AD. Based on the changes before treatment, a reliable change index (RCI) was established to define treatment response.

Results

1. Results for the AQT deteriorated significantly before treatment (p < 0.05) and results for the MMSE was unchanged (p = 0.09). Both AQT (p < 0.0001) and the MMSE (p < 0.05) improved after 2 months of treatment.

2. AQT improved significantly more than the MMSE (p = 0.03) when the changes before and after treatment (expressed as percentages to accommodate for the different scales) were compared.

3. The calculated RCI was ≥16 seconds for AQT and ≥3 points for the MMSE. These cut-offs falsely classified ≤5% as treatment responders when no treatment was given, which showed that the cut-offs were correctly established to account for natural test variability. After 2 months of treatment, AQT identified 34% of the patients as treatment responders and the MMSE identified 17%, which was significantly fewer (p=0.02).

4. Those patients identified as treatment responders after 2 months according to AQT continued to perform significantly better than the non-AQT responders after 6 months of treatment. The mean difference in AQT score between the groups was 22.3 seconds (p < 0.0001). Unfortunately, corresponding data for the MMSE were not available.

Comments

AQT was more sensitive in evaluating the treatment effect than the MMSE, when analyzing group data (mean changes of the scores) and individual data (treatment responders). The treatment effect was evaluated after 2 months. If evaluated earlier the treatment might not yet have had any effect. If evaluated later the disease progression becomes more prominent, which makes it difficult to identify treatment effects if not using a placebo group.

The patients identified by AQT as responders after 2 months performed significantly better than the nonresponders after 6 months. This indicates that AQT not only is sensitive in early treatment evaluation, but also predicts who will continue to benefit from the treatment.

The cut-offs used to define treatment response were primarily established to compare the tests. However, an MMSE cut-off of ≥3 points has previously been suggested to indicate a significant change in healthy subjects and patients with AD (Eslinger et al., 2003, Iverson, 1998, Qaseem et al., 2008, Tombaugh, 2005). The AQT cut-off of ≥16 seconds suggests that patients with AD have a much greater natural variability in AQT speed than healthy subjects for whom the proposed cut-off is ≥5 seconds to indicate significant change (Wiig et al., 2009). The cut-off of ≥16 seconds was best suited for the entire population. However, it is probably higher for individuals with slow naming speeds and lower for individuals with fast naming speeds.

The results from this study can have implications for the choice of test to use when evaluation treatment for patients with AD in clinical practice and in therapeutic trials.

5.4 Paper IV

It is important to diagnose AD and other dementias early, to initiate care and follow-up in time (Leifer, 2003, Modrego, 2006). Early identification will be even more important in the future if disease-modifying treatments are developed, which will probably require an early therapeutic start (Carter et al., 2010).

It is not easy to predict AD and other dementias at the early stage, called mild cognitive impairment (MCI), because many other nonprogressive disorders can cause MCI. Currently, the most successful method for predicting those who develop AD is analysis of cerebrospinal fluid (CSF) (Hampel et al., 2008).

The number of patients with dementia is increasing, especially in developing countries, and it is estimated that five million new cases of dementia occur each year (Ferri et al., 2005). It is not possible for all patients to undergo CSF analysis because of its costs and accessibility. It would thus be advantageous if brief cognitive tests could also be used to predict AD and other dementias since these tests are inexpensive, readily available, and well tolerated by patients. We therefore compared CSF analysis and brief cognitive tests in 99 patients with MCI at a memory clinic. The CSF measures examined were Aβ42, total tau and P-tau, and the cognitive tests were AQT color-form, clock drawing, the MMSE and the orientation and delayed recall parts of the MMSE (MMSE (orientation & recall)). The physicians who diagnosed the patients were blinded to these data.

Results

1. Fifty-two patients (52.5%) progressed to dementia (MCI-dementia) and 47 patients (47.5%) remained stable (MCI-stable) during a mean period of 4.8 years (range 3.0–7.5 years), which corresponds to a dementia incidence of 10.9% per year. Among those who progressed to dementia, the prevalence of AD was 76.9% (40 patients), vascular dementia (VaD) 11.5% (6 patients), DLB 5.8% (3 patients), progressive supranuclear palsy (PSP) 3.8% (2 patients) and semantic dementia 1.9% (1 patient).

2. When predicting MCI-dementia and MCI-stable with logistic regression analysis, the model with cognitive tests (MMSE (orientation & recall) and AQT) classified 80% of the patients correctly. The best CSF model (Aβ42, P-tau and age) classified 75% correctly and had a poor fit of the model to the data (Hosmer and Lemeshow goodness-of-fit test < 0.05). Age, Aβ42 and P-tau classified 84% correctly when predicting MCI-AD and "MCI-stable and other dementias". MMSE (orientation & recall) and clock drawing classified 81% correctly.

3. When comparing the area under the curves (AUCs) of the regression models, no significant differences were found between CSF and cognitive tests in predicting MCI-AD or MCI-dementia (p = 0.38 and 0.58). However, the combination of CSF and cognitive tests classified 85% of the MCI-AD and "MCI-stable and other dementias" correctly, which yielded a significantly better AUC than cognitive tests (p = 0.04).

Comment

No significant differences were found between CSF and cognitive tests in predicting MCI-dementia or MCI-AD. However, cognitive tests correctly classified slightly more patients correctly than CSF when predicting MCI-dementia and the reverse condition was found for MCI-AD. The combined use of CSF and cognitive tests was significantly better than cognitive tests alone to predict MCI-AD.

These results correspond well with clinical practice, which uses CSF to identify AD pathology, not to predict dementias in general. The cognitive tests were not only accurate at predicting development of future dementia, they were also able to specifically predict future AD. MMSE (orientation & recall) was particularly good at differentiating MCI-AD from "MCI-stable and other dementias", which is in agreement with previous studies on cognitive profiles of AD and other dementias (Brandt et al., 1988, Jefferson et al., 2002). The MMSE was better than AQT at predicting both AD, and the other dementias as a group, which contradicts previous suggestions about the value of AQT in early cognitive impairment (Nielsen et al., 2007b). However, the AQT alone was able to identify patients with MCI-DLB and MCI-PSP, and differentiate them from patients with other demen-

tias and stable MCI with a sensitivity and specificity of 100% and 87%, respectively.

A methodological issue is that the predictive value of cognitive tests depends on the level of cognitive impairment, more so than CSF biomarkers. The present MCI population had a mean MMSE score of 27.2 points ± 1.7 points. If the patients had been referred to the memory clinic earlier, the predictive value would probably be lower for the cognitive tests, but remain the same for the CSF biomarkers.

This is the first study to validate brief cognitive tests against CSF biomarkers. It showed that brief cognitive tests that take less than 15 minutes to administer have a similar ability to CSF biomarkers in predicting the outcome of patients with MCI, and that the combination of both methods provides significant added value in predicting progression to AD compared with cognitive tests alone.

6 Conclusions

6.1 Paper I

Cube copying can be used for evaluating acetylcholinesterase inhibitor (AChEI) treatment in Alzheimer's disease (AD). It should not be used alone, but should be combined with the Mini-Mental State Examination (MMSE) or other cognitive tests which assess visuospatial ability poorly. Assessment of three-dimensionality (3-D) can be a substitute for a more time-demanding cube-scoring method.

6.2 Paper II

The identification of (1) a non-3-D cube drawing, (2) an impaired clock drawing and (3) the MMSE orientation score × 3 ≥ total MMSE score, can aid in the differentiation between dementia with Lewy bodies (DLB) and AD. If at least two of the three were fulfilled, DLB was differentiated from AD with a sensitivity of 85% and a specificity of 75%.

6.3 Paper III

A Quick Test of Cognitive Speed (AQT) is more sensitive than the MMSE in detecting early treatment response to AChEI treatment in AD. AQT detected twice as many treatment responders than the MMSE after 2 months. After 2 months, AQT also identified those patients who continued to benefit from the treatment after 6 months.

6.4 Paper IV

The brief cognitive tests MMSE, clock drawing and cube copying can predict AD and dementia in mild cognitive impairment (80–81% accuracy), just as good as the cerebrospinal fluid (CSF) biomarkers tau, P-tau and Aβ42 can (75–84% accuracy). The combined use of cognitive tests and CSF biomarkers provided significant added value compared with using to cognitive tests alone, when predicting AD.

7 Discussion

This thesis has improved the validity of the brief cognitive tests cube copying, clock drawing, the Mini-Mental State Examination (MMSE) and A Quick Test of Cognitive Speed (AQT) in treatment evaluation and differential diagnosis of dementias, and prediction of progression in mild cognitive impairment (MCI). New interpretations and fields of application have been proposed for these tests. However, it is important to realize the limitations. Firstly, these results should be tested in other populations. Secondly, brief cognitive tests only form one piece of information in diagnostics or treatment evaluation. The medical history of a patient is the most important factor, and results from other instruments must also be taken into account. Furthermore, brief cognitive tests should not replace assessment of activities of daily living (ADL) or a more thorough neuropsychological assessment.

7.1 Diagnostic considerations

An issue that arose in the papers of this thesis, and in most other papers in the field of neurodegenerative diseases, is the lack of a diagnostic criterion standard. In papers II and IV, the diagnostic value of the brief cognitive tests was evaluated against "probable" clinical diagnoses. Knopman et al. (2001) found that when evaluating these "probable" diagnoses against neuropathology, the average sensitivity and specificity for AD were 81% and 70%, respectively, and the average sensitivity and specificity for DLB they were 22–50% and 87–100%, respectively.

Neuropathology was for a long time thought to be the criterion standard of diagnostics. However, its diagnostic accuracy differs greatly depending on the method used and it can no longer be regarded as the "true" diagnosis (Brunnstrom and Englund, 2011). Therefore, this research area needs further studies to be conducted on the definition of the diagnoses *in vivo*. In the meantime, the clinical criteria are probably the best available.

In April 2011, the new clinical criteria for AD were published (McKhann et al., 2011). They were the first revision in 27 years (McKhann et al., 1984), and introduced the criteria for "probable AD dementia with increased level of certainty". These new criteria included clinical follow-up to objectively ensure a progressive cognitive decline, in addition to the old criteria for "probable AD". Patients with AD in this thesis fulfill the new criteria for "probable AD dementia with in-

creased level of certainty", which strengthens the diagnoses and the results of the studies.

7.2 Future issues

Future patients visiting memory clinics and primary care units will probably be better educated, examined at an earlier disease stage and have more culturally diverse backgrounds. It is likely that these factors will render many common tests, such as the MMSE, less useful. Consequently, there will be a greater demand for culturally independent tests with no ceiling effect, such as AQT and similar tests.

Research in the field of AD and other dementias is mostly focused on expensive, high-tech instruments such as beta-amyloid imaging with positron emission tomography various analyses of cerebrospinal fluid (CSF) and volumetric atrophy measurements with magnetic resonance imaging (MRI). These can contribute to better diagnosis and prediction of the diseases, a better understanding of the pathogenesis of the disease, and they are also a likely way to get published in a high impact journal. However, the estimated prevalence of dementia is 34 million people worldwide and it is predicted than over 100 million people will suffer from AD by the year 2050 (Brookmeyer et al., 2007, Wimo et al., 2010). The increase will be highest in developing countries due to greater life expectancy and the adoption of a more Western lifestyle (Ferri et al., 2005). Given these estimations, expensive instruments are not likely to play a major role in diagnostics and treatment evaluation worldwide. Instead, medical history and inexpensive, brief cognitive tests will be more likely to constitute the basis of diagnosis and treatment evaluation. Therefore, it is increasingly important to focus on validating brief cognitive tests and provide clinically relevant information on their interpretation and field of application.

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