

Reserve in mild cognitive impairment – new approaches

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Cover: the Psychograph, a device intended to state personality traits of a person by way of measuring the shape of the skull. Invented by Henry C. Lavery in the 1930s, USA (about 100 years after phrenology had been abandoned in European academia)

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Esse est percipi (to be is to be perceived)
George Berkeley (1685-1753), bishop of Cloyne

*To my wife, children and parents
- with love and statistics*

Abstract

The concept of reserve stems from the observation that premorbid factors, e.g. education, result in variation in the response to any kind of brain pathology. As subjects with higher reserve tolerate more neuropathology, symptomatic expression of pathology is delayed. It is thus predicted that neuropathology should be more pronounced in those with higher reserve as compared to those with lower at the same level of clinical severity. Most research within the reserve paradigm has been conducted on patients with established diagnoses, mainly Alzheimer's disease, but knowledge on the modifying effects of reserve in preclinical, Mild Cognitive Impairment (MCI), and early phases of dementia is limited.

The main purpose was to investigate if use of cerebrospinal fluid (CSF) biomarkers, would enable studies of reserve in earlier phases. Specifically, the 42 amino acid form of beta-amyloid (abeta42), mirroring amyloid plaques depositions, and CSF total tau (t-tau), reflecting axonal degeneration, were used as surrogate measures for neuropathology. Another purpose was to explore if patients with higher reserve diverge from patients with intermediate and lower reserve in terms of CSF pathology, and cognitive functioning in various disease phases. As premorbid intelligence Quotient (IQ), cognitive functioning prior to manifest disease, may be a better proxy for reserve than education, the final objective was to construct a test for assessment of premorbid IQ in Swedish.

In summary, we found that patients with higher reserve were distinguishable from those with intermediate and lower reserve with regards to abeta42 pathology, but not clinical manifestations. The incongruence between pathology and clinical outcome indicates compensation for neuropathology. We also found that abeta42 may be sensitive to disease progress when taking level of reserve into account. Patients with higher reserve with stable MCI had lower concentrations of CSF t-tau, but comparable abeta42 concentrations. This finding may either indicate a true protective effect for education, or suggests that higher education promotes cognitive stimulation resulting in better axonal integrity. Also, a test for assessment of premorbid IQ, NART-SWE, was successfully constructed and found to have satisfactory psychometric properties. The results of these studies may contribute to earlier identification, and consequentially treatment of patients with higher reserve at risk for dementia.

Populärvetenskaplig sammanfattning

Reservbegreppet avser förklara varför det inte finns något direkt samband mellan patologi i hjärnan och sjukdomsuttrycket. Personer med högre reserv, t ex utbildning, högre IQ före insjuknande (premorbid IQ) eller större hjärnvolym, bibehåller med hjälp av kompensatoriska strategier tankefunktioner längre trots längre gången hjärnsjuklighet. Begreppet förutsäger också att den underliggande patologin vid samma grad av sjukdomsuttryck alltid är mer påtaglig hos individer med högre reserv jämfört med de som har lägre reserv. Forskning inom ramen för reservbegreppet har främst gjorts på patienter i relativt sent sjukdomsskede, i huvudsak på patienter med Alzheimers sjukdom, men kunskap om hur reservkapaciteten modifierar den kliniska bilden i potentiellt tidigt sjukdomsskede av demens, dvs. lindrig kognitiv störning (Mild Cognitive Impairment; MCI), är mycket begränsad.

Under de senare åren har biomarkörer från cerebrospinalvätska (CSF) använts för att studera in vivo patologi hos patienter med rapporterade minnessvårigheter. De mest välstuderade CSF-markörerna är total tau (t-tau), som reflekterar axonal degeneration och beta-amyloid 42 (abeta42) som är huvudkomponenten i amyloida plack. Huvudsyftet med avhandlingen var att undersöka hur reserv modifierar det tidiga sjukdomsuttrycket vid demens, i synnerhet tankefunktioner, med hjälp av CSF biomarkörer. Ett annat syfte var att undersöka om patienter med högre reserv skiljer sig från de med måttlig och mindre reserv vad gäller CSF patologi och symptomatologi i olika sjukdomsfaser. Ett tredje syfte var att utveckla ett test för att bedöma premorbid IQ vilket kan ge bättre indikationer på reservkapacitet än utbildning som är det vanligaste måttet på reserv.

Vi fann att MCI-patienter som vid tvåårsuppföljningen utvecklade demens med högre reservkapacitet hade tecken på mer amyloid sjuklighet än de med måttlig och lägre kapacitet vid både baslinjeundersökning och tvåårsuppföljning. Däremot var grupperna jämförbara vad gäller mått på tankefunktioner, vilket tyder på att patienter med högre reserv kompenserar för sin patologi. Abeta42 visade sig också spegla graden av sjuklighet över tid, vilket man tidigare inte kunnat påvisa. Då vi studerade patienter med MCI som förblev stabila över en tvåårsperiod fann vi att patienter med högre reserv hade mer intakt axonal integritet men likvärdig amyloid patologi jämfört med patienter med lägre reserv. Resultatet tyder på att högre reserv inte enbart fördröjer symptomen utan också sjukdomsprocessen. Slutligen konstruerades ett test med tillfredsställande testegenskaper för bedömning av premorbid IQ. Resultatet av studierna kan bidra till tidigare upptäckt av demenssjukdom hos patienter med hög reservkapacitet och därmed också behandling.

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List of original papers

The dissertation is based on the following four studies, referred to in the text by their roman numerals.

I. Rolstad S, Nordlund A, Eckerström C, Gustavsson MH, Zetterberg H & Wallin A. **Biomarkers in Relation to Cognitive Reserve in Patients with Mild Cognitive Impairment – Proof of Concept.** *Dementia and Geriatric Cognitive Disorders*. 2009;27(2):194-200.

II. Rolstad S, Nordlund A, Eckerström C, Gustavsson MH, Zetterberg H & Wallin A. **Cognitive reserve in relation to Abeta42 in patients converting from MCI to dementia - a follow-up report.** *Dementia and Geriatric Cognitive Disorders*. 2009; 28 (2):110-115.

III. Rolstad S, Nordlund A, Eckerström C, Gustavsson MH, Blennow K, Olesen PJ, Zetterberg H & Wallin A. **High education may offer protection against axonal degeneration in patients with MCI.** *Journal of Alzheimer's disease*. (in press)

IV. Rolstad S, Nordlund A, Eckerström C, Gustavsson MH, Zetterberg H & Wallin A. **The Swedish National Adult Reading Test (NART-SWE): a test of premorbid IQ.** *Scandinavian Journal of Psychology*. 2008 Dec;49(6):577-582.

Abbreviations

(in alphabetical order)

AAN	American Academy of Neurology	MD	Mixed Dementia
Abeta42	the 42 amino acid long amyloid beta peptide	MMSE	Mini Mental State Examination
Ach	Acetylcholinesterase	MRI	Magnetic Resonance Imaging
ADL	Activities of Daily Living	NART	National Adult Reading Test
AD	Alzheimer's Disease	NART-SWE	National Adult Reading Test, SWEdish version
ANCOVA	ANalysis of COVariance	NFTs	NeuroFibrillary Tangles
ANOVA	ANalysis Of VAriance	NUD	Non Ultra Descriptum
APOE	APOlipoprotein E	PCA	Principal Component Analysis
APs	Amyloid Plaques	PET	Positron Emission Tomography
BNT	Boston Naming Test	PIB	Pittsburgh Compound B
BR	Brain Reserve	PIQ	Performance Intelligence Quotient
BRC	Brain Reserve Capacity	PPA	Primary Progressive Aphasia
CBF	Cerebral Blood Flow	P-tau	Phosphorylated tau
CDR	Clinical Dementia Rating	RAVLT	Rey Auditory Verbal Learning Test
CR	Cognitive Reserve	RCFT	Rey Complex Figure Test
CSF	CerebroSpinal Fluid	SCI	Subjective Cognitive Impairment
DTI	Diffusion Tensor Imaging	SD	Standard Deviation
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders version IV	SPECT	Single Photon Emission Computed Tomography
EEG	ElectroEncephaloGraphy	SPSS	Statistical Package for Social Sciences
ELISA	Enzyme-Linked ImmunoSorbent Assay	STEP	Stepwise Comparative Status Analysis
fMRI	Functional Magnetic Resonance Imaging	SVD	Subcortical Vascular Dementia
GAI	General Ability Index	TIA	Transient Ischemic Attack
GDS	Global Deterioration Scale	TMT	TrailMaking Test
HIV	Human Immunodeficiency Virus	T-tau	Total level of microtubule stabilizing protein tau
IADL	Instrumental Activities of Daily Living	USD	United States Dollar
ICC	Intra Class Coefficients	VAD	Vascular Dementia
ICV	Intracranial Volume	VCI	Vascular Cognitive Impairment
I-FLEX	abbreviated form of the Executive Interview	VIQ	Verbal Intelligence Quotient
IQ	Intelligence Quotient	VOSP	Visual Object and Space Perception battery
LP	Lumbar Puncture	WAIS-III	Wechsler's Adult Intelligence Scale version III
MCI	Mild Cognitive Impairment	WAIS-R	WAIS-R = Wechsler's Adult Intelligence Scale Revised
MCI-con	Mild Cognitive Impairment, converting to dementia	WMH	White Matter Hyperintensities
MCI-sta	Mild Cognitive Impairment, stable		

The aging population

World population is generally aging, which is most evident in wealthier countries. Among countries classified by the United Nations as more developed (constituting 1.2 billion of the world population, 2005), the median age rose from 29.0 in 1950 to 37.3 in 2000, and is predicted to rise to 45.5 by 2050. The corresponding figures for the world as a whole are 23.9 for 1950, 26.8 for 2000, and 37.8 for 2050 (1). As for Sweden, mean age is expected to rise from 79.3 to 84.1 for men, and from 83.3 to 86.5 for women from 2009 to 2050 (2). One of the obvious costs of longevity and change in population constitution, is diseases of old age of which various forms of dementia are recognized as a global public health problem (3). Dementia is most often diagnosed later in the disease course when cognitive impairment, decline in abilities of thought inferred from behavior (4), has impact on activities of daily living (ADL), e.g. paying bills, or attending to personal hygiene. Cognitive decline associated with risk of dementia may not be easily discriminated from that of normal aging.

Cognition

Cognitive decline refers to impairment in any mental ability used in everyday life to accomplish different tasks, or to overcome obstacles of thought. Cognitive abilities are functional properties of the individual inferred from behavior (4), and may be conceptualized in various ways. For the purpose of this thesis, however, cognitive subsystems, domains, will be conceptualized in harmony with established recommendations (5): memory functions, speed and attentional functions, language, executive functions and visuospatial functions. Contrary to other mammals, memory in human encompasses several distinct subsystems (6).

In general, **memory functions** refer to the ability to recall and learn information which may be either declarative, i.e. conscious learning of information, or procedural; unconscious acquisition of skills such as learning to swim. As for learning of factual information, e.g. rehearsal

of historical dates or thesis reading, a distinction between semantic and episodic memory has been proposed (7). Semantic memory encompasses knowledge of words, grammar and concepts. In short, the semantic memory subsystem enables comprehension of language, expressed ideas, and problem solving. Episodic memory does not cover general facts, but rather personally experienced events tied to a specific time point or place.

Speed and attentional functions enables processing of internal and external stimuli (8), and is considered to be a system of limited capacity involving processing in several stages occurring in diverse brain systems (9). Learning of word lists would in example require direction of attention towards the target words in order for learning to take place. This would be an example of memory driven action in opposition to a stimulus driven reaction where the subject is in less control of her attentional capacity (10). Another distinction in the attentional system is that between tonic and phasic attention; vigilance, sustained attention, or attentional shifting in response to changing stimuli (9).

Executive functions generally refer to the ability to perform independent purposeful, self-serving, and goal oriented behavior (9). A key term in relation to executive functions is that of executive control, alternatively cognitive control. Executive control is the ability to coordinate lower level motor and sensory processes into a common denominator on the basis of intrinsic goals (11). In example, tasks requiring inhibition of an automatized response, such as indicating all occurrences of “and” in a paragraph, require control over lower level cognitive processes. Executive functions are hence also closely related to attentional functions, but concern the orchestration of attentional functions rather than attention per se (12).

Visuospatial functions may be defined as processing of stimuli of visual and spatial nature. These functions encompass the mental representations of real world objects and the relationship between such objects (13). Processing of visual material include basal perceptual operations such as separating out a figure from its background to more complex tasks, e.g. construction of a

multidimensional object from several separate parts, or finding ones way in a new environment.

Finally, **language functions** refer to verbal abilities which, in example, cover naming, comprehension and communication of spoken or written material, vocabulary, and verbal fluency. Verbal functions are unique to man, and as other cognitive subsystems, language functions depend on functions within other cognitive systems, especially memory and executive functions (14)

Normal aging and cognition

In general, normal aging reduces the ability to perform cognitive operations, and alters the way they are performed. More specifically, studies typically show that perceptual speed, working memory and long-term memory are reduced as an effect of age. Verbal ability, estimating accumulated knowledge, has however, not been found to be affected by aging (15). Though, it should be noted that many studies addressing the issue of cognitive aging are cross-sectional, that is comparing individuals at the same time that may be born at different times (16), and may thus not be suited to reflect time related changes. This methodological problem is referred to as cohort effects. Notwithstanding, similar patterns have been found when analyzing longitudinal data. In example, reduced processing speed, working memory, ability to recall word lists, and intact verbal ability were reported for healthy older adults in the Victoria Longitudinal Study (17).

Several attempts to identify causes of age-related decline have been proposed. These attempts may be dichotomized as either psychological/behavioral or neurological in nature. One dominant construct in the psychological literature is that of speed of processing which accounts for most age-related variance on a broad spectra of cognitive tasks (18). The main arguments for the role of processing speed in relation to age-related cognitive decline, which is supported by several studies spanning thousands of subjects (19-23), is that general cognitive performance is degraded when processing becomes

too slow for certain cognitive operations to be carried out. Also, the product of basal cognitive operations may no longer be available when later stages of cognitive processes are complete. In other words, there is a time frame for basal cognitive operations which may impede the result of later stage cognitive processes. Another behavioral approach to aging is that of working memory mediated cognitive decline. In short, working memory along with processing speed decrease with age, and mediates the observed variance in age-related cognitive decline (15). A third, related concept, focuses on how impaired inhibitory processes results in vulnerability to distraction (24). In example, older individuals perform tasks worse than younger individuals when performing task in presence of competing stimuli. Finally, a different perspective on cognitive decline stresses the importance of audition and visual acuity as predictors of performance on a broad range of cognitive tasks (25). Sensory functions are independent of cognition in adults of 60 years or less, but have been found to become interrelated in late life. A proposed explanation for the evolvement of sensory functions as mediators of cognition in late life is that older individuals engage in less specific tasks than younger individuals. This results in what has been coined dedifferentiation: neural specificity decrease and broaden, and become available to a wider range of inputs.

The aging brain

Magnetic Resonance Imaging (MRI) has been used to examine structural and volumetric differences in relation to aging. Two studies reported that, over a period of five years, the greatest decreases in volumes were in the hippocampus, a structure located in the medial temporal lobe of major importance for learning, the caudate, located in the basal ganglia, essential for information encoding, cerebellum, and the prefrontal areas. Shrinking is minimal in the entorhinal cortex, a structure that is pre-processing input signals located in the posterior end of the temporal lobe forming the main input to the hippocampus. Visual cortex has been found to be unaffected (26, 27). Gray matter volumetric shrinking has also been reported for periods over 2 years. One study reported shrinkage in

frontal and parietal cortex in healthy individuals of 59 years of age or above. Some shrinkage has also been found in the temporal and occipital lobes (28). Another study reported that global gray matter decreased linearly with age. Shrinkage was significantly more pronounced in males as compared to women (29). However, sex differences have not been reported by others (30). One study, unexpectedly found cortical thinning in the calcarine cortex, located near the primary visual cortex, and in the frontal cortex near the primary motor cortex (30). Thinning of calcarine cortex has been proposed as a possible neurobiological linkage to the finding that decline in visual function in old age is associated with declining cognitive performance (16).

The MRI technique Diffusion tensor imaging (DTI) provides an index of the structural integrity of the axonal bundles beneath cortex, the white matter, by measuring the rate and direction at which water diffuse through the white matter. One study applied DTI on healthy older individuals and found reduced structural integrity in frontal regions of the brain (31). Another study found integrity to be more reduced in ventromedial and deep prefrontal regions as compared to prefrontal regions (32). Another MRI technique, also providing information about white matter health, is White Matter Hyperintensities (WMH). This technique presents areas of high intensities on T2 weighted MRI scans; areas with high intensities appear bright against normal tissue. WMH provides information on signal abnormalities from white matter, likely resulting from demyelination, inflammatory disease, trauma, or other neuronal damages. Studies on normal aging and WMH have reported similar results to those applying DTI: frontal regions are affected by aging. Also, as in the case with the study reporting cortical thinning in the calcarine cortex, occipital areas have been found to be affected by aging (33). Significantly reduced white matter integrity in occipital areas was also reported in another study (34). In sum, the morphological findings in the elderly indicate that the most pronounced shrinkage and functional loss is associated with frontal regions with others being relatively spared.

Brain – cognition – aging

Shrinkage of entorhinal cortex, which is not associated with normal aging, was found to predict poor memory performance over a five-year period in older adults (26). This finding was corroborated by another study which also found hippocampal shrinkage to be associated with poor performance on memory tests (35), others have not replicated this observation (36). Some studies have sought to find a relation between working memory and the role of frontal volumes, but the relationship remains obscure. Counterintuitively, an association between *increased* orbitofrontal volumes and *reduced* working memory capacity has been found in older adults (37). Another study found no relationship for working memory with frontal volumes, but reported that performance on an executive test correlated with higher volumes (38). It was also found that WMHs predicted performance on the Wisconsin-Card-Sorting Task, a test measuring several aspects of executive functions and to some degree vigilance, but not performance on tests assessing working memory. Albeit not directly relating to cognition per se, significantly reduced WMHs over a 20-months period was found in older individuals with impaired mobility as compared to older controls (39). The finding could be interpreted as dedifferentiation.

Whereas studies using MRI provide information about brain structure and volume, functional imaging techniques (fMRI or Positron Emission Tomography, PET) allows for visualizations of how the brain is functioning by measuring blood flow and oxygenation. Studies using fMRI have, in contrast to the previously mentioned structural and behavioral studies, found increased neuronal activity in healthy older adults as compared to younger adults. When performing tasks assessing verbal long-term memory (40, 41) and working-memory (42), younger adults exhibited activation in focal left prefrontal areas. In contrast, older adults showed activation both left and right prefrontal activation. It has been speculated that the increased activation in older adults may be attributable to that older brains have to work more in order to encode information (43). It has also been suggested that contralateral activation is due to inefficient functioning of inhibitory mechanisms, and thus related to the

hypothesis of executive cognitive deficit (16). However, bilateral cognitive activation has been found to not be limited to working memory related tasks but also in relation to learning of category tasks and visual encoding (44, 45). As bilateral activation also leads to higher performance in older individuals (46, 47), increased activation is likely not a product of inefficient inhibitory mechanisms. A related finding is that overactivation, as compared to younger individuals, in prefrontal areas in older individuals have been associated with improved memory (48). There is also some evidence that increased frontal bilateral activity is linked to improved memory when hippocampal activity is decreased in older individuals (49). A follow-up study found that this effect was not merely attributable to age, as the relationship also was confirmed when older adults were matched with younger adults on the basis of performance (50). An equivalent pattern of increased bilateral frontal activation and decreased hippocampal activation was found when older adults performed tasks involving working memory and attention (51). In another study, older individuals with the most pronounced hippocampal shrinkage over a ten-year period exhibited the most evident frontal bilateral compensation (52).

Dopaminergic receptors are vital with respect to attention and regulation of responses to external stimuli. By using radioligands binding to dopaminergic receptors, in vivo imaging of receptors is possible. It has been reported that dopaminergic receptors decrease by approximately 1 % per year after the age of 18 in caudate nucleus (53), a structure involved in located within the basal ganglia involved in control of voluntary movement and is playing a key role in learning and memory formation. As for the relation between dopaminergic receptors and cognition, one group of researchers found finger tapping, measuring fine motor speed, to be correlated with density of dopaminergic receptors in striatum (54), a key input station located in the basal ganglia. Others reported that dopaminergic binding was far more important than age in relation to performance on tests of episodic memory and attention (55).

Dementia

Generally, dementia may be defined as progressive decline in cognitive function due to damage or disease beyond what might be expected from normal aging alone. The origin of the word dementia is latin (de – apart + mens – mind) and could be translated “out of mind”. Dementia is not one single disease, but a heterogeneous syndrome of more than 200 diseases, most of which are infrequent (3). The syndrome of dementia may be caused by various underlying diseases, each characterized by particular signs and symptoms in combination with a presumed underlying neuropathology. Although dementia is far more common in the elderly population, it may occur in earlier adulthood. Given that age is a prominent risk factor for dementia (56), and as the world population at large is becoming older, dementia is increasingly becoming a global health problem and is not restricted to the Western world. As normal aging generally results in reduced ability to perform cognitive tasks, shrinkage in some areas of the brain, and reduced white matter integrity, preclinical dementia is not easily distinguished from signs and symptoms of normal aging. Also, depending on type of dementia, there is considerable variation with respect to which symptoms become manifest. According to DSM-IV criteria (57), the threshold for dementia is impairment of ADL, and not cognitive or structural changes. Even though pathological findings on e.g. MRI and deviating cognitive functions may be observed in an early disease phase, the diagnosis of dementia is not to be made until a threshold of reduced ADL has been passed.

In two recent reports the worldwide prevalence, the total number of cases of a disease in a population at a given time, of dementia in 2000-2001 was estimated at about 24-25 million individuals (58, 59). Comparative figures for Sweden were estimated to be about 160.000 (58). A meager majority of those with dementia in the world, 52 %, lived in less developed regions (59). It was estimated that about 6.1% of the population of 65 years of age and older suffered from dementia, of which 59% were female. Incidence, the number of new cases, of dementia in 2000 was calculated to be 4.6 million. The number of individuals suffering from dementia was forecasted to increase to 63

million by 2030 and to 114 million by 2050, the majority of which will live in less developed regions. Most studies of prevalence of dementia focus on subjects of 65 years of age or older. However, dementia also affects younger subjects. In a larger catchment area in the UK, figures for dementia were 54 per 100 000 for those aged 30-64, and 98 per 100 000 for subjects between 45-64 (60).

The worldwide direct costs of dementia in 2003 were estimated to be between 129 and 159 billion USD (61). This estimate does not include expenses associated with informal care; i.e. loss of income due to care of family member. However, as dementia is more prevalent in older ages added informal costs may be relatively modest. In a study from 2006 total annual costs, including formal as well as informal care, for individual patients with dementia was estimated to be between 60.700 and 375.000 Swedish krona depending on severity of the disease. An average individual cost was calculated to 172.000 (62).

Alzheimer's disease

Alzheimer's disease (AD) is the most prevailing cause of dementia. According to one report, AD has been proposed to account for as much as 60-70% of all dementia cases (56). The classical clinical features of AD usually involve impairment of memory, visuospatial and language functions (63-70). Functional and behavioral disturbances are characteristic of the disease. Loss of function with regard to higher-level activities of daily living, e.g. paying bills, are common in the early disease stage, whereas difficulties in carrying out basic activities of daily living, such as eating, are typical of AD in advanced phases (71). Late stage disturbances involve: motor and sensory abnormalities, gait disturbances, and seizures (72).

AD is a neurodegenerative disorder, characterized by degeneration of neurons and their synapses, amyloid plaques (APs), and neurofibrillary tangles (NFTs) (73). The process of degeneration may start approximately 20-30 years prior to manifest AD (74). In example, an autopsy study of 2661 cases reported that about 20 % of all 30-year olds had NFTs in transentorhinal cortex (Braak stage I

and II) (75). The neurodegenerative process will increase APs and NFTs and eventually reach a threshold for covert symptoms. APs are accumulated extracellular protein fragments, amyloid, which are normally broken down, but in AD form to insoluble plaques. NFTs are insoluble twisted fibers found within neurons primarily consisting of a protein called tau. Tau is part of a structure named microtubule which aids in the transport of nutrients from one nerve cell to another. In the last few years, cerebrospinal fluid (CSF) biomarkers have become available to assess in vivo pathology in patients with memory complaints. Axonal degeneration is reflected in the CSF by the total level of the microtubule stabilizing protein tau (T-tau) (76), and hyperphosphorylated tau (p-tau) (77, 78), whereas APs are mirrored by lowered concentration of the 42 amino acid long amyloid beta (Abeta42) peptide (79-81). In a recent multicenter study, a combination of Abeta42/p-tau ratio and T-tau identified incipient AD with a sensitivity of 83%, and specificity of 72% for AD (82). Neurochemical biomarkers have recently been proposed to be included in new diagnostic criteria for AD (83), but separation from other dementia forms such as frontotemporal, vascular, and Lewy body dementia is not flawless (84).

Postmortem studies have found that the brain structures of the earliest alterations in AD are the located in the medial temporal lobe, particularly the entorhinal cortex, and hippocampus (85). These findings have been corroborated by volumetric magnetic resonance imaging (MRI) studies, which have reported that the entorhinal cortex and hippocampus are affected in mild AD, and show reductions in volumes of 20–25% relative to healthy controls (86-90). Shrinkage is most often reported to be most pronounced for the right hippocampus (91), but dominant shrinkage has also been seen in the left hippocampal volume (92). Other structures have been suggested to show volume decline in the early phase of AD, e.g. gyrus cingulate (93). It has been found that the brain regions showing the most significant rates of atrophy change as the disease advances, and that regional atrophy is existent prior to covert symptoms (94). Functional imaging studies have reported deviations in the posterior parietotemporal lobes rather than medial temporal lobe structures.

Reduction in metabolism has been found in the general region of the posterior cingulate gyrus in early AD (95).

Genetic studies have identified the epsilon 4 ($\epsilon 4$) allele of apolipoprotein (*APOE*) as a vulnerability locus, the position in the chromosome of a gene, for late-onset AD (96), debuting at 65 years of age or later. Twin studies have reported that genes may have a key role in more than 60% of AD vulnerability (97). It has been proposed that *APOE* may account for 50% of this genetic vulnerability (98). Recently, two new genes, *CLU* and *PICAM*, have been identified and associated with AD, together explaining about 10% of the risk for late-onset AD (99).

During the last decade, acetylcholinesterase inhibitors have been used for symptomatic treatment in mild and moderate AD (100). Acetylcholinesterase (ACh) inhibitors reduce the rate at which acetylcholine is broken down, thereby increasing the concentration of ACh in the brain and reducing the result of the loss of ACh caused by the death of cholinergic neurons. One acetylcholinesterase inhibitors, Donepezil, also has indication for treatment of severe AD (101). As of yet, there is little evidence, to support the notion that the risk of AD is reduced if pharmacological treatment is initialized prior to symptoms becoming covert (102).

Vascular dementia, mixed dementia and other subtypes

The second most prevalent cause of dementia is likely vascular dementia (VaD) accounting for about 15-20% of all dementia cases (56). However, it has also been suggested that VaD is the most common form of dementia, with figures as high as 50%. The high degree of variance with regard to prevalence figures is by all probability due to differences in patient populations and diagnostic and pathological criteria for VaD (103, 104). VaD has been classified and sub-classified in many ways as it covers a broad clinicopathological spectrum (105). It may be caused by various types of vascular pathology in the brain, such as large vessel (large territorial or strategical infarctions) and small vessel (lacunes and

white matter hyperintensities) disease (106, 107). Due to a high degree of variability with regard to vascular disease it has been difficult to reach an agreement on general neuropathological criteria for VaD (108). However, two subtypes VaD exhibit a rather homogenous clinicopathological picture: poststroke dementia and subcortical VaD. Poststroke dementia may be defined as dementia occurring close in time to a thromboembolic or hemorrhagic stroke. The clinical criteria for poststroke dementia is transient ischemic attack (TIA) or stroke with focal neurological symptoms (105). The primary types of brain lesions in subcortical VaD (SVD) are lacunar infarcts and ischemic white matter lesions. Vessel-wall damage of the long penetrating arteries and the thalamoperforant arteries in the subcortical region are considered the primary etiologies in SVD (106). Patients with SVD often display a history of multiple vascular disorders, i.e. arterial hypertension, or diabetes. Episodes of TIA or stroke may have gone unrecognized. The course of SVD is usually continuous and slowly progressive (109).

As compared to AD, some studies have found subjects with VaD to perform worse on neuropsychological tests assessing executive and visuospatial functions (63, 65). A strict dichotomization between AD and VaD has been debated, and there is reason to believe that most subjects appear on a continuum between the two pathologies. In example, mixed dementia (MD) may be defined as a dementia syndrome caused by two or more pathological processes in the brain: signs of both AD and cerebrovascular disease in the brain (110). There is no agreement on the prevalence and incidence of MD. It has been proposed that MD is the most common form of dementia as both neurodegenerative dementia and cerebrovascular disease increase with age (111).

Other frequent causes of dementia include frontotemporal lobar degeneration and dementia with Lewy bodies, abnormal aggregations of protein developed inside neurons. It is often difficult to reliably distinguish between subtypes of dementia. Therefore, epidemiological studies often focus on dementia as a whole, occasionally dividing the two most frequent subtypes; AD and VaD.

The continuum normal aging – dementia

Traditionally, changes in memory have been seen as a consequence of normal aging (112, 113), but more recent evidence suggest that decline in memory and other cognitive functions may represent incipient dementia (114, 115). Several concepts have previously attempted to define unhealthy cognitive aging possibly resulting in future dementia: malignant senescent forgetfulness (116), age-consistent memory impairment (117), aging-associated cognitive decline (118), and age related cognitive decline (119). Objectively confirmed cognitive decline was eventually found to be associated with an increased risk of converting to dementia. Consequently, interest in cognitive decline as a possible preliminary stage of dementia increased. Concepts such as Age-associated memory impairment (120), Cognitive Impairment no dementia (121), and Mild Cognitive Impairment (122) became targets for studies. The concept that has been most recognized is likely Mild Cognitive Impairment (MCI) which has been used to describe the potential transitional stage between normal cognitive function and mild dementia. The term MCI was originally introduced as stage 3, preceding the mild dementia stage, in the Global Deterioration Scale (GDS) published in 1988 (123). About a decade later it was proposed as an elaborated concept by Petersen et al. (122). The risk of AD was originally considered to be associated with memory impairment and other cognitive domains relatively intact. Cognitive impairment has commonly been operationalized as results 1.5 standard deviations (SD) below age means on memory tests. Eventually the MCI concept was revised to incorporate other subtypes/risk profiles and dementia aetiologies (124). The annual conversion rate of MCI to AD has most often been reported to be between 10-15% (122, 125), but conversion rates as high as 30-40% (115, 126, 127) have been reported.

Whereas MCI requires some form of objective decline in IADL or cognitive functions from a previous level of functioning, subjective cognitive impairment (SCI) has also attracted some attention in the literature. In terms of GDS staging, SCI corresponds to stage 2, and is conceived to be separated from that of normal aging and precede MCI (128). The prevalence of SCI in subjects of 65 years or more has

been reported to be between 25 and 56 % (129-131). There is currently little information on the topic of the prognosis of SCI as studies most often also have included subjects with MCI. Van Oijen et al. reported that the risk of AD was three times greater in subjects with SCI as compared to those without (132). Others have, however, not found such an association (133). A recent study linked SCI with AD pathology; 31 of 60 patients with SCI had a CSF AD profile (134).

Morphologically SCI has been linked to decreased brain grey matter in the frontotemporal, medial temporal lobe, other neocortical regions (135), and also reduced left hippocampal volumes in comparison with healthy controls (136). SCI has also been associated with depression, but has not been thoroughly studied outside the context of MCI (128). One study did however exclude subjects with MCI from the analyses and found that subjects with SCI had higher depression and anxiety scores than elderly without any subjective cognitive impairment (137).

Cognitive impairment in subjects with non-average intelligence

MCI criteria to some extent contain references to the fact that there is variability with regard to how individuals initially function cognitively. Use of norms based on education have been discussed for the most recent criteria (124) - the golden standard has been to apply 1.5 SD below age means as cut-off for cognitive impairment. Even if norms adjusted for educational level are utilized, there is a possibility that general cognitive level prior to disease, premorbid IQ, will obscure the actual level of impairment. This concern has previously been raised by others (138-140). In example, a patient with high premorbid IQ - also coined high cognitive reserve alternatively high brain reserve capacity - may have to deteriorate more than 1.5 SD in order to perform average results on cognitive tests. Also, norms adjusted for education do usually only discriminate those with 10 years or more of education from those with less. There is not only a potential of false negatives, patients with high premorbid IQ performing above cut-off criteria, but also of false positives, detection

of impairment in patients with lower premorbid IQ who do not have impairment, only low initial capacity.

The reserve concepts

In general the reserve concepts propose explanations for the observation that there is no direct relation between pathology and the clinical manifestation of the pathology. In example, Katzman et al. described 10 cases of older adults with above normal cognitive functions who at autopsy exhibited mild AD pathology – plaque counts were 80 % as compared to a group with dementia (141). Why did these cases not present any clinical symptoms of AD despite presence of histological pathology? The authors found that these patients had higher brain weights, and larger and more preserved pyramidal neurons, the primary excitatory neurons in the prefrontal cortex and corticospinal tract, as compared to AD-patients and non-brain-injured controls. Katzman speculated that more large neurons and higher brain weights may have offered some kind of reserve. While there have been many attempts to define reserve, the most cited concepts are those of Brain Reserve (BR) and Cognitive Reserve (CR), the latter introduced by Stern (142, 143). In the literature, these concepts are often used interchangeably as they provide similar predictions. BR and CR are, however, focused on different anatomical levels (144), and do also diverge with respect to whether the brain actively copes with pathology or not.

Even though most studies on the reserve concepts has been conducted in the field of neurodegenerative disorders, with AD being a model disease, the reserve concepts may be generalizable to all situations where an individual endures brain pathology. Research on the reserve concepts has also been conducted in other fields, e.g. Parkinson's dementia (145), HIV-related cognitive dysfunction (146-148), and multiple sclerosis (149). It has been argued that AD has some unique aspects in relation to the study of the reserve concepts: AD pathology affects cortical circuitry thus resulting in general impairment in cognitive functioning. Also, as opposed to stroke, the anatomically affected locations are similar across patients. These

characteristics allow for generalization and hypothesizing in regards to mechanisms of the reserve. Finally, AD is a slowly progressing disease, which renders possible studies of interactions between reserve and level of severity (142).

Brain reserve

The observation that there may be a substantial dissociation between pathological brain damage and cognitive and functional performance is not a novel one. In 1937, Rothschild noted that there was a lack of correspondence between brain structure and cognitive performance. Subsequent studies reported a broad distribution of senile plaques observed at autopsy, but a lack of correspondence with cognitive impairment prior to death. Cognitive impairment was present only above a certain threshold of plaque density (73, 150). The lack of coherence between brain damage and cognitive performance spurred the development of the concept of brain reserve, and more specifically the threshold model of brain reserve. The threshold model revolves around the idea that there is a critical cut-off for pathology, a threshold, below which pathology will result in clinical symptomatology. Perhaps the most frequently cited description of the BR concept has been formulated by Satz (151). His model describes brain reserve capacity (BRC) as a theoretical entity linked to adaptive behavior in relation to brain insult and disease. BRC could be operationalized as synapse count, overall brain size, or in terms of specific disease related functional markers. In general, larger brain size is considered to be better. Even though BRC is mainly an anatomical model, psychosocial factors such as education and intelligence may be used as indirect measures of BRC. The rationale for including indirect measures of the reserve as indirect measures of the BRC, is that enriched environments increase synapse numbers, cortical thickness and dendritic branching (152).

The BRC model take into account individual differences in BRC: individuals may differ in regards to how much pathology can be tolerated before symptoms become clinically apparent. A certain amount of pathology, i.e. plaque counts, may result in an AD

diagnosis in patient 1 but not in 2 as her BRC is higher. AD will however occur once neuropathology has reached an invariable threshold which is equal for all individuals regardless of initial capacity. It has been pointed out that BR models, or more specifically threshold models are passive in nature (142). In a recent review, several reasons why threshold models, should be regarded as passive were given (144): There is a fixed cut-off beyond which impairment will occur for everyone. Also, threshold models are quantitative in nature in the sense that repeated instances of brain insult sum together, and it is assumed that equal amount of brain damage result in the same amount of damage for everyone. Thus, individual differences are found with respect to degree of amount of damage tolerated due to varying degrees of initial BRC.

Evidence of the concept of brain reserve

Some neuroimaging studies have found positive correlations between intracranial volume (ICV) and onset of dementia (153). A positive association has also been found for ICV and cognitive performance in AD-patients (154). Others have, however, not confirmed this association (155). Also, positive correlations have been reported between ICV and cognitive performance in healthy subjects (156). One study reported smaller ICV in AD-patients as compared to controls (157). An epidemiological study found an association between head size and cognitive performance in non-demented elderly subjects and future cognitive decline (158). Associations have also been found between head size and AD (153, 159, 160). Despite that a number of studies have reported findings in favor of the BR concept, it has been argued that many studies only test some of the assumptions that underlie BR. Christensen found, in a review of the BR literature, that many studies do not separate the buffering effects of cognition on brain volume (161). Furthermore it was pointed out that a true BR design should explicitly specify type of brain insult, describe the origin of the reserve (cognitive strategy or brain volume), specify the way the reserve contributes (e.g. better brain recruitment), and the expected outcome from such processes (e.g. improved performance due to larger brain) (161). Currently, only a few studies fulfill these

proposed criteria. In example, Staff et al. (162) tested if brain reserve accounted for a significant variance contributed by childhood mental ability and age inflicted brain burden as measured by WMH. They found that education and occupational attainment, but not ICV, contribute to reserve and help maintain cognitive function in old age. Another study, found that education modified the effect of diffuse and neuritic plaques on cognition. More specifically, education was found to protect speed and attention, and semantic memory the most (163, 164).

Whereas a number of studies report evidence in favor of BR, studies using a true BR design, have not found anatomical measures to contribute independently to the reserve. Studies applying less stringent BR designs have however found a measure of brain size, head circumference, to independently contribute to BR. In example, it has been reported that higher education (bachelor's degree or above) adds to the reserve if head circumference is small (< 49 cm.), but no complementary effect was found for large head size (≥ 55 cm.) (165). Even though BR incorporates indirect measures of the BRC, i.e. education, occupational attainment, and Intelligence Quotient (IQ), these measures are hypothesized to contribute to brain capacity rather than being a feature of the reserve per se. The BRC rests on the notion that larger brain size, or more of any other hypothesized measurable anatomical feature, is better. However, it has been reported that larger head size does not add to the reserve. In example, head circumference correlated with scores on a comprehensive cognitive screening instrument only for those with circumference below 55 (160).

Cognitive reserve

Whereas the BR concept focus on the brain's resilience, the concept of CR assumes that individuals actively cope with brain damage using available cognitive processing resources, or by utilizing compensatory approaches (142). In terms of the CR concept, reserve, or more specifically neural reserve, is defined as inter-individual discrepancies with regards to cognitive processing in the healthy

brain. An individual with more neural reserve is considered to have more efficient or flexible brain networks and capacity to solve cognitive tasks. Greater reserve will likely enable brain networks to cope in the event of brain pathology. Another key notion in the CR framework is that of neural compensation which refers to the cognitive response to brain damage (144). Thus, the concept of CR deviates from that of BR with respect to being an active instead of passive model. Consequently, two patients with equal amount of BRC may respond differently to the same degree of brain damage depending on CR. There is no fixed cut-off for functional impairment. It could thus be argued that CR, as opposed to BR, stresses how function may be maintained in presence of brain damage (144). The concept of CR predicts that at any level of assessed clinical severity, the underlying pathology is more advanced in subjects with more CR as pathology accumulates for a longer period prior to becoming clinically apparent (166). Consequently, the concept of CR predicts that subjects with more CR will undergo a faster deterioration once the compensatory capacity is insufficient due to presence of more neuropathology (142).

Education is commonly used as a measure of CR. Some studies do however indicate that literacy may be a better proxy as it is a direct measure of CR (167), and others suggest that premorbid IQ is a more powerful measure than educational attainment (139, 168, 169). It has been argued that educational attainment is a more flexible proxy for CR than premorbid IQ as it accounts for life-time experiences (166) such as leisure activities (170), occupational achievement, and educational attainment independently contribute to CR. However, educational attainment may rather reflect opportunity than ability especially in the case of elderly women, and among groups with restricted economical resources (139). Also, findings point to the possibility that patients do not provide correct information, alternatively provide distorted information when enquired about their occupational or educational attainment (171, 172). As patients with lower education and socioeconomic background may also be at risk for exposure to toxic materials, malnutrition, or perinatal damage there is also a possibility that education is a surrogate for other risk factors rather than being of accumulated measure of

reserve per se (142). However, a recent study investigated the construct validity of reserve capacity in a multi-ethnic population as defined by current verbal IQ/semantic knowledge, premorbid IQ and educational level, and found that they were highly correlated. Also, executive functions were found to be related to verbal IQ and premorbid IQ (173). The authors suggested nonetheless that executive functions should not be considered as a part of the reserve construct, as earlier research has shown that executive functions not likely mirror separate individual capabilities (174).

Evidence of the concept of cognitive reserve

Most epidemiological studies report less frequent incidence of dementia and AD, and lower prevalence of AD in highly educated populations (175, 176). In a recent review, Valenzuela and Sachdev (177) found that 10 out of 15 epidemiological studies reported a protective factor for education after adjusting for age. It should be noted that protection in this case is limited to whether the patient receives a diagnosis or not. The reviewed epidemiological studies contain little information on cognitive performance or pathology. There are also some studies that have not found a relationship between incident dementia and education (178-180). An increased risk for AD has been reported for individuals with lower education and lifetime occupational attainment (181). Higher education has also been reported to slow down cognitive and functional decline (112). There is also some evidence that deterioration will be faster for patients with high CR when the compensatory capacity is insufficient due to presence of more severe neuropathology (182, 183). Others have, however, not corroborated this finding (184).

Studies using Cerebral Blood Flow (CBF) have found lower resting CBF in AD patients with higher education (143); higher premorbid IQ (169); more advanced level of leisure activities, and higher occupational status (170, 185). These findings suggest that AD-pathology is more pronounced in patients with higher cognitive reserve. Also, activation studies using Positron Emission Tomography (PET) have found a negative relation between educational level and

brain glucose metabolism after adjusting for dementia severity (186). The temporal and parietal cortices, which are commonly affected in AD, showed noticeably reduced uptake of glucose in highly educated patients. In another study, increased uptake of the ligand [¹¹C]PIB was found in the lateral frontal cortex in highly educated patients with AD (187), indicating more amyloid pathology in patients with higher education. A recent larger community based study found that, for any level of cognitive functioning, those with higher brain or cognitive reserve had more indications of vascular brain pathology, WMH (188). The modifying effect was more pronounced in women.

On reserve and protection

The concepts of Brain Reserve (BR) and Cognitive Reserve (CR) have been used to elucidate the lack of a clear association between brain pathology and clinical manifestation. Both concepts may use education as a proxy for reserve, and predict that pathology should be more pronounced in those with higher reserve regardless of assessed clinical severity (142, 151). Whereas BR focuses on anatomical differences as the source of resilience, the focal point of CR is rather how the brain uses its networks to overcome the effects of neuropathological damage. However, physiological variability is a necessary underpinning of neural networks, and thus anatomical differences are also implied in the CR model. The main differences between the concepts are foremost whether or not the reserve is active or passive, and with regards to model type, quantitative or qualitative.

None of the reserve concepts predict that higher reserve provides protection from neuropathology per se, rather they predict that higher reserve will either delay, mediate, or slow the symptomatic effects of the neuropathology. Another line of evidence, much of which has emanated from the so called Nun Study, suggests that, which to some extent stands in contrast to findings from most studies on the reserve concepts, early life linguistic ability, protect against AD pathology. More specifically these studies have found a strong correlation between linguistic ability in early life, as assessed by idea

density (189) and grammatical complexity (190), and absence of neurofibrillary tangles in the hippocampus and neocortex at postmortem (191, 192). Whereas the reserve concepts predicts that protection will take place in the sense that the reserve allows for more pathology to accumulate before symptoms of dementia become apparent, findings related to linguistic ability report a protective effect against AD-pathology per se. Also, more recent studies have found neuronal hypertrophy, volume increase, in nuclei, cell bodies and nucleolus in neurons of regions topographically associated with AD in patients with AD neuropathology exhibiting no cognitive impairment prior to death (193, 194), a condition coined asymptomatic AD. Patients with asymptomatic AD have also been found to have higher idea density in early life but not grammatical complexity as compared to age-matched controls and AD patients (195). Another study has also reported that environmental enrichment, a paradigm to study the influence of surroundings upon brain in non-humans, decrease or slow concentrations of Abeta peptides and amyloid depositions (196). These studies suggest that protection may not only take place at a symptomatic level.

Objectives and implications

With few exceptions, findings related to the reserve concepts in dementia are derived from patients with established dementia diagnoses, mainly AD. One of the exceptions, within the frame of the brain reserve concept, reported that having an ICV in the smallest quartile was a risk factor for MCI (197). The emergence of novel in vivo CSF biomarkers for pathology may allow for studies of the reserve in an earlier phase than most previous studies. Besides enabling insights in how cognitive processes are mediated at an early stage, such studies may also have the potential to aid in the process of diagnostics, and thereby also treatment. An equal amount of pathology may be mediated by reserve which may have the consequence that individuals with higher reserve may not meet diagnostic criteria as it rests on the notion of functional impairment. Studies on the topic of reserve typically rely on rather low cut-offs for education - higher education is, as is the case with most

neuropsychological norms, defined as 10 years of more of education. Thus, knowledge of patients with high or very high reserve is limited.

Specific objectives

- Are CSF biomarkers useful for identification of reserve in a clinical MCI-population?
- Do patients with higher reserve diverge from patients with intermediate and lower reserve in terms of CSF pathology?
- How is the relation between reserve, symptomatology and CSF pathology at various stages of an early neurodegenerative disease?
- Is it possible to develop a reliable and valid proxy for reserve based on premorbid IQ in Swedish?

Methods

Setting, protocol, and recruitment

The participants in the studies I-IV were included in the ongoing Göteborg MCI study (138), initialized in 1999, of which these are sub-studies. Approval from local ethics committee (diary number: L091-99, date: 15-March-1999) also comprise these studies. The Göteborg MCI study is a clinically based longitudinal study with biannual investigations including neurological, psychiatric, cognitive screening, neuropsychological testing, MRI, SPECT (Single Photon Emission Computed Tomography), EEG (electroencephalography), and sampling of blood and CSF. Follow-ups were performed on a 24-month interval (± 2).

Patients were referred to the memory clinic by physician (3/4) or by self-referral (1/4). Controls were primarily recruited from senior citizen organizations and via information meetings on the topic of dementia. A few controls are spouses of subjects in the study. Requirements for controls were that they should be physically and mentally healthy, and not subjectively experience or show signs or

symptoms of cognitive impairment. The controls were thoroughly interviewed by a research nurse about their somatic and mental health by a research nurse prior to inclusion in the study.

The memory clinic in Mölndal which is part of the Sahlgrenska University Hospital, where the patients and controls of the Göteborg MCI study were recruited, is the only clinic with the main purpose to investigate cognitive disturbances and dementia in the Göteborg region (population, 2008: 900 322 (198)).

The Göteborg MCI-study: classification and diagnostic procedures

Staging of impairment

The Göteborg MCI study use the Global Deterioration Scale (GDS) to grade level of cognitive impairment (123). The diagnosis of MCI, previously described in detail (138), was made by means of clinical consensus assessment based on medical history, checklists and instruments for cognitive symptoms. The following instruments and checklists were used: Stepwise comparative status analysis (STEP) (199), Mini Mental State Examination (MMSE) (200), Executive interview (I-FLEX) (201) and Clinical Dementia Rating (CDR) (202). For inclusion, subjective and objective (corroborated by an informant) anamnestic evidence of progressive cognitive impairment for more than 6 months was required. Furthermore, objective cognitive symptoms according to the checklists and instruments were mandatory. No objective signs equaled GDS stage 1, healthy cognitive status, resulting in exclusion from the study at baseline. In general, GDS stage 2, comparable to subjective cognitive impairment (SCI), was operationalized as outcomes in accordance with the following: STEP = 0, I-Flex < 3, MMSE \geq 28, and CDR sum of boxes \leq 0.5. GDS 3 required any outcome to meet the following criteria: STEP = 1, I-flex \leq 3, MMSE \leq 27 - \geq 25, and CDR sum of boxes \leq 1.5 and not more than 1 box = 1. If one of the following criteria were fulfilled: STEP > 1 for items 13-20, MMSE < 25, CDR sum of boxes \geq 2 or more than 1 box = 1, patient was staged as GDS 4 and diagnosed with dementia. Patients with GDS > 4 were not included at baseline. GDS scores > 4

at follow-up generally resulted in modifications to protocol; i.e. an abridged protocol was followed. Patients with major depressive, other severe psychiatric disorders, or acute/severe systemic disorders were excluded.

Diagnosis of dementia

Diagnosis of AD was based on the NINCDS-ADRDA criteria for probable AD (72). The mixed dementia diagnosis was given when the patient fulfilled AD criteria but had signs of significant vascular disease and AD-atypical cognitive symptoms on neuropsychiatric examination. The diagnosis of cortical vascular dementia (VaD) was based on NINCDS-AIREN criteria and subcortical VaD on the Erkinjuntti criteria (106, 203). The diagnoses of primary progressive aphasia (PPA) and Lewy body dementia were based on established criteria (204, 205). The non-ultra descriptum (NUD) diagnosis, unspecified dementia, was given when the patient fulfilled general criteria for dementia but the clinical picture was not in agreement with any established dementia disorder (206).

Classification of vascular burden

The procedure for identification of patients with vascular disease has previously been described in detail (207). In short, vascular burden was identified as follows: (a) symptoms of transient ischemic attack, and/or stroke and moderate white matter changes, and/or lacunae formation, and/or signs of infarction on MRI; or (b) occurrence of two (or more) expressions of (non-cerebral) vascular disease and moderate white matter changes, and/or more than two lacunae and/or signs of infarctions on MRI. Patients with no more than one vascular disease without complications and insignificant (mild) white matter changes or few lacunae, or absence of cerebrovascular influence, were coded as not having vascular burden.

Participants in studies I-IV

Study I was a cross-sectional baseline study of MCI-patients subsequently converting (MCI-con) to dementia (table 1). A group of patients with stable MCI (MCI-sta) was included for reference purposes. Study II was based on an extended sample of converting patients from study I, and included longitudinal analyses. Study III, also longitudinal, comprised an expanded sample of the stable MCI reference group included in study I. The first three studies included in the thesis focused on various stages of the continuum between normal aging and dementia in relation to the reserve concept. These studies used education as a proxy for reserve using diverse definitions. Patients converting from MCI to dementia in study I were grouped on the basis of educational attainment. High reserve was defined as 15 years or more of education in order to ascertain that the potentially unique association between higher reserve and CSF pathology was studied. Cut-off corresponded to lowest achievable level of university diploma in Sweden. Comparatively, the applied cut-off is rather strict, but similar rationales have been applied in other studies (140, 187). Study II followed a similar rationale but also subdivided the group with lower CR into low (6-9 years) and intermediary reserve (11-14 years). Twelve years or more of education, corresponding to sample median, was used as a cut-off for study III.

Study IV was primarily cross-sectional in nature albeit a retest reliability assessment was included. The main theme of study IV was to develop a test for assessment of premorbid IQ. Such a test may be used as an alternative to education as a proxy for reserve. Healthy controls and patients with diagnosis of AD were included in study IV.

Table 1. *Characteristics of participants included in studies I-IV*

Study	N	Male/ Female	Age	MMSE	Educational years	Topic/type of study/ outcome measures
I	148	65/83	64.8 ± 7.5	28.2 ± 1.6	11.7 ± 3.6	reserve/baseline/ biomarkers, cognitive tests
II	66	28/39	66.4 ± 7.1	27.5 ± 1.6	10.7 ± 3.5	reserve/longitudinal/ biomarkers, cognitive tests
III	102	49/53	63.5 ± 7.8	28.7 ± 1.3	12.5 ± 3.6	reserve/longitudinal/ biomarkers, cognitive tests
IV	96	35/61	67 ± 7	26.9 ± 3.9	11.8 ± 3.5	development of proxy for reserve/baseline/IQ scores

MMSE = Mini Mental State Examination

Table 2. *Overview of main group classifications in studies I-IV*

Study	Period of data collection	No. of controls	No. of MCI-sta	No. of MCI-con	No. with AD ¹
I	Oct 1999 – Apr 2008	0	91	57	0
II	Oct 1999 – May 2008	0	0	66	0
III	Jan 2000 – Sept 2009	0	102	0	0
IV	Oct 2003 – Jul 2007	53	0	0	43

MCI-con = converting Mild Cognitive impairment, MCI-sta = stable MCI,
AD = Alzheimer's disease, ¹ Diagnoses of subgroups not described

Neurochemical analyses

Neurochemical data were used as outcome measures in the studies I-III. CSF samples were collected at baseline and 2-year follow-up by lumbar puncture (LP). Both LPs were performed in the morning to exclude an influence on the results by the possible fluctuations in biomarker concentrations during 24 hours. Twenty mL of CSF was collected in a polypropylene tube, immediately transported to the local laboratory for centrifugation at 2,000 × g at +4°C for 10 min.

The supernatant was pipetted off, gently mixed to avoid possible gradient effects, and aliquoted in 2 mL portions in screw-cap polypropylene tubes that were stored at -80°C , without being thawed and refrozen, pending biochemical analyses. All CSF analyses were performed on one occasion. CSF T-tau and A β 42 concentrations were determined using a sandwich enzyme-linked immunosorbent assay (ELISA) constructed to measure total tau (T-tau) (208) or A β 42 (209). As no ELISA constructed to measure phosphorylated tau (P-tau) was available at the when the Göteborg MCI study was initialized, analyses of p-tau are missing for most patients of the studies and therefore not included.

Neuropsychological assessment

According to the American Academy of Neurology (AAN)(5) a neuropsychological assessment should include the following cognitive domains: *speed and attention, learning and episodic memory, visuospatial functions, language and executive functions and intelligence/general cognitive capacity*. Several aspects of function should be assessed within each domain, in order to obtain as complete a picture as possible of the cognitive status of a subject. General cognitive capacity/intelligence should not be considered a cognitive domain per se, but rather a complementary measure against which results of the neuropsychological examination may be compared. Scores on IQ batteries, e.g. the Wechsler's Adult Intelligence scale III (210), will however in patients with cognitive impairment likely be reduced. Thus, intelligence batteries may not provide accurate information on premorbid cognitive level of functioning. If no previous assessment for direct comparison is available other approaches, e.g. assessing cognitive functions that do not easily deteriorate, assessment of premorbid cognitive ability may provide better estimates. When the Göteborg MCI study was initiated no measure of premorbid IQ existed in Swedish. The adaptation and construction of such a measure is the purpose of study IV.

In harmony with recommendations from AAN, the neuropsychological examination in the studies I-III encompassed tests of speed and

attention, learning and memory, visuospatial, language and executive functions (table 3). For studies I-III, three to four tests were selected within each cognitive domain from the Göteborg MCI study neuropsychological battery, as previously described in detail (138). As selection of neuropsychological tests in the Göteborg MCI study battery was subject to slight revision over time, rate of completion for each test varied. The neuropsychological tests used in studies I-III were selected based on rate of completion; most recently added tests were not included.

Table 3. Neuropsychological test battery: Cognitive domain and function.

Cognitive domain	<i>Specific functions</i> and neuropsychological tests
Speed and attention	Digit Symbol (WAIS-R), Trail making A and B
Learning and memory	<i>Verbal episodic memory:</i> Rey Auditory Verbal Learning Test, <i>Non-verbal episodic memory:</i> Rey Complex Figure
Visuospatial functions	<i>Perception:</i> Silhouettes (VOSP), <i>Spatial organisation:</i> Rey Complex Figure copy, <i>Construction:</i> Block Design (WAIS-R)
Language	<i>Comprehension:</i> Token Test, subtest V, <i>Confrontation naming:</i> Boston Naming Test, <i>Abstraction:</i> Similarities (WAIS-R)
Executive functions	<i>Mental control:</i> PaSMO, <i>Distractibility:</i> Stroop Test, Victoria version, <i>Judgement and calculation:</i> Cognitive Estimation Test

WAIS-R = Wechsler's Adult Intelligence Scale – Revised, VOSP = Visual Object and Space Perception Test, PaSMO = Parallell Serial Mental Operations

Description of neuropsychological tests

For studies I-III, three tests were used for assessing speed and attentional functions. Digit Span, a subtest included in the WAIS-R battery (211), measures attention span and working memory. In Digit Span the patient is asked to repeat series of digits forward and backward of increasing length. Also included were versions A and B of the Trailmaking test (TMT) (212). In the A version the patient is presented with a sheet of paper containing numbers 1 through 25 which are to be connected in ascendant order as fast as possible.

Version B of the task also contains numbers but these are to be sequentially connected with letters in ascendant order. Version A provides information about survey ability and speed whereas version B also measures alternating attentional functions.

Two tests measuring several aspects of memory and learning functions were also included in studies I-III. Rey Auditory Verbal Learning Test (RAVLT) provides information about episodic memory, learning capacity and recognition (213). It consists of a list of 15 nouns that are read to the patient five times. After each reading the patient is to repeat as many words from the list as possible. Thereafter a 15 word distraction list is read to the patient. The patient is asked to repeat this list only once. Thereafter the patient is requested to recall the first list without new rehearsals, immediately and after 30 minutes. Finally, the patient is asked to identify the words which were not recalled at the last repetition from a list with the target words which also contains semantically and phonetically similar non-target words. Rey Complex Figure Test (RCFT) recall is a non-verbal immediate and delayed memory test (214). In RCFT the patient is to draw from memory a previously copied complex geometric shape. The patient has not been informed that the figure is later to be drawn from memory.

Whereas the RCFT recall task measures visuospatial memory, the RCFT copy task assesses visuospatial functions. More specifically, the RCFT copy task assesses spatial orientation and construction. Also included among the selected visuospatial tests was the Silhouettes subtest from the Visual Object and Space Perception battery (VOSP) (215), which has been developed for the purpose of measuring spatial perception; the ability to separate a figure from its background. Thirty silhouettes depicting animals and everyday objects are to be identified correctly. Also included was Block Design from WAIS-R (211), a measure of spatial construction, consisting of nine blocks with three different patterns. The patient is asked to use these blocks in order to reconstruct and convert two-dimensional patterns presented in an increasing order of difficulty to tridimensional equivalents.

Token Test part V is constituted of 22 spoken instructions that the subject is to act upon using objects of different shapes and colours (216). It is thus a test of language comprehension. Another language test, Boston Naming Test (BNT) consists of 60 drawings of objects presented in ascending order of difficulty (217). BNT assesses naming ability. Also included was the subtest Similarities from WAIS-R which is used for assessment of concept formation and abstract reasoning (211).

The Victoria version of the Stroop Colour Word Test was one of the included tests of executive functions (presented in 218). More specifically, Stroop measures inhibition of automated responses. The patient is instructed to name the colour of words describing colours with ink deviating from the described colour. Another included test was the Cognitive Estimation Test which consists of ten questions requiring the patient to make reasonable estimates (presented in 218). Finally, Parallel Serial Mental Operations is a measure of mental control and tracking (138). The test is similar to TMT part B, but the subject is asked to perform the sequential tracking of letters and numbers mentally.

As study IV was on the subject of development and adaptation of a test for assessment of premorbid IQ, other tests were selected for the purpose of validation. Controls were presented with a short form of WAIS-III (219), the General Ability Index (GAI) (220) which is composed of the unweighted sum of the Verbal IQ (VIQ) (subtests: Vocabulary, Similarities and Information) and Performance IQ (PIQ) (subtests: Matrix Reasoning, Block Design and Picture Completion). These subtests are generally thought of as good measures of crystallized and fluid ability, and demonstrate high loadings on the g-factor, or general mental ability. As WAIS has floor effects for AD patients (221, 222) MMSE was used as a measure of current level of intellectual functioning for all subjects. Both patients and controls were also presented with the test constructed to assess premorbid IQ, the Swedish adaptation of National Adult Reading Test (NART), NART-SWE. In short, NART-SWE is a word reading test and it is based upon the premises that (1) reading correlates highly with IQ; (2) reading is more relatively insensitive to neurological damage; (3)

reading of irregular words is more resistant to cognitive decline than is reading of regular words and (4) reading relies on previous rather than present knowledge (223). NART consists of a list of 50 irregular words that are to be pronounced. Incorrect pronunciation indicates that the word is not present in the subjects' vocabulary. National Adult Reading Test (NART) (224-226) is likely the most thoroughly validated test for assessment of premorbid capacity (221).

Statistical analysis

For all studies, binominal data, distribution of diagnoses and sex, was investigated using chi-square alternatively Fisher's exact test when appropriate. In studies I-III, all baseline data comparisons between groups were performed using analysis of covariance, ANCOVA with age as covariate where applicable. Alternatively, analysis of variance (ANOVA) was utilized. Principal Component Analyses (PCA) were also performed in order to assess overall performance on the neuropsychological battery. PCA derived weighted averages were then analyzed using ANCOVA. For Studies I-III eta-squares (η^2) alternatively partial η^2 are reported as an index of effect size in the statistical tests. Eta-squares may vary between 0 and 1. When $\eta^2 > .15$ effects are 'large' in magnitude, and when $\eta^2 > .06$ effects are 'medium'. Partial eta-squares are to be interpreted in a similar fashion, except large in magnitude equals $\eta^2 > .14$. In study II, post-hoc comparisons were performed using the Sidak's test. Paired t-tests were utilized for longitudinal comparisons within groups in this study. In studies II-III, longitudinal comparisons were performed using mixed between-within subject analysis of variance (repeated measures ANCOVA).

In study IV, inter-rater reliability was estimated using the Analysis of variance (ANOVA) based intra class coefficients (ICC) (Fleiss & Shrout, 1978; Fleiss & Shrout, 1979; McGraw & Wong, 1996). Internal consistency was calculated using Cronbach's alpha. Decision on final composition of the wordlist was based on a stepwise analysis of errors made per word, and alpha if deleted. Correlations were calculated with Pearson's correlation coefficient. ANOVA was used for group comparisons. Finally, stepwise linear regression was performed

in order to investigate which variables, including NART-SWE, predicted IQ.

All statistics were performed using Statistical Package for Social Sciences (SPSS) versions 15-18.

Table 4. Comparisons and main statistical methods used in studies I-IV.

Study	Group comparisons	Main statistical methods
I	MCI-sta – MCI-Con, MCI-Con: ≥15 yrs – <15 yrs of education	ANCOVA, ANOVA
II	≤9 yrs – 11–14 yrs – ≥ 15 yrs of education	Repeated measures ANCOVA,
III	≥12 – ≤ 11yrs of education	Repeated measures ANCOVA
IV	Controls – AD, Controls, retest	ICC, Cronbach’s alpha, ANOVA, linear regression

ANCOVA = analysis of covariance, ANOVA = analysis of variance, ICC = Intra class Coefficients

Results

Study I

The main objective of this study was to investigate the possibility of using the CSF biomarkers t-tau and abeta42 as indicators of pathology in relation to cognitive reserve. The hypothesis was that patients subsequently converting to dementia (MCI-con, N = 57, M 22 / F 35, Age M = 66.8 ± 7.1) would have lower education than those with stable MCI (MCI-sta, N = 91, M 43 / F 48, Age M = 63.7 ± 7.6), and that converting patients with higher education would have lower concentrations of abeta42 and higher concentrations of t-tau than patients with lower education.

The main findings were that significantly fewer of the MCI-con had higher education using a 15-year cut-off as compared to those with MCI-sta ($p = .02$). Concentrations of Abeta42 were significantly lower in the MCI-con group with higher education (N = 9, M 6 / F 3, Age M

= 68.4 ± 6.8) as compared to those with lower education (N = 48, M 16 / F 32, Age M = 66.5 ± 7.2) ($p = .01$, $\eta^2 = .11$), suggesting that accumulation of plaques was more pronounced in those with more reserve despite the groups being comparable in terms of level of severity of impairment, age, and neuropsychological performance.

Study II

Study II sought to investigate if neurochemical biomarkers would reflect reserve over a two year course of neurodegenerative disease. Another topic for this study was to explore if patients with intermediate reserve (N = 23, M 8 / F 15, Age M = 63.5 ± 7.9) were separable from those with lower (N = 28, M 8 / F 20, Age M = 68.4 ± 6.1) and higher reserve (N = 15, M 11 / F 4, Age M = 66.3 ± 6.3) in terms of neurochemical pathology.

The most noteworthy findings from study II were that patients converting to dementia with higher education had lower Abeta42 concentrations at both time points, as compared to converters at the same level of severity of impairment with intermediary and lower education (figure 1). Also, Abeta42 concentrations declined significantly within the intermediary and higher education groups. There was also a general significant negative association between education and A β 42 concentrations. Despite indications of more amyloid pathology in the group with higher reserve, performance on neuropsychological tests was on a par with those with lower and intermediate reserve, which could be interpreted as compensation for pathology.

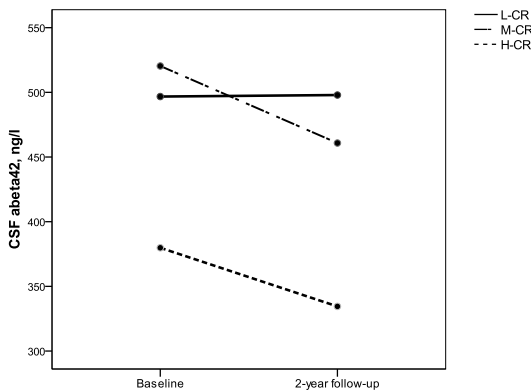


Figure 1. Figure displays CSF Abeta42 concentrations (nanograms/liter) over a two year period for patients converting to dementia at 2-year follow-up in relation to three levels of cognitive reserve (lower reserve = L-CR, medium reserve = M-CR and higher reserve = H-CR). Covariate in the model, age, evaluated at the age of 66.2.

Study III

As most studies on the topic of the reserve concept target patients with established dementia, one of the aims with the dissertation was to investigate the influence of reserve on pathology in the early phases of neurodegenerative disease. In studies I and II more pronounced amyloid pathology was found in preclinical dementia patients with higher reserve. The potential influence of reserve on degree of neurochemical pathology in patients remaining cognitively stable is however not known. Thus, we sought to explore the influence of reserve on pathology in patients who do not convert to dementia during a two-year timeframe. Is there a similar tendency, more pathology in those with more reserve as defined by sample median of 12 years, or is a protective effect to be expected?

Stable MCI-patients with higher reserve (N = 62, M 34 / F 28, Age M = 62.7 ± 8) had lower concentrations of t-tau after adjusting for age, vascular burden, specific apolipoprotein genotype, and standardized neuropsychological performance over a two-year period, as compared to patients with lower reserve (N = 40, M 15/ F 25, Age M = 64.9 ± 7.4), $p = .003$. Results are depicted in figure 2.

Patients were assessed as equivalent with respect to level of severity of impairment (GDS 3 and GDS 0.5), and distribution of neuropsychological impairment. Also, the groups displayed similar CSF Abeta42 concentrations implying similar degree of brain amyloid pathology (227). Furthermore, educational level predicted a significant proportion of the total variance in t-tau concentrations. T-tau did not separate the highly educated from those with lower education in studies I-II. Also, patients with primary neurodegenerative etiology displayed significantly higher concentrations of T-tau in the previous studies, which suggested that t-tau was not a valid general pathology marker in relation to the reserve concept. However, this finding was not replicated in study III, which suggests that the response to pathology may diverge depending on neurodegenerative stage. T-tau may thus be a better preclinical marker than abeta42, which may be a more sensitive marker in a later phase.

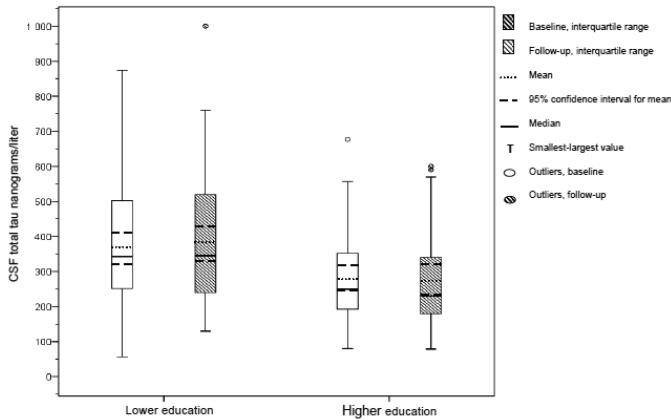


Figure 2. Boxplot of CSF total tau concentrations for patients with stable MCI grouped on the basis of educational attainment. *Sex, age, APOE E genotype, standardized average cognitive performance, and vascular burden included as covariates.*

One possible interpretation is that education is protective rather than a mediator between pathology and clinical expression prior to manifest disease. This interpretation may be in harmony with findings from the Nun study, which reported strong correlations between high linguistic ability in early life and absence of neurofibrillary tangles in the hippocampus and neocortex at postmortem (191, 192). Another study found small head circumference to be associated with lower educational attainment in individuals with risk for AD (228). Also, higher brain volume has been related to higher IQ (229), and IQ is associated with educational level (230). These findings point to the possibility that lower educational level may indicate early vulnerability, or indicates an early pathological manifestation of underlying disease. Another possible interpretation is that lower t-tau is associated with a more favorable response to incipient amyloid pathology. Such an interpretation is substantiated by evidence indicating that enriched environments stimulate neurogenesis (231), and reduce AD pathology (196). Consequently, higher education may promote cognitive stimulation resulting in better axonal integrity.

Study IV

Education may reflect opportunity rather than cognitive capability (140). Also, it has been reported that patient reported information regarding educational attainment may be inaccurate (171, 172). As several studies suggest that premorbid IQ may be a better indication of previous level of cognitive functioning (139, 168, 169), thus development of a test of premorbid IQ in Swedish may enable more refined analyses of reserve capacity. Also, accurate methods for assessment of premorbid IQ allow for more precise evaluations of extent of cognitive impairment.

National Adult Reading Test (NART) (232-235) is considered the most thoroughly validated test for assessment of premorbid IQ (236). NART consists of a list of 50 irregular words that are to be pronounced. Correct pronunciation of a word indicates that the word has been in the patient's vocabulary even though she may no longer know its meaning. It was initially developed for a British-English population, but has also been adapted into various languages such as American-English (237, 238), Dutch (239), Danish (240), and Norwegian (241). Adaptation of a version of NART to a language based on regular pronunciation rules, has been stated to be difficult (242). Even so, a Norwegian version, which is a language based on irregular words, of NART has previously been established (241). The purpose of study IV was to construct a Swedish version of the National Adult Reading Test (NART-SWE), and to investigate its validity and reliability on healthy controls (N = 53, M 18 / F 35, Age M = 66.1 ± 7.7) and patients with mild Alzheimer's disease (N = 43, M 17 / F 26, Age M = 68.2 ± 7).

As Swedish pronunciation rules also are fixed, NART-SWE was generated using loan words – foreign words established in the target language. Seventy-nine words were generated and reduced to 50 words by means of assessing inter-rater reliability for each individual word - intra class coefficient value (ICC), and internal consistency - Cronbach's alpha (α). NART-SWE has satisfactory psychometric properties: Inter-rater (ICC = .94) and retest reliability ($r = .92$) as well as internal consistency was very high ($\alpha = .93$). Controls' scores

on NART-SWE correlated highly with a measure of IQ – an abbreviated version of Wechsler’s Adult Intelligence Scale III (WAIS-III), the General Ability Index (GAI). Also, NART-SWE predicted a significant proportion of controls’ IQ score. As NART-SWE is supposed to measure vocabulary indirectly by means of pronunciation, correlation with a measure of current vocabulary for the controls would indicate criterion validity. NART-SWE correlated highly with the WAIS-III vocabulary subtest ($r = .78$). Educational years did not contribute to the model. Patients ($M = 36.8 \pm 7.4$) and controls ($M = 38.2 \pm 6.6$) performed similarly on NART-SWE, $p = .32$. It may thus be concluded that NART-SWE is a valid and reliable instrument for assessment of premorbid IQ.

Discussion

The main objective of the thesis was to investigate if CSF biomarkers could enable new insights into how reserve, as defined by educational level, mediates the influence of pathology on clinical manifestations in early phases of neurodegenerative disease. A specific aim was to explore if patients with higher reserve diverge from patients with intermediate and low reserve in terms of CSF pathology and cognitive functioning. The final objective was to construct a test in Swedish for assessment of premorbid IQ, which may be a better proxy for reserve than education, and to investigate its validity and reliability.

Patients with higher reserve were distinguishable from those with intermediate and lower reserve with regards to CSF abeta pathology, but not in terms of specific cognitive performance and global cognitive impairment. The incongruence between pathology and clinical outcome indicates compensation. We also found that abeta42 may be sensitive to disease progress when level of reserve is taken into account. Patients with higher reserve with stable MCI had lower concentrations of CSF t-tau, but comparable abeta42 concentrations. This finding may either indicate a true protective effect for education, or suggest that higher education promotes cognitive stimulation resulting in better axonal integrity. Also, a test for assessment of

premorbid IQ, NART-SWE, was successfully constructed. The test was found to have satisfactory psychometric properties.

Generalizability of findings

The generalizability of the studies included in the dissertation may be limited. In our studies, sample sizes were limited, and patients were recruited from a clinical sample. Patients were, however, recruited from the only memory clinic in a larger catchment area. Still there may be a selection bias relating to mechanisms for referral and study inclusion. According to internally unpublished data only about 17 % of all patients passing through the memory unit matching inclusion criteria for age were subsequently included in the Göteborg MCI-study. Analyses are in progress to examine whether the patients included differ from those who were not. As for the referral procedure about 1/3 of the patients included in the Göteborg MCI-study were so called self-referrals. There may be a risk that the self-referrers diverge from the normal population with respect to intellectual capacity. In order to address a self-referral the patient has to seek and locate information that may not be easily found. Another requirement is that a form has to be filled in and submitted correctly. Whether or not the patients differ on the basis of referring procedure has yet to be analyzed.

Another aspect that may limit the generalizability of the findings is the relatively young age of the included MCI patients. The mean age of other studies including patients with MCI is typically higher (243-246). Also, the mean age for patients converting to dementia was lower than for comparable studies (126, 247), which points to the possibility that patients have either been enrolled in an earlier phase, or that the Göteborg MCI-study targets younger patients at risk for dementia than other studies. Nonetheless, given that age is the most powerful predictor of dementia, there is a risk that the relatively low mean age suggests inclusion of benign cases of MCI.

Diagnostic considerations

Most studies on the topic of the reserve concept have been conducted on samples of patients with established diagnoses (166). In study I we used the general diagnosis of dementia which did not allow for more refined analyses of how different etiologies may have affected the outcome. As diagnoses at follow-up were not available for all patients, we performed a sub-analysis excluding patients exhibiting no CSF pathology, applying cut-offs previously presented from the Göteborg MCI-study (248). Whereas this analysis reduced the likelihood that differences in biomarkers concentrations were related to an uneven distribution of etiologies, it did not ascertain it. In our follow-up study, including a slightly expanded sample of patients and specific diagnoses, we did not find any significant difference regarding distribution of diagnoses.

Furthermore, the definition of stable MCI in studies I and III is not straightforward. There is clearly a risk that patients with stable MCI develop dementia later on as the time interval of two years may be too short to detect changes. Thus, stable only refers to stable over a two-year interval and not non-progressive MCI. The reason for selecting such a short time-frame was simply to compare those who progressed to dementia to those who did not in terms of characteristics and influence of reserve in diverse phases of neurodegenerative disease. The short time span was also determined by availability of data - few patients with a GDS 3 score had undergone the 4-year follow-up at the time of analysis.

Most MCI-studies use results on neuropsychological tests, commonly 1.5 standard deviations below mean, to classify MCI (122). In the Göteborg MCI-study, patients with MCI exhibit subjective signs and symptoms of cognitive impairment (GDS 2) which may be corroborated by checklists and basal cognitive measures (GDS 3). Such a procedure is in harmony with proposed classification procedures for MCI (249). The main rationale for not using neuropsychological tests as classification instruments is to enable use of tests as outcome measures. In studies I-III only patients with GDS 3, requiring objective signs of impairment, were included.

Classification of level of severity of impairment in the Göteborg MCI-study is rigorous and based on a relatively fixed algorithm to classify on the basis of scores on different instruments and checklist. Furthermore, compliance to criteria for each patient is verified on the basis of clinical consensus assessment. However, there is a risk that the GDS rating in some cases may be founded on relatively small and insignificant changes; e.g. decline by 1 point on MMSE may lead to a change in rating from GDS 2 to 3. The importance of such small changes has yet to be analyzed. Recently, two-year outcome of patients with MCI, defined as GDS 2 or 3, in the Göteborg MCI-study was analyzed, and it was reported that 25 % of those who had been followed-up had converted to dementia (250). When patients with GDS 2 were excluded from the analysis, conversion to dementia over a two-year period was about 38 % (251). Although the procedure to classify MCI in the Göteborg MCI-study have resulted in comparatively high conversion rates (122, 125), the significance of small changes in scores and the resulting change in level of impairment of severity scores has yet to be determined.

On proxies for reserve and groupings

To ascertain that only patients with high cognitive reserve were compared, a rather strict cut-off of 15 years of education was used to divide patients with higher reserve from those with intermediary or lower reserve. Using 15 years as cut-off differentiated between patients with higher and lower CR, whereas 10 years did not. The arbitrariness of education as a proxy for reserve may have resulted in insufficient power to discriminate between patients with intermediary and lower CR in studies I-II. Nonetheless, we found that Abeta42 correlated negatively with education in study II, which suggests an overall influence of reserve on the pathological expression.

It has been argued that the relative strength of education as a proxy for reserve is its ability to account for life-time experiences (166). There is, however, some indications that education primarily is a product of socio-economic background, and thus rather mirror

opportunity than ability (139). Also, several studies have found reading ability and premorbid IQ to be more capable measures of reserve than educational attainment (139, 168, 169).

Notwithstanding, educational and occupational attainment, and leisure activities have been found to contribute independently and synergistically to reserve capacity (144) Also, IQ has been found to change over time (252), and NART-predicted IQ at middle age to be influenced by childhood cognition, education, and parental occupation (253).

The main argument for choosing education over premorbid IQ in studies I-III was that the Göteborg MCI study was initialized at a time when no measures of premorbid IQ existed in Swedish. As a result of the construction of NART-SWE data collection of premorbid IQ has been initialized, but preliminary analyses do not indicate that NART-SWE is a more powerful measure than education. This could either be due to the limited sample size that the analysis was conducted on, alternatively educational level is a better surrogate for reserve. Data on occupational attainment have been collected but not analyzed. Another drawback concerning substitutes for reserve is that information regarding leisure activities has not been collected systematically.

Which concept – CR or BR?

The BR concept focuses on anatomical differences as the source of resilience. The studies included in the dissertation include no direct measures relating to brain size. Although outcome measures may be theoretically linked to anatomical differences, e.g. t -tau to axonal integrity, the proxies used or developed for the included studies, education and premorbid IQ, are rather related to the concept of CR. As opposed to BR the focal point of CR is rather how the brain uses its networks to overcome the effects of neuropathological damage. Studies conducted within this framework may often provide insights into how compensation for pathology is reflected in the brain at a network level; e.g. investigate how reserve mediates brain activation by using functional imaging techniques (254). The studies included in

the dissertation do not provide insights into how compensation manifests in the brain, and may thus not be considered to directly test the underpinnings of the CR framework. Assumptions of both concepts contribute to explain the variability in response to brain pathology (165), and rather than testing specific features of the concepts, study III explored the use of a novel marker for neuropathology in relation to reserve.

Applicability of CSF biomarkers

The biomarkers used as surrogates for pathology in studies I-III are commonly associated with Alzheimer's disease (AD). However, t-tau and Abeta42 are often reported to have lower specificity than desirable; biomarkers do not quite separate AD from other dementia forms such as frontotemporal, vascular, and Lewy body dementia (84). Abeta42 has also been found to be reduced in patients prior to onset of vascular dementia (255). Also, some evidence suggest that there may be converging pathogenic mechanisms between cerebrovascular and Abeta plaque pathology (256), and neurovascular dysfunction has been found to reduce beta-peptide clearance (257). One study questioned whether Abeta42 is a true marker of plaque pathology as no relation between concentrations of Abeta42 and plaques were found at post-mortem (258). However, reduced CSF levels of Abeta42 in AD have been found in numerous studies (259). The phenomenon mirrors, at least to a certain extent, the deposition of Abeta42 in senile plaques, with lower concentrations diffusing to CSF. Accordingly, studies have found a strong correlation between low Abeta42 in CSF and high numbers of plaques in the neocortex and hippocampus (260), and high retention of Pittsburgh B in PET scans that directly reflect plaque pathology in the living brain (227).

Some other general limitations to use of CSF biomarkers apply. The results obtained are likely not directly comparable to others as inter-center variations have previously been reported to be considerable (82). Another potentially problematic aspect regarding use of CSF biomarkers as surrogates for pathology is that they typically have a skewed and non-normalized distribution. Even so, we applied

parametric statistics in studies I-III. This decision was not only guided by the fact that parametric statistics are more powerful than the non-parametric counterparts (261), but also that longitudinal group comparisons, as performed in studies II-III were not possible using non-parametric statistics. A prerequisite for analysis of variance based methods is that the samples to be compared should have equal variances; homogeneity of variance. Levene's test was used to assess homogeneity of variances (262), and we found that the samples were suitable for comparisons. Also, for comparisons not involving mixed between-within subject analysis, we corroborated the findings using the relevant non-parametric alternatives, i.e. Mann-Whitney U test or Kruskal-Wallis test, but the results remained essentially unaltered (data not shown). Analyses were also re-performed using transformed (log and square root transformation) variables for skewed data, but neither this did alter the results (data not shown).

CSF biomarker pathology

In studies I-II, we found that patients converting to dementia with higher reserve had lower concentrations of abeta42 as compared to patients at equal level of severity of impairment with lower reserve. This indicates that patients with higher reserve have more neuropathology, specifically amyloid pathology, which is the expected outcome according to the reserve hypothesis. The biomarkers used to examine differences in levels of pathology are primarily associated with AD-pathology. To reduce the probability that findings were related to differences among groups regarding distribution of diagnoses or divergent etiologies, we conducted sub-analyses including only patients with either primary etiology or pathological CSF values. For studies I-II, we found that abeta42 was applicable as a general pathology marker, but not t-tau.

In study III, including non-converting MCI-patients, the opposite pattern was found: patients with higher reserve exhibited lower concentrations of t-tau as compared to patients with lower reserve. This result may indicate that patients with higher reserve have less

axonal degeneration, tauopathy, alternatively higher axonal integrity. T-tau did not distinguish patients with higher reserve from those with lower in our previous studies on the topic, and we also found that t-tau was not a suitable marker for general pathology in converting patients. In this study, exclusion of patients with vascular burden did not alter the findings albeit resulting in higher effect sizes – more pronounced differences. A plausible explanation for the incongruence with respect to type of pathology may be that this study targeted a potentially earlier phase of dementia than did the previous studies. This points to the possibility that t-tau is a better preclinical marker than Abeta42 which may be a more sensitive marker in a latter disease phase.

The finding that patients with higher education displayed less tauopathy is not quite in harmony with the reserve concept, which predicts that pathology should be more pronounced in those with higher reserve as compared to those with lower reserve at the same level of clinical severity. However, most evidence originate from studies on patients with established diagnoses – mainly AD – and this study targeted patients in a potentially earlier disease phase. One possible interpretation is that education is protective rather than a mediator between pathology and clinical expression prior to manifest disease. This interpretation may be in harmony with findings from the Nun study which found strong correlations between high linguistic ability in early life and absence of neurofibrillary tangles in the hippocampus and neocortex at postmortem (191, 192). Also, one study reported small head circumference to be associated with lower educational attainment in individuals with risk for AD in later life (228). As higher brain volume has been related to higher IQ (229), and IQ is also associated with educational level (230) there is a possibility that lower educational level indicates early vulnerability, alternatively reflects an early pathological manifestation of underlying disease.

An alternative interpretation is that lower t-tau indicates axonal integrity, and thus reflects a more favorable response to incipient amyloid pathology. This interpretation may be substantiated by evidence pointing to the possibility that enriched environments

stimulate neurogenesis (231), and also reduce AD pathology (196). Higher education may thus promote cognitive stimulation resulting in better axonal integrity. Thus, axonal integrity may offer protection in the earlier stages allowing for accumulation of more amyloid pathology at a later stage.

Abeta42 - a potential stage marker?

It has been proposed that diagnostic markers can be divided into three clusters: disease state, stage and rate markers. A disease state marker distinguishes the disease of interest from other types of related disorders over the entire disease course. A stage marker provides an indication of how far the disease has proceeded, and a rate marker mirrors the rate of the disease (263). Abeta42 has generally been considered a disease state marker rather than a stage marker (264). A few studies have found Abeta42 to be stable, at least from 2-years prior to conversion to dementia, and thus a suitable surrogate marker for drug efficacy (209, 265). Also, amyloid depositions, as assessed by PIB-PET, have been found to remain relatively constant in patients with AD (266). It has, however, been largely unknown if stability remains when taking cognitive level into account. In study II, we did not find any significant effect for time between groups for either Abeta42 or t-tau. When within-group changes were investigated we found that concentrations declined within the groups of those with intermediary and higher reserve. As may be expected, no significant changes in CSF biomarker concentrations were found for patients with stable MCI. Thus, there is a possibility that Abeta42 may be more sensitive to changes in its level of severity of impairment than previously reported (265, 267).

Compensation and cognitive decline

Some studies have previously investigated the linkage between CSF biomarker concentrations and neuropsychological test results. In general, these studies have found associations between deviating CSF biomarker profiles and general cognitive performance, and between t-

tau and episodic memory (248, 264, 268, 269). No studies have investigated how reserve mediates neuropsychological performance in the presence of CSF pathology.

In studies I-II we found no group differences on a comprehensive battery of tests despite indications of more amyloid pathology in those with higher reserve. Accordingly, it may be speculated that patients with higher reserve compensate for pathology, as the expected outcome would rather be worse performance. On the other hand, absence of differences could be considered to be associated with higher premorbid performance in those with higher reserve. Consequentially, deterioration may have undergone for a longer period of time for those with higher reserve, given that cognitive performance was comparable to those with lower reserve. Thus, this could reflect a masking effect obscuring the actual level of severity of impairment score, as assessed by GDS, CDR and diagnosis. However, as amyloid burden has been associated with accelerated cognitive decline (270, 271), patients with higher reserve would have been expected to display faster cognitive decline than those with lower reserve, given that they had indications of higher amyloid burden. We find that an equal rate of decline for both reserve levels speak in favor of the notion of compensation for pathology. Furthermore, as the diagnostic procedures of the Göteborg MCI-study are rigorous, the patients' previous levels of functioning have been taken into account. Most likely confounders have also been either controlled or adjusted for. The findings were hence not likely due to ascertainment bias; i.e. obtained by non-random sampling and attributed to the phenomenon studied instead of biased sampling method.

In study III, on the topic of reserve in stable MCI, patients with higher reserve outperformed those with lower on a general performance measure and on a test-by-test basis. With respect to the distribution of impairment, as assessed by performance 1.5 standard deviations below age mean, the results were however comparable. Better general performance in patients with higher reserve despite equal distribution of cognitive impairment may be seen as compensatory. Then again, previous performance may have been well above present. As main results, lower t-tau in those with higher

reserve, were not quite in agreement with the reserve hypothesis, compensatory mechanisms may not be expected. However, lower t -tau may be interpreted as a compensatory mechanism to incipient amyloid pathology. This interpretation is not quite in harmony with the reserve concept predicting compensation at a symptomatic rather than a neuropathological level.

According to the concept of CR, patients with higher reserve should display faster cognitive deterioration when the compensatory capacity is insufficient to sustain a neuropathology that has become too extensive. We did, however, not find evidence to support this notion. Our results are rather consistent with a recent study in which educational level was found to be associated with cognitive performance but not with rate of decline (184). On the other hand, patients included varied from a potentially early preclinical dementia phase to mild dementia, neuropathology was hence not likely to be too extensive, which would cause an inability to provide compensatory support.

Implications

Premorbid performance in patients with higher reserve may be 1-2 standard deviations above mean on cognitive tests (272). Consequentially, cognitive functions may have to decline as much as 3-4 standard deviations in order to become diagnostically apparent. There is not only a potential of false negatives, patients with high premorbid IQ performing above cut-off criteria, but also of false positives, detection of impairment in patients with lower premorbid IQ who do not have impairment, only low initial capacity. Adjustment for premorbid level of intellectual functioning is therefore of paramount importance in order to identify cognitive decline in elderly in an early phase. This is further strengthened by the presumption that treatment only will have optimal effect if initiated early. The results of the studies included in the dissertation may enable earlier identification and consequentially earlier treatment of patients with higher reserve at risk of dementia.

In order to consider a previous level of functioning assessments should incorporate tests of premorbid IQ, e.g. NART or equivalents, alternatively, implement IQ-based norms adjusting for predicted cognitive level (140). Current established diagnostic criteria rely on impairment of activities of daily living and not decline from initial premorbid levels as a threshold. That has the unfortunate consequence that patients with higher CR will have to deteriorate for a long period before receiving a diagnosis and treatment. An effort to bridge the gap between the shortcomings of established criteria for AD and current knowledge has been done by proposing, a revision (83) of the NINCDS-ADRDA criteria (72). The proposed revision specifically addresses the need for earlier intervention by applying technological advances, e.g. reliable biomarkers, in diagnostics, but do not stress the need to take into account decline from a previous cognitive level of functioning.

Conclusions

Patients with higher reserve were distinguishable from those with intermediate and lower reserve with regards to abeta42 pathology, but not clinical manifestations. The incongruence between pathology and clinical outcome indicates compensation for neuropathology. Our results speak in favor of the notion that neurochemical biomarkers may be valid surrogates for pathology in relation to the concept of reserve in various phases of dementia. We also found that Abeta42 may be a potential stage marker when reserve is taken into account. T-tau does not appear to be a valid surrogate for pathology prior to conversion and at time of diagnosis. However, lower t-tau but comparable abeta42 concentrations in stable MCI-patients with higher reserve may indicate a true protective effect for education, alternatively education promotes cognitive stimulation resulting in better axonal integrity. Also, the constructed test for assessment of premorbid IQ, NART-SWE, has the potential to enhance diagnostic procedures and act as an alternative proxy to education. As patients with higher reserve may compensate for neuropathology, symptomatology may be masked. Thus, special attention should be paid to highly performing patients with cognitive complaints, in order

to maximize treatment potential and efficacy. The results of these studies may contribute to earlier identification, and consequentially treatment of patients with higher reserve at risk for dementia.

Future directions

Patient and control data on NART-SWE are currently being collected, and it will later on be possible to examine if premorbid IQ is a more powerful measure of reserve than education in an expanded sample. We also plan to study the MCI concept in relation to premorbid IQ. As pointed out, there is a clear risk of misidentifying individuals when a previous level of functioning is not taken into account. Studies using neuropsychological performance adjusted for premorbid IQ may give more precise information as to if there actually is an impairment, and if so to which extent.

In future studies we also plan to investigate potential interactions between cognitive systems and neurochemical pathology. In the cognitive aging literature there are several hypotheses regarding which cognitive system, i.e. speed/attention, mediates successful aging the most, and modeling of interaction effects for cognitive systems on pathology may enable further insights into how pathology is coped with. Is there any cognitive system that reduces the effect of pathology? Are there cognitive components that facilitate aging? Target groups for such studies are healthy older controls, but also patients at various disease stages.

We will also use structural anatomical measures in conjunction with proxies of cognitive reserve. This will allow for studies illuminating various theoretical aspects of the two concepts of reserve. Also, it may be possible to study to which extent anatomical measures and measures of reserve are complementary and synergistic.

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