Development of nursing programme to assist medical treatment in early onset Alzheimer's disease

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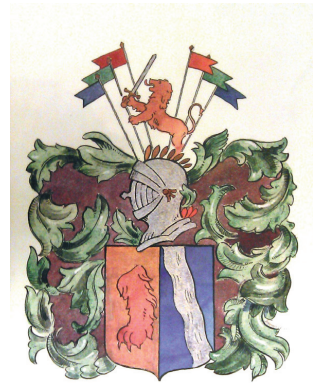
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ABSTRACT

Alzheimer´s disease (AD) is accompanied by neural degeneration with loss off dendrites and synapses. The ganglioside GM1 has been shown, but not in AD, to have positive influence on the nerve cells and stimulate growth of dendrites and synapse formation. Mental stimulation has also been shown to have similar and therapeutic positive effects. Theoretically those two treatments could together give an answer of it is possible to reverse impairments in AD.

In two studies GM 1 was given intrathecally, to pass the blood brain barrier, in combination with a training treatment. In the first one year study five patients with AD were activated by daily activities carried out at home by the spouses. They were supported with the activation but this diminished with time. The study indicated that the patients increased their willing to and of active performances. The effect of GM1 was very dos dependent and showed increased levels of transmitters. A mix of some improvement and decreased values was shown in the neuropsychological assessments. The study was summarised in Paper I.

In the next one year study the GM1 treatment was combined with a newly developed programme with Simulation, Activation and Training carried out by professional in a homelike setting (paper II). The patients were highly engaged in the SATprogramme. The evaluations of neuropsychological examinations indicate individual more preserved and slight improvement than decreased values. The increased levels of transmitters may suggest GM1 exerting a neurotrophic effect.

Paper III described the SATprogramme, the systematic training, the various form of direct and indirect stimulation, and of practical performance of cognitive, social and physical activities of daily life. The results demonstrated after one year the patients had shown ability to an active participating, specified in the complex activity performance, ability to use of remaining abilities in compensatory strategy, and competence to learn and use a new tool, a personal computer system. The examinations showed scores of preserved and improvement ability.

Paper IV evaluates monthly reaction from the spouses of the patients, which provided information of the daily life at home as related to AD. These notes were voluntary comments given during one year. Four themes emerged of which the partner's social and activity level was evident. The results suggested educational interventions to be tailored to spouses with use of different caregiving perspective due to the visually complex symptoms and of recognizing healthy emotions which may prevent problems of incidents.

Paper V assessed linguistic development during the one year treatment in the SAT programme. The language sessions was interlaced in the cognitive and social training in which a computer further stimulated the patients to use their preserved language ability. The assessment showed that a group pattern occurred of language comprehension, the cornerstone of everyday life. The scores were maximum on reading comprehension and reading aloud during the whole assessment in spite of their dyscalculia or poor arithmetic ability.

These studies suggest that in order to improve cognitive functions in pharmacological interventions to further enhance the treatment effect, by offering a rich homelike setting, and practical activities of normal daily life, adapted to individual capacity. The studies imply the importance of adequate intervention of use of various ways to stimulation of remaining abilities to practical performance in active participating of daily life. The studies stress the need in order to reach optimal treatment, to use a combination of a pharmacological agent and the influence of adopted environmental stimulation. This is probably necessary to influence the neural degeneration of patients with early onset mild to moderate AD.

SVENSK SAMMANFATTNING

Vid Alzheimers sjukdom (AD) sker en tilltagande nedsättning av kognitiva funktioner vilket orsakas av degenerativa förändringar i hjärnan med förlust av nervcellsutskott (dendriter) och kontaktpunkter (synapser). Gangliosid GM1har vid behandling av hjärnskador visats stimulera utväxt av dendriter och bildning av nya synapser. Mental stimulering har också visat sig att ha liknande positiva effekter. Teoretiskt skulle dessa två behandlingar tillsammans ge ett svar om det är möjligt förbättra funktion vid AD.

I två studier har gangliosid GM1 givits direkt in i hjärnans hålrum, detta för att passera blod- hjärn-barriären. Behandlingen har kombinerats med en mental stimulering. I den första ettåriga studien var fem patienter med AD aktiverade med dagliga uppgifter i bostaden av sin make/maka. Det visade sig att aktiveringen minskade gradvis under behandlingsåret. Studien indikerade att patienterna ökade sin villighet till aktivitet och också att utförande uppgifter. Analyser av ryggvätska tydde på ökade nivåer av transmittorsubstanser. De neuropsykologiska mätningarna visade inga säkra tendenser. Studien är sammanfattad i Arbete I.

I den följande studien, Arbete II, kombinerades GM1 behandlingen med ett nyutvecklat program med Stimulering, Aktivering och Träning (SAT), som leddes av utbildad personal i en hemlik miljö. Patienterna var i hög grad engagerade i programmet. Utvärderingarna av neuropsykologiska mätningar tydde på svag förbättring eller oförändrar funktion. Ryggvätskeanalyser antydde positive effekter.

I Arbete III beskrivs den systematiska träningen, SATprogrammet, de olika formerna av direkt och indirekt stimulering samt även av praktisk utförande av kognitiv, social och fysiska dagliga aktiviteter. Resultaten pekar på att efter behandlingsåret så hade patienterna visat förmåga till ett aktivt deltagande, utförande av komplexa aktiviteter, förmåga att använda kvarvarande förmågor som kompensatoriska strategier och kompetens att lära sig och att använda en dator, vilket de inte gjort tidigare. Utvärderingar visade på bibehållen eller förbättrad förmåga.

I Arbete IV utvärderas månadsvisa anteckningar, gjorda av patienternas make/make under behandlingsåret. De gav kunskap om det dagliga livet i hemmet, och hur det påverkades av sjukdomen. Fyra teman framkom i en kvalitativ analys. Resultaten antyder att utbildning skall vara anpassad till äkta make/makars olika perspektiv, bl. a gällande vissa komplexa symptom. Det är också viktigt att lära sig förstå friska känsloutbrott för att undvika feltolkning.

 I Arbete V skattas den språkliga utvecklingen under behandlingsåret. De språkliga övningarna var sammankopplade med den kognitiva och sociala träningen och i vilken en dator ytterligare stimulerade patienterna att använda sina språkförmågor. Patienterna hade maximumpoäng i läsförståelse och högläsning genom hela skattningen trots nedsatt räkneförmåga.

Dessa studier lyfter fram att en rik hemlik omgivning med praktiska aktiviteter som användas i dagligt liv och anpassad till individidens kapacitet kan användas för att stimulera kognitiva funktioner. Detta kan också vara ett komplement till läkemedelsbehandling av AD och tillsammans möjliggöra en större förbättring, framförallt vid behandling med nervcellsstimulerande läkemedel. Studierna lyfter fram vikten av att utnyttja bevarade funktioner för att kompensera för förlorade förmågor. Trots att patienterna hade en demenssjukdom, mild till måttlig AD, fanns möjlighet till nyinlärning.

CONTENT

ABBREVIATIONS

AD	Alzheimer's disease
ADL	Activities of Daily Living
APA	American Psychiatric Association
BAS	Body Awareness Scale
BBB	Blood-Brain Barrier
Cochrane	Cochrane Library
CGI	Clinical global impression
CNS	Central nervous system
CSF	CerebroSpinal Fluid
CT	Computerized Tomography
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
ECG	ElectroCardioGraphy
EAD	Early onset Alzheimer's disease
EEG	ElectroEncephaloGraphy
ELISA	Enzyme-Linked ImmunoSorbent Assay
fMRI	Functional Magnetic Resonance Imaging
GBS	Gottfries-Bråne-Steen scale
ICD-10	International classification of diseases, 10th edition
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MPA	Medical Products Agency
MRI	Magnetic Resonance Imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
NGA	Norsk Grunntest for Afasi
PET	Positron Emission Tomography
rCBF	regional Cerebral Blood Flow
RO	Reality Orientation
SAT	Stimulation-Activation-Training
SBU	SBU · Statens beredning för medicinsk utvärdering
SPECT	Single Photon Emission Computed Tomography
STEP	Stepwise comparative status analysis
UKU	Side-effect rating scale
WHO	World Health Organisation

1   INTRODUCTION

Dementia has been classified as a major worldwide health challenge in elderly persons by the World Health Organisation [1] due to the progressive aging of the population, the creating of a dependence on other people, and a major cause of institutionalization. The most common form of dementia is Alzheimer's disease, representing about 60% of all dementia cases, and the second form is vascular dementia. When incidence data carried out from eight population-based studies of dementia and subtypes in seven European countries (including Sweden) was compared and pooled, 60 to 70% of all demented cases were diagnosed with AD [2].

In modern society dementia is widespread and the worldwide social cost of dementia based on prevalence estimates, a population of 34.4 million demented persons, was estimated to $422 billion US dollars ($) in 2009. This includes $142 billion for informal care [3]. In Sweden the direct costs in year 2009 are rough estimated to 2069.8 (millions US$) for 145535 persons and including informal care 1.6 h/d or 3.7 h/d the total cost was 2899.2 (millions US$) respective 3987.7 (millions US$) [3].

The progressive loss of nerve processes is the neurobiological basis of the progressive deterioration in AD, characterized by ongoing neurodegeneration [4]. As there is yet no cure for AD, the goals for treatment is temporary retardation of the progress of the disease, which is reflected in the general pattern of decline and in the continuous deterioration of cognitive and social functioning.

Synapse loss as primary event in early-onset AD has been suggested [5] and is together with nerve cell loss the probable basis of the cognitive reduction. Recent development in neurotrophic factor research has opened for new treatment strategies in neurodegenerative diseases. Factors with possible effect/influence on the density of synapses could have a positive effect on the disease. Gangliosides, especially ganglioside GM1, have been shown to have neuritogenic and neurotrophic activity. GM1 is in CNS concentrated in the pre-and postsynaptic membranes of the synaptic terminals, in the synaptic junction [6]. Treatment with ganglioside GM1 has in clinical trials shown to made beneficial effects on brain damage as well as in stroke.

The brain's ability to reorganize itself by forming new neural connections throughout life is called neuroplasticity. Mesulam [7] described neuronal plasticity as a life-long process that mediates the structural and functional reaction of dendrites, axons, and synapses to experience, attrition, and injury. The manifestations of neuroplasticity in the adult CNS include alterations of dendritic ramifications, synaptic remodeling, axonal sprouting, neurite extension, synaptogenesis. GM1 might therefore be able to exert a positive effect on the loss of synapses in AD, which is supposed to reflect the reduced cognitive function in the disorder.

In a previous study it was evident that subcutaneous or intra muscular injection of GM1 ganglioside for three months had no clinical effects on cognitive and emotional disturbance in AD [8]. The study also showed the GM1 cannot pass the blood-brain barrier. Accordingly, it was necessary to develop: a technique for infusion of GM1 into the brain for treatment of neurodegenerative disorders in the brain.

Early research on how brain aging and AD are influenced by activating stimuli, which affect neuronal functioning, suggest that environmental stimuli, transmitters and trophic factors can all influence the brain. We have combined two of these factors in a hope to obtain functionally relevant effects. Within the hypothesis to "use or lose it", was said that activation of neurones may promote functional cell survival or even prevent cell death [9]. There was also in the research, support of the hypothesis that at least a certain amount of neuronal survival and plasticity in AD remains, and is "use-dependent". Active interaction of the AD subject with the environment was required for plasticity to take place. These points to plasticity in the brain, suggesting that mental activation can modulate symptoms. Another form of plasticity related to memory was found in the hippocampus in which the plasticity occurs at synapse level. Further, it was suggested that a certain level of neuronal plasticity persists in AD [10].

The basic thoughts of this project were thus: if treatment with ganglioside GM1 could have positive effects, a stimulation - activation- training **with cognitive, social and physical activities** was combined as an additive therapeutic treatment. The programme (intervention) was made to use and supply retained functions of the patient to compensate for impairment [11, 12, 13, 14]. If any clinical improvements are observed of the therapeutic use of such a training program and of ganglioside GM1 administration, this would show that it was possible to improve brain function in AD.

Therefore the first treated patients and their respective caregiver are important participants to provide a well-carried out and well-followed up of the conducted extensive combined treatment. Especially important is the developed programme: to describe the content, the individual design, the execution in the real world, and information to and from the close caregivers of the patients.

The new technique for administration of GM1 and the addition of training made it necessary to get knowledge of: how the practicability of ganglioside GM1 administration was feasible; how the practicability of a training programme developed to enhance the remaining capacity of the patient to be used in active participating was feasible; how ganglioside GM1 and the performance of this training programme exert influence on the treatments given; in that purpose there were use of extensive and continuing of examinations of standardized assessment tools together with empirical data based on all assessment tests, form, imaging techniques and interviews. Evaluation, qualitative and quantitative methods provide knowledge about how well the collected data correspondence to the dimensions it was meant to deliver. A well done description of the interventions can then be used as knowledge before new start of interventions; it is the way we teach each other, to provide what is happening during the ongoing research.

This thesis, intends to provide new knowledge from nursing care aspects; about providing optimal therapeutic treatments in early onset AD patients, about dementia care nursing treatments intended to induce brain stimulation; about containing of utilizing compensatory approaches in a training programme with regards to brain damage and home living conditions; about influences, treatments, managements, supervisions, and possible adverse events of these new treatments.

This thesis intends to provide knowledge about: the capacity of each patient to actively participate in all activities within the programme; about the patients' experiences of the treatments given; and of spouses' depicted opinions of the treatment based on the everyday life at home.

1.1 The complex of investigations in Alzheimer's disease

The disease is named after Alois Alzheimer. He published a case report in 1907 on a woman with impairments supplemented with post mortem neuropathological findings of neurofibrillary tangles and senile plaques that have subsequently become the hallmarks of AD [15]. Such a definition means that the diagnosis is only definite at autopsy, but a probable diagnose can be made on the basis of a thorough clinical examinations weighed together with information gathered from supplementary investigations [16].

A well specified clinical diagnose is necessary in both clinic and research , and a correct diagnosis would also lead to a better understanding of the needs of the patients and thereby better care and quality of life. A correct diagnose is therefore crucial in pharmacological treatment.

Pathology. There is a consensus that the main microscopic findings in the AD brain are neurofibrillary tangles (NFT), senile plaques (SP) and degeneration of neurons and synapses [15, 17, 18]. NFT are one of the hallmarks of AD and composed of abnormal fibrillary material which has accumulated in the cytoplasm of neurons [19]. SP consists also of an acellular core material formed by beta-amyloid and surrounded by a variety of neural and glial processes. The term neuritic plaques [20, 21, 22] is used synonymously. β-amyloid is the key protein component deposited in senile plaques in the brain in AD.

Diagnostics. Clinical diagnosis can be based on different criteria-based diagnostic systems. The most commonly used are: the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) [16] and or the revised 1984 criteria with the note that: "... all patients who met criteria for "probable AD" by the 1984 NINCDS-ADRDA would meet the current criteria for probable AD dementia mentioned in the present article" [23]; the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III-R) [24], and or 4th edition DSM-IV [25]; and the International Classification of Disease, (ICD 10th revision) [26].

When this study was carried out, the best diagnosis method was NINCDS-ADRDA [16]:

Definite AD: requires in this criteria histopathological evidence of AD, which is regarded as the gold standard, plus clinical evidence for probable AD.

Probable AD: requires deficits in two or more areas of condition; progressive worsening of memory and other cognitive functions, no disturbances of consciousness, onset between the ages 40-90 and absence of systemic brain disorders that could explain the memory or cognitive decline. The diagnosis is supported by progressive deterioration of specific functions such as aphasia, apraxia, agnosia and impaired ADL.

Possible AD: is diagnosed when the patient has dementia with a clinical course that resembles AD, but also has a second brain disorder or systemic illness that is sufficient to produce dementia but is not considered to be the cause of the dementia. The patient has a progressive deficit in the absence of any other cause.

New strategies for the diagnoses of Alzheimer´s disease have been proposed after this study was made [27]. These criteria include also analyses of structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analyses and are centred on a clinical core of early and significant episodic memory impairment.

Clinical diagnosis of subgroups

The German psychiatrist and neuropathologist Alois Alzheimer was the first to describe this disease in 1907, a heterogeneous dementia disease [15]. Several studies have shown differences between early-onset AD, type I (<65 years of age) and late-onset of AD, type II. Criteria of early onset AD and late onset AD have been presented.

Patients in early-onset AD have a greater frequency and intensity of parietal symptoms, [28, 29] and normal blood-barrier function [28], more aphasia, agnosia and apraxia [30]. Patients with AD type II, mainly in late onset, have mild tendency to develop delirium, but mild if any parietal-lobe symptoms [31].

According to fundamental biochemical differences between the two major forms of AD, results in a study suggested a pronounced loss of nerve endings in early-onset AD [32]. Instead, the white matter changes are more frequent and more severe in patients with late onset [33].

Clinical diagnosis of early onset AD

To meet the demands of matching the development of e.g. new techniques for biochemical investigations on the etiology and pathogenesis and new drugs for AD, criteria for the clinical diagnosis of "pure" AD has been presented. Research criteria for the clinical diagnosis of "pure" (classic) AD are documented by Wallin and his colleagues [32] are as follows. The characteristic symptomatology of "pure" AD is instrumental deficits. These deficits comprise visual agnosia, sensory aphasia, apraxia (in "pure" AD, the onset is insidious and the progression is even).

In mildly demented AD patients the symptoms are often vague and diffuse, usually with memory as the most obvious finding. In moderately demented AD patients, a clear brain-regional symptom pattern has usually developed such as predominance of instrumental deficits. In severely demented patients the instrumental symptomatology may be obscured by the appearance of personality deficits and the global severity of dementia. These research criteria are used in this thesis.

Symptomatology in Alzheimer's disease

The clinical picture and course of AD is assumed to reflect the biologic changes induced by the underlying disease. The aspect of the clinical course of AD is multidimensional. There are many scales for stages of the symptomatology, such as 7 STAGES in the GDS scale (Global Deterioration Scale [35] but in this thesis the three-stage model proposed by Sjögren and associates [30] has been used.

STAGE 1. Manifest mnestic disturbances is the most prominent and incipient symptoms of dementia and observation of predominant aspontaneity and reduced initiative. The symptoms are often vague and diffuse and develop insidiously such as functions of speech, and disorientation in space. Disturbance in gait in earlier stages was localized in the forebrain.

STAGE 2. The cardinal cortical disturbances dominate the symptoms, which are referred to as parietal symptoms as of dysphasia, dyspraxia, dysgnosia, and visuospatial disturbance, together with a progressive worsening of memory. There is a pronounced deterioration of speech faculty. Aspontaneity is predominant relatively common, occurrence of rigidity and high degree of increase of muscle-tonus occurs. Disturbance in gait and movements for

normal gait is observed in earlier stages. Initiative to walk is reduced. The gait disturbance in combination with changes in muscle-tonus is pronounced and characteristic.

STAGE 3. The mental functions are severely impaired as the parietal symptoms become more and more concealed. There is preservation disturbances and the disturbance in gait at an early stage shown in the terminal stage a type "marche a petits pas" with a localization in the basal ganglia. Pronounced hypokinesis, the features are stiff, expressionless and mask-like. The well-known picture of a vegetative status are shown and also a picture of complete dementia with a rapid physical decline.

Another often used clinical definition of mild, moderate and severe dementia is lined out in by the American Psychiatric Association [24] in the Diagnostic and Statistical manual of Mental Disorders:

Mild dementia. Although work or social activities are significantly impaired, the capacity for independent living remains, with adequate hygiene and relatively intact judgment.

Moderate dementia. Independent living is hazardous, and some degree of supervision is necessary.

Severe dementia. Activities of daily living are so impaired that continual supervision is required, e.g., unable to maintain minimal personal hygiene; largely incoherent or mute.

1 .2 Clinical investigations used in the studies

Neurologic and neuropsychiatric identification of regional brain syndromes in dementia was outlined by stepwise comparative status analysis of regional brain syndromes (STEP) [36].

This tool is a clinical method to assess emotional and motivational functions, the capacity for mental flexibility, instrumental functions, mental speed, basic neurological functions and general cognitive functions. When these functions are disturbed, STEP is then a clinical method to assess these deficits and their interactions recognizes the predominant symptomatology.

The outcome of the analysis of STEP is specific patterns of neuropsychiatric deficits. This status examination relies on the examiner's observations and a structured interview with the patient and the relative. The STEP status variables are: Primary variables (n = 35), Compound variables (n = 8), Complex variables (n = 7). The protocol is recording of scores (five score variables: 9, 0, 1, 2, 3) of the Primary Variables (n=35), the Compound Variables (n=8) and the Complex Variables (n=7).

Neuropsychological assessment. Common used tests are of attention, language, memory, visuospatial skills, executive function, intelligence, and motor speed. These assess the major domains of neuropsychological functions as considered in Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology [37]. However, not all tests are used with each patient. Tests used in this thesis are referred to authors such as Fuld [38], Wechsler [39], Lezak [40], Rosen and associates [41].

The Mini Mental state Examination (MMSE) was used as a screening instrument of several cognitive functions such as orientation, attention, recall, constructional ability and the use of language. Scores range between 0 (complete failure) and 30 (representing full marks), where score 0-23 indicates a state of dementia [42].

Linguistic assessment. Norwegian Basic Aphasia Assessment "Norsk Grunntest for Afasi " (NGA) was used for linguistic assessments. It is a Norwegian standardized test, based on patients with aphasia, for measuring degree and type of aphasic impairment. A detailed description of NGA, including its rationale, reliability, validity and origins is given by Reinvang under the heading Norwegian Basic Aphasia Assessment [43]. The standard test measures fluency, comprehension, repetition, naming, reading and writing, which are the complexity of linguistic problems common in patients diagnosed with AD. There is no such test or scale available based on or for patients with AD. The NGA is commonly used and carried out by speech language pathologist, educated in NGA assessment.

Psychiatric physic assessment. The Body Awareness Scale (BAS) was used for psychiatric physic assessments. It is constructed by Roxendal and also tested in her thesis in treatment and evaluation in psychiatric physiotherapy [44]. The general purpose is to give the physiotherapist information about the patient's body awareness including body consciousness and body management. In practical use this has two purposes, as to describe dysfunctions as components and to measure change between different ratings in order to

evaluate the effect of treatment. All items in the scale have the scale-steps 0-3, where half-steps should also be used, "0" represents the healthy situation and "3" an extremely pathological. The evaluator had to be educated in the scale which also is interrater reliability tested [45]. The original version of BAS scale is in Swedish language.

Dementia assessment. Gottfries-Bråne-Steen geriatric rating scale (GBS) [46] is

an assessment of the dementia syndrome and was used for measurements of dementia symptoms. The scale is divided into 3 subscales measuring impairments of motor performance (6 items), intellectual (11 items) and emotional (3 items) impairment and a fourth subscale measuring six symptoms such as confusion, irritability, anxiety, agony, reduced mood, and restlessness. The intellectual subscale measured impairment of orientation in space, orientation in time, personal orientation, recent memory, distant memory, wakefulness, and concentration; inability to increase tempo, absentmindedness, long-windedness, and distractibility. The emotional subscale measured emotional blunting, emotional lability, and reduced motivation. The motor functions measured motor insufficiency in undressing and dressing, motor insufficiency in food intake, impaired physical activity, deficiency of spontaneous activity, motor insufficiency in managing personal hygiene, and inability to control bladder and bowel. The GBS scale have seven steps and are used to score impairment and symptoms and score 0 - 1 is considered normal, > 2 - 4 moderate impairment >4 - 6 severe dysfunction. The scale has been revised and translated in about 20 different language and is reliability and validity tested [47, 48, 49]. The motor performance part of the GBS scale has good correlation with Katz and Akpom; ADL index [50].

Laboratory tests. Both blood samples and cerebrospinal (CSF) examinations were

made.

Cerebrospinal fluid (CSF) is produced in the brain and can be therefore considered to be a window to the brain. Analysis of CSF provides information of the level of the given ganglioside GM1, of possible damage to the blood brain barrier (BBB), determination of antibodies to gangliosides, as well as about inflammatory or infectious processes in the brain.

Examination of CSF biomarkers is important in treatment of patients to assess in vivo pathology. These biomarkers were e.g. as available and used for examinations of: cytology, monoamine metabolites HVA, 5-HIAA and HMPG (monoamine systems is one of the

cornerstones of biological psychiatry), corticotrophin-releasing factor, neuropeptides as DISP, NPY and somatostatin. Methods for the biomarkers related to AD as Aβ 1-42, T-tau and P-tau were not available at the time of this study.

 Blood tests included complete haematological status, electrolytes, kidney, liver and thyroid function tests, vitamin B_{12} and folate levels. Further was a determination of specific antibodies to GM1 and of protein in serum, which is a part of check of the BBB. It also included test for normal IgG index for detection of immunoglobulin production in the brain, and to exclude thyroid disorders, hyperparathyroidism and vitamin deficiency.

Brain imaging. Magnetic resonance imaging (MRI) can measure atrophy with high accuracy, also in specific parts of the brain as the hippocampus. Computed tomography (CT) can visualize both treatable condition such as subdural haematoma and also estimate degree of brain atrophy. It is generally known, that the brain in AD there are a degree of ventricular and cortical changing [51, 52].

Single Photon Emission Computed Tomography (SPECT) can be used to measure cerebral blood flow. SPECT can show signs of focal cerebral lesions, but not with high accuracy. This technique can identify the reduction in metabolism and cerebral blood flow (rCBF). In AD a temporo-parietal reduction is usually seen.

Electroencephalography (EEG) can show changes in electrical activity indicating focal cerebral lesions and used in this study. An analysis prior to and after the treatment of the computer-generated EEG power spectrum can confirm changes. These changes of activities, frequency, and/or irregular firing patterns over the courses of drug infusion in different areas, are important findings of the pathological pattern occurring in AD.

Results made on the basis of through clinical examinations for the clinical diagnosis of AD may be weighed together with the information gathered from supplementary investigations such as brain imaging, EEG and laboratory tests for evaluation of the disease [16].

Global treatment efficacy and side effect assessment. Clinical Global Impression (CGI) [53] is a global clinical rating scale, which documents the treatment efficacy and side-effect. The main groups are: Severity of illness, Global improvement, Efficacy index, and Therapeutic effect with Side effects. The assessment on this scale should be performed independently of the assessment on the cognitive battery. The UKU side-effect

rating scale is from Scandinavian Society of Psychopharmacology Committee of Clinical Investigations [54]. This scale is made up by 48 different symptoms, used in this study. Both the symptoms themselves and the extent of the symptoms (range 0-3) are defined. For each side-effect, the causal relationship to test treatment is evaluated.

1 .3 Clinical symptoms: early-onset, mild, moderate AD

Signification and empirical research studies

Memory. The impairment of short-term memory is one of the earliest and most prominent symptoms of the disease. Short-term memory refers to performance in memory tasks over a very short period of time [55]. It is believed that the information resides briefly in an active memory state and then is either recalled directly, lost or encoded further for transmission to the long-term memory, i.e. for more permanent storage.

The long-term memory is divided into episodic, semantic and procedural memory, all of which are of important in daily living [56].

The episodic memory deficit is pronounced early in the disease, probably due to brain changes in areas critical to episodic memory [57]. This memory draws on a widespread network of brain structures; thus, changes at multiple sites in a large distributed network are capable of disrupting performance [see 58]. Results from studies indicate that patients with AD in the early onset of the disease are able to utilise cognitive support in episodic memory task. However, they need more support than the healthy aged to show improvement. They need support which had to be provided during both encoding and retrieval, such as in a study using motor activity [59].

Semantic memory refers to the component of long-term memory, which represents our knowledge of objects, facts, as well as words and their meaning [56]. Results from a study indicate as follows: mildly and moderately demented AD patients' ability to utilize cues following a motoric encoding may be preserved later in the disease than they are able to utilize cues after a semantic encoding [60].

Procedural memory, the learning of motor tasks, undergoes little decrement until the late stages of the illness [13]. It is important to maintain this resource of the patient, e.g.

enhancing self-esteem, when carrying out tasks independently and of social activities in daily intercourse.

Aphasia. Early in the course of AD the reduction in functions of speech is observed which was followed with a pronounced deterioration of speech faculty. In the second stage this deterioration is followed of the aphasic disturbances which all is one of the chief symptoms as proposed by Sjögren and his colleagues [30] in their three clinical course of AD.

Communication. Evidence for communication disruption early in the course of AD has been provided [61]. In a review, Emery [62] summarised studies and found that in patients in the early stage of AD: vocabulary became impoverished, speech circumlocutory, and that confrontation naming was progressively impaired. It was suggested that the aphasia profile in AD should be named "Alzheimer aphasia". In her opinion, the relationship between semantics as a dimension of language (analysis and interpretation of meaning) and semantic memory on the theoretical front needed to be worked on.

Naming errors have been suggested, as including in analyses, that a major factor behind the naming problems in AD is a semantic memory loss [63]. Impaired naming has been commonly seen as a prominent deficit in AD, [64, 65] and that anomia is in part due to loss of lexical semantic information [66].

Pragmatic ability has to deal both with lexical and memory function. Within the social context of the person with AD includes the conversational partner, who greatly can influence the person's with AD ability to produce discourse [67].

Reading disorder occurs in the early stages of the disease. In reading, the patients are quite often able to read words but frequently fail to comprehend their meaning. Reading therefore appears to occur via the lexical rather than the semantic or sub lexical routes [68].

Writing deficits appeared to be a more sensitive indicator of language dysfunction in AD than anomia [69].

Oral spelling has in AD been found to be more impaired than written spelling [70]. In calculation procedures the difficulties may already appear at an early stage of AD [71].

Executive processes. Executive functioning refers to a heterogeneous and wide-ranging set of cognitive operations, including allocation of attention, inhibitory control, hypothesis

generation, and self-monitoring, as well as other skills believed to be governed by the prefrontal cortex [72, 73].

Planning and function in complex situations, e.g. executive function tasks primarily required concurrent manipulation of information, is reduced early in Alzheimer's disease [74]. These impairments in the capacity, to combine performance on two simultaneous tasks, have a considerable impact on function in AD. Executive processes are clearly a mixture of control mechanisms.

Included in the executive processes are selective attention, scheduling of different mental operations and the ability to co-ordinate mental activity in a way that facilitates problem-solving activity.

Later, Collette et al. [75] suggested deficits in executive functioning performance in AD as: the inhibition abilities and the capacity to co-ordinate simultaneously storage and processing of information. The results also confirm that some deficits may be in the first stages of AD.

__Apraxia__ is defined as loss of ability to carry out familiar purposeful movements, difficulty making voluntary gestures, all in the absence of motor or sensory impairments. The rhythm and the co-ordination of the movements, which is necessary for normal gait, were in the early stages of AD observed by Sjögren and his colleagues [30]. Patients with mild AD had impaired postural control as compared to healthy subjects which showed that this control is affected already at mild stages of AD [76].

Ideomotor apraxia (impairment in the selection of the elements that constitute a movement) and ideational apraxia have been evaluated in different stages. In a study with 142 patients with dementia, 35% of apraxia was found in the mild stage, 58% in the moderate stage, and 98% in the severe stage of dementia. Ideomotor apraxia was apparent in mild dementia when considered separately [77]. Another study confirmed these results [78].

Motor disturbances are usually associated with mental disorders. A way of limiting unnecessary motor deficiencies in everyday functional performance is the use of the BAS scale (Body Awareness Scale) [44] that describes and measures the patient's body awareness, body consciousness and body management changes. This scale was used over time in a pilot study in early-onset mild to moderate AD and the result showed improvement based on the decreased observed and examined items [79]. However, aspects of the impact on functional

performance were found in a study in which activity level and postural control were evaluated. The patients with mild AD were found to be less active in e.g. social outings, car rides, household activities and car maintenance and had lower scores on a balance scale (timed up-and-go test; walking-in-figure test) compared with healthy elderly persons [80].

Myoclonus (shock-like contractions of a muscle or group of muscles) was rarely observed in patients with mild AD in a multicentre study [81].

Agnosia. Agnosia is a class of recognition disturbances that are confined to a single modality. Agnosia refers to the inability to recognise the import of sensory impressions; the varieties correspond with several senses and are distinguished as auditory, gustatory, olfactory, tactile and visual. In Agnosia there is an inability to recognize objects using one of the senses, even though the sense in question is intact. Perception is the conscious mental registration of a sensory stimulus, to be perceptive. Depth perception is the ability to recognize or relative distance to different objects in space. Recognition is the act of recognizing or state of being recognized.

Prosopagnosia is the inability to recognize faces. This is due to damage to the underside of both occipital lobes but yet having the knowledge that a face is a face and can identify the facial parts (nose, mouth, etc). Noted in a study was that in about one fourth of the mild-to moderate patients with AD had person- identifications disturbances. Most common was transient, sporadic misidentifications and least was prosopagnosia [82].

Visual selective attention is impaired at the stage of disengaging from the target, divided attention appears to be particularly impaired, while phasic arousal appears to be only minimal affected in the early stages of AD [83, 84].

The majority of patients with AD, who exhibit prominent but selective visual impairments, appear to have deficits in visual selective attention.

Visuospatial symptoms. Spatial disorientation is common in the early course of AD. The patients get lost in their surroundings, placing objects in inappropriate locations, and fail to produce more elementary figures [30, 85, 86]. Coslett and Saffran [87] found that Alzheimer's disease may selectively disrupt specific visuospatial processing mechanisms. These are including visual selective attention, process-mediating object recognition, and the spatial map (registered object localisation, object dimension). Inherent in the attention process

are the ability to attend to sensory inputs, selective or screening out other competing inputs and split or divided attention between more than one tasks [84]. Of interest are arguments presented by Frith [88], who associates attention not with a single resource pool but with two separate functions, that is: selectivity of information for processing and capacity limitations.

Visual field loss [89] and inability to perform figure-ground discrimination tasks as well as recognition of tasks that are visually presented in AD have been reported [90]. Pathological changes in the primary and association cortex have been reported in AD [91, 92, 93].

1 .4 Gangliosides

Gangliosides are plasma membrane lipids, glycosphingolipids containing sialic acids, with the hydrophobic portion embedded into the membrane and the carbohydrate portion extending into the extracellular environment [94], originally found and named in 1942 by Klenk. The ganglioside concentration is much higher in the brain than in other organs, highest in adult cerebral and cerebellar grey matter [95]. Loss of gangliosides in brain in Alzheimer's disease was first reported 1965 and is an indication of reduced amount of plasma membrane in the brain [96].

The research of possible biological function of gangliosides has been ongoing for a long time. Such as these which are attributed to their extracellular oligosaccharides, interaction with positively charged ions, their existence in membrane clusters, and also the involvement in cell recognition, adhesion and differentiation [97, 98, 99]. Further research is of their neuronotrophic (concerned primarily with survival and maintenance of the neuron) and neuritogenic activity (involving of neuronal processes) [100] as well as their more informed use as neuro-therapeutic drugs [101].

Quantitative estimation of sialic acid and quantitative estimation of gangliosides in senile human brains was 1957 performed in ongoing ganglioside investigations at our laboratory. Some years later a nomenclature for separation of human brain gangliosides, involving its four major gangliosides: GM1, GD1a, GD1b, and GT1b, was proposed by Svennerholm [102, 103, 104], followed by the evidence that ganglioside GM1 in CNS is concentrated in the pre- and postsynaptic membranes of the synaptic terminals, in the synaptic junction [6].

Treatment with ganglioside GM1

Positive effects of GM1 treatment on neuronal damage in the CNS and of nigrostriatal dopanergic neurons have been reported in animals [105, 106, 107,108, 109]. GM1 has given the best amelioratory effect of the major gangliosides. Similar results of experimental cerebral ischemia indicated, that GM1 can reduce the extent of infarct volume and neurochemical deficits associated with the ischemic event [110].

In human studies, at this time, ganglioside GM1 was used in diseases as stroke and in treatments to enhance recovery after central nervous system (CNS) injury [111].

According to the treatment of stroke, the results exhibited neurological improvement [112]. In acute cerebral ischemic stroke, treatment with GM1 showed evidence to produce significantly greater degree of neurologic improvement than placebo treatment [113]. The beneficial effects of GM1 treatment on the damaged dopamine system in various animal and in vitro models went on to assess GM1 treatment in Parkinson's disease [114].

In Alzheimer's disease, with use of *parenteral administration*, the result of ganglioside GM1 treatment offered no overall symptomatic benefit to the patients [115]. This negative result was also shown of 3 months GM1 treatment [8] although a high level of labelled GM1 in serum. However, no detection of GM1 in the cerebrospinal fluid (CSF) indicated that GM1 not had passed the blood-CSF barrier in that study. Some years later again the result in a study in AD showed that parenteral GM1 treatment failed to produce improvement in cognitive test [116].

Intracerebroventricular administration of ganglioside GM1 is a new way to overcome the blood-brain barrier by an administration of a drug directly in the brain. This method was developed in a pilot study [117] in our treatment project for patients suffering from early onset AD. This means a treatment with an operation of an implanted system to get continuously infusion of GM1 into the brain. The surgery included implantation of catheters connected with a drug pump. The drug pump was to be refilled with subcutaneous injections. These are documented in this thesis with start in Paper I.

Amyloid beta-protein and gangliosides

 GM 3 and GM1 are newly suggested to accelerate the deposition of the amyloid beta-protein as amyloid angiopathy and senile plaques, respectively, in the Alzheimer brain [118]. These observations indicate that neuronal gangliosides are involved in the accumulation of circulating beta-amyloid to form complexes that are expressed in AD brain. In spite of this gangliosides have been shown to improve brain function. These aspects, however, points to the need of future studies of the therapeutic potentials of gangliosides in AD [119].

At the time of the study, acetylcholine esterase inhibitors or the partial glutamate inhibitor memantine were not registered in Sweden and there was no specific treatment of Alzheimer´s disease.

1.5 Perspectives on treatment of early onset mild to moderate AD

In AD, degenerative changes are accompanied by a reduction in a number of mental functions. In all, they overall impact on the patients' participating in daily living.

Mental activity is reflected in activation of different brain areas [120]. Specific lesions of the brain produce specific alterations in behaviour, and these are reflected in characteristic functional changes in the brain [121].

The clinical fact, that AD patients with parietal symptoms damage are not all the same, means there is variability in the expression of their cognitive problems. Individual design is then a reasonable approach of treatments to overcome disablement caused by impairment, activity limitations and participation restrictions of the patients.

Research findings, where the techniques to map brain activation in relation to mental performance have been used, suggest that the pattern of activations of the brains is changed in patients with mild and moderate AD. The results also suggest that it would be possible to use a patient's remaining capabilities in therapeutic treatments to overcome deficiencies in lost functions.

Another pattern is also formed during memory tasks [122], whether other frontal and non-frontal areas are utilised [123] in early-onset AD compared with normal adults, and by

forming new networks [124]. These findings points to plasticity in the brain, suggesting that mental activation can modulate both aspects. The results suggest mechanisms by which it can be possible for the AD brain to compensate for neurodegenerative changes.

Neuroplasticity allows to compensate for disease and to adjust the neuron activities in response to new situations or to changes in their environment. The brain's ability to reorganize itself by forming new neural connections remains throughout life. In order to reconnect, the neurons need to be stimulated through activity [125].

The brain activity in the cortical sensory areas in Alzheimer's disease is comparably little affected by the neural degeneration [11, 12]. Further, patients with AD have been found to have preserved learning of motor procedures [13]. These evidences open for use of the patient's perception to compensate other impairment in performance of tasks, activities, and properties of things.

Clinical studies

Cognitive stimulation is often mentioned in studies of training in dementia. In one of these studies, the results of 5 weeks in 10 sessions showed no change in the ADL scale, no improvement in behaviour but improvement on MMSE. This programme relied strongly on mental imagery [126].

Memory training in form of problem solving solely of the given material and with use of conversation was done one hour a day, six days a week, by family members. The results showed that the patients maintained the problem-solving skills over a period of 8 months [127].

The spaced retrieval technique is another form of memory training designed to teach a patient to use a memory aid. This involves active attempts to recall information over expanding intervals of time. Improvement was found when appropriate support was given [128].

Procedural learning is relative well-preserved in AD. The activities in a study by Zanetti et al. [129] were basic (e.g. washing face) and instrumental (e.g. reading a brief sentence) performed during 3-week training (1 h/d, 5 d/week). All ten patients showed improvement in their performance of the tasks trained.

Therapeutic activities in a kit called the BAG (Be Active with Games) were provided to be used at home in a study by Hutchinson & Marshall [130]. The BAG had been developed for individuals in all stages of AD. The kit, containing 20 therapeutic activities, was found useful by some of the 21 caregivers while for others it was an additional burden.

Specific computer-based training with use of a touch-screen-function on a monitor was developed for four patients with mild to moderate AD. They were instructed to by step touching correct screen areas to complete the task. About fifty to 100 photographs from their surroundings and biography were taken. Training frequency was 3-4 times per week, two training phases and each lasting 4 weeks. No significant changes were seen although the levels of motivation were high. There were, however, signs of emotional activation. Three patients were able to maintain parts of the trained skills over a period of 4 weeks [131].

1 .6 Available specific therapies in dementia

Considering use of activation and training programme

Several nursing methods have been suggested in the care of patients with dementia. Evaluation of studies in meta-analysis may give a suggestion of benefit or perhaps warning of problem with a therapy. There is no evidence for positive effects of a number of different therapies e.g. Reminiscence therapy, Validation therapy, Music therapy, Multisensory therapy (Snoezelen) according to reviews in the Cochrane Library [132] or SBU systematic review [133]. It is also sometimes hard to see the degree of dementia of the included patients. The reason may be that the therapy covers all stages and thus may well be used in all stages of dementia. However, these therapies are not applicable on the patients with early-onset, mild to moderate AD in this thesis, and will therefore not be discussed.

Reality orientation. By conducting a systematic literature review, the effectiveness of classroom reality orientation (RO) of patients with dementia, AD, was evaluated [134]. The evidence of their meta-analysis indicates that RO has benefits on both cognition and behaviour for dementia suffers but no evidence of long-term effects.

Specific Reminiscence programme was included in the SBU reviews for patients in mild dementia. This intervention was designed as an individual treatment. Significant improvement was found of social wellbeing [135].

Physical activity programmes, were evaluated in the Cochrane Library [136]. Insufficient evidence was found to determine the effectiveness in managing or improving on cognition, function, behaviour, depression, and mortality in people with dementia. However, a meta-analysis (more than 300 articles) on the effects of different form of underline exercise training, in SBU systematic review, found increased fitness, physical and cognitive function and positive behaviour . The subjects were 65 years of age or older including dementia, Alzheimer's disease and related cognitive impairments. Exercise yielded statistically significant positive effect [137].

1 .7 Therapeutic and medical treatment

Empirical studies

Pharmacological treatment. There are three cholinesterase inhibitors in clinical use. These drugs increase acetyl choline by inhibition of the degradation. They are registrated for use in mild to moderate Alzheimer's disease. Despite the slight variations in the mode of action of the three cholinesterase inhibitors there is no evidence of any differences between them with respect to efficacy. Addition of memantine can give slight improvement [138]. Long-time treatment with cholinesterase inhibitors and memantine prolongs the time when referral to nursing home is necessary [139].

Cognitive stimulation programmes benefit cognition in people with mild to moderate dementia over and above any medication effects according to consistent evidence from multiple trails [140]. One form of mental exercise is described as cognitive stimulation. This involves a range of activities, including discussion of past and present events and topics of interest. The review included 15 trails. The findings suggested that cognitive stimulation has a beneficial effect on the memory and thinking test scores of people with dementia.

Rehabilitative intervention for patients with AD and their caregivers for 4 months, in 60-minutes sessions a week, were of the effect evaluated by Onor and her colleagues [141]. All patients had mild to moderate AD, were aged 60-80 years, and had been receiving acetyl cholinesterase inhibitors for more than six months. The results showed that the patients with

mild to moderate AD had a more stable cognitive status and improved mood. For the caregivers, the efficacy of the psycho educational program was reported in terms of increasing and preserving their coping skills and enhancing their perception of the value of support groups.

A computer-based cognitive rehabilitation program for patients with mild AD was carried out in 4-week periods. The patients were medical treated with acetylcholinesterase-inhibitor (AchE-I) treatment at a stable dose (5 mg/day for donepezil and 6 mg/day for rivastigmine). A single session about 13-45 minutes was held on 4 days per week, covered a 4-week period. There was then a break, which lasted 6-2 weeks before next (same) single session. The patients as a group showed a significant improvement on mini mental scores, in areas of verbal production, and on executive functions but not in affective and functional areas [142].

Intensive reality orientation therapy (ROT) was the target of the cognitive rehabilitation, with active participating of the caregiver, in the evaluation of the efficacy of the combination of donepezil therapy. The donepezil therapy was combined with regular daily 45-min class meetings for 3 weeks with active participating of caregivers all the time. This was compared with donepezil treatment alone. The patients were in the mild to moderate stage of AD. Test was at baseline, at the end (3 weeks), and after 2 months of follow-up. The results of the combined therapy showed significant improvement in MMSE and ADAS-Cog, without changes in impaired ADL and instrumental ADL. There were no significant changes in MMSE in drug-only treated patients after 3 weeks, with a non-significant tendency to improvement in ADAS-Cog. Their results suggest benefit of an intensive ROT program that seems to be maintained as far as ROT is continued by the caregiver [143].

Language enriched physical fitness interventions provided by undergraduate students in Arizona University, have showed promising results [144]. The 24 participants had mild-to moderate form of AD, aged 54-80 year and with MMSE score 15-29 ("AD Rehab group"). Socialization experiences consisted of supervised volunteer work and cultural or recreational activities.

In this student-treatment provider concept, the study participants were 24 individuals of which 11 participants completed 2 semesters of treatment (1-year completers), 5 patients completed

4 semesters (2-year completers), 4 patients completed 6 semesters (3-year completers), and 4 completed 8 semesters (4-year completers).

In comparisons with the "CERAD sample", a slower rate of decline for the "AD Rehab group" was suggested. The stabilization of global and cognitive performance was not apparent after completed only 2 semesters. However, after 4 or longer semesters the cohorts showed no significant between-year changes after their first year. This was in measuring global functioning and on 5 or 6 of the cognitive and language measures.

1 .8 Prospects behind development of SATprogramme

Nursing and care within health and environment

The concepts inherent in nursing are generally said to be the ***individual, nursing, health*** and ***environment*** [145]. As health and disease are mostly associated with objective physiological and psychological measures, Brenner and his colleague [147] chose to use the terms "wellbeing" and "illness". Wellbeing reflects the lived experience of health, and illness, the lived experience of the disease.

In Travelbee's nursing theory [147], care can be seen as an activity. The purpose of nursing is to assist an individual, family or community to prevent or cope with the experience of illness and suffering and, if necessary, to find meaning in these experiences (health teaching) [147]. The purpose of nursing is achieved through the establishment of human-to-human relationship. This is a mutually significant experience, a reciprocal process. The responsibility for establishing and maintaining rests with the professional nurse practitioner. The relationship is characterized by rapport and includes all elements necessary: the original encounter, emerging identities, empathy (is a mutual understanding), and sympathy (see page 119, 136).

Communication is viewed as a process which can enable the nurse to establish a human-to-human relationship and thereby fulfil the purpose of nursing. Every interaction affords an opportunity to meet the ill person's nursing needs. About the concept communication, a major belief of her work is :"...that it is the task of the professional nurse practitioner to plan, direct and guide purposefully the interaction with the ill person in such a way as to fulfil the purpose

of nursing" (page 93). Travelbee avoided using the term patient-nurse, which may come from her own experience as a psychiatric nurse practitioner, teaching psychiatric nursing or as a director of graduate education [148]. Concept of Travelbee is springboards in the thesis.

Care as a structure process is on the basis of four phases, in which Tronto [149] distinguishes four ethical elements of care. These are *attentiveness* (being open to the needs of others), *responsibility* (for changing problematic conditions), *competence* (being competent, otherwise refraining from action) and *responsiveness* (respond to each other's expressions during caregiving/receiving. The activities performed may then be regarded as a process of interaction, an assessment of needs between persons and in a social context.

Health and environmental influence is in nursing a prominent concept. Florence Nightingale had it as a core concept in nursing and she had health as grounded in the environment. She thought disease was a reparative process. The nurse should manipulate the environment, helping the diseased patient at least to live a better life until death (see [150]). King [151] viewed health as a continuous adaptation to stress in the internal and external environment in order to achieve the maximum potential for daily living. Therefore, essential for nurses is an understanding of the ways that human beings interact with their environment to maintain health.

Since Alzheimer' disease is at present incurable, looking at concepts of nursing in this way is relevant. Cu it emphasises the experience of meaning in the situation rather than dgkpi related to the curing of the disease. Concepts of Travelbee [147] and Tronto [149] are springboards in Paper I-V.

Patient - the environmental hierarchy and interaction

When humans encounter and perform in various environments, a process of interaction occurs. This process is between persons and environments, and environmental factors (which influence this process) and is named "layer" as examined by Barris et al. [152].

The individual's choice of which environment to explore involves influence. Such is by constraints, values, and interest but are also volitional.

Arousal, an "internal state with subjective and physiological manifestations" [152], is said as a concept which connects volitional traits with properties of the environment.

The central "layer" around the person is *objects* which is the materials of our daily life. These are: availability (refers to presence); complexity (reflects skill and leaning required for its use), flexibility (pertains to potential of using it in many variety way) and have a symbolic meaning (e.g. objects become symbols of power, prestige, independence). Next "layer" is *tasks* e.g. everyday tasks, and thereafter, the *social groups* and also organizations with number of people and function. The final "layer" is *culture* which is shared by a group. Together these "layers" represent an *environmental hierarchy*.

These "layers" influence the individual's decisions both to encounter and performances in these environments. A modified content of Roann Barris et al. [152] recommendations is springboard in Paper III.

Patient - environment and connection to individual needs

Demented patients need increased environmental clarity to compensate for cognitive and functional deficiencies and also adjusted surrounding for psychological wellbeing. A congruence model of person-environment interaction has been proposed and discussed in a conceptual model by Kahana [153]. It is a congruent model of environmental characteristics and individual needs. That is in the role of understanding the impact of environmental settings and contribution to wellbeing.

Two broad areas of congruence were discussed. These are dimensions based on environmental differences and also dimensions based on individual differences.

In the segregate dimension, the concept may refer to the heterogeneity or homogeneity of the setting. This is for example level of function and may contrast living or participating with a group of persons much like oneself/ different from oneself. The congregate dimension refers to closeness, which is the degree of privacy possible to get in the setting. It is also the institutional-control of residents, which refers e.g. to the degree of tolerance of resident autonomy that is tolerated. According to Kahana (page 102) it may be expected that along these dimensions should lead to a sense of wellbeing, satisfaction, and adequate function in the institution. The congruence model of Eva Kahana [153] is springboard in Paper III.

Patient - environment demands on functional capability

Environmental demands can create barriers which hinder task performance by demands to functional capabilities. Successful task performance is dependent on a match between task

demands and human capabilities. By using the purpose to reinforce independence, the winning may thereby contribute to wellbeing among people.

A modified technique of Human Factor, which implies a step-by step task demand analysis, has been demonstrated by Czaja et al. [154], which is a method from Human Factors Engineering. The model conceptualizes change as occurring in multiple stages. This means to break a task or activity into subtasks or steps. This action, with defining the cognitive and physiological performance requirements, is involved in each kind of step - to reach the goal. The modified technique of Czaja et al. [154] is springboard in Paper III.

Patient - environment contact in upholding stimulation

Frings [155, 156] described that in the signal transduction process, each sensory cell detects specific stimuli and the nerve impulses are conveyed to and provide CNS with vital information about the body and its environment. When it comes to cortex, the complex information is then integrated and can be used to generate sensible behaviour why, in that way, nervous system thresholds contribute to individual's behavioural repertoire by this provided information. Therefore the equipment in form of different colour, sizes and tools are a part of stimulation which provides in the training setting, important stimuli.

Schultz [125] provides empirical support for the proposition that man needs constantly varying forms of sensory stimulation to function adaptively in his/her environment. This form of function is of importance in treatment of patients with Alzheimer's disease (AD). Schultz [125] provided in his book evidence of productions, such as of physiological effects with threshold changes, cognitive and learning effects, perceptual and motor effects in sensory restriction research. In the part of sensory variation as reinforcement, his propositions do demonstrate the reinforcing effects of a change in stimulation. Further that a change in sensory variation can have reinforcing properties leading to the learning of instrumental behaviours (page 28). For adult was also that "... effective functioning depends on the continued maintenance of contact with an appropriately rich sensory environment " (page 194). The brain's anatomy is immensely complex and the structure and interconnections of its parts are still not fully understood. By allowing various form of stimuli to reach the patients' senses they can experience and thereby put the remaining sense faculty into practice in performance of activities of daily living. In this thesis of practical performance during the

patient's active participating, in both internal and external surrounding, Schultz proposition [125] is within the discussion in Paper III.

Patient - expectations to use of remaining abilities

Ability to perform tasks or an activity can be seen in the light of concepts used by Nordenfelt [157] in his outlining of what it means if a person is able to perform actions.

Nordenfelt, his prerequisites or concepts is related to a set of circumstances. These are that the participant's internal resource for performing the action is sufficient. These are also that it must be a practical possibility of performing the activity or task. The circumstance is also that there must be right opportunities. In this thesis, Nordenfelt's contains of his outlining has been considered.

From the patients' point of view, based on that they are able to perform dependent or independent actions, it might be hard to always understand their own limits. A belief may have occurred before the start of the therapy. That might be that the instructor skill qualities should help them to solve problem and limit negative influence of circumstances within performance of daily activities.

From the nursing care point of view, these prospects is reasonable and ought to be within the modifying or duties to hold each patient's remaining capacity to perform tasks or activities, and further, to be related to a set of reasonable circumstances within the patient's real social life. Practical possibility to perform activities should well be a part by providing specified, (regarding place and time) and explanation of all tasks in an exact and detailed way the. The right opportunity means to provide the patient by and use of a location in which it is easy to do the performance. This view is well a part within the equipped training setting provided and the patient is in that way seen to be provided with individual right opportunity.

Right opportunity is important, as if there is no opportunity, this may induce the risk to fails. This risk is always there, as the presence of ability may vary especially in Alzheimer's disease.

2 AIM

Overall aim

The overall aim of this thesis was to investigate and describe a training programme, within nursing aspects, for the impaired activity concomitant AD as a therapeutic treatment to assist in a innovative treatment with a continuous intracerebroventricular administration of ganglioside GM1 in the treatment for patients suffering from the early-onset, mild to moderate AD.

The specific aims were:

In Paper I: to elucidate how treatment with GM1 and home based activation and training influenced patients with early onset AD and spouses' reaction to the treatment.

In Paper II: to examine whether intracerebroventricular infusion of ganglioside GM1during one year, in conjunction with activation and training of the patients, could improve cognitive impairments in patients with early onset, mild to moderate Alzheimer's disease.

In Paper III: to describe the content and the individual design as well as the execution and outcome of a newly developed stimulation-activation-training (SAT) programme.

In Paper IV: to extend the knowledge, from a close partner's monthly perspective during one year, of everyday life with a partner suffering from early-onset, mild to moderate Alzheimer's disease.

In Paper V: to study the linguistic development within regularly performed language activities during one year of patients with early onset, mild to moderate Alzheimer's disease.

3   METHODOLOGY

The background to this combined treatment strategy is a long time collaboration between basic and clinical researchers which started in our Experimental Neuroscience Section and Psychiatric Section, Sahlgrenska University Hospital-Mölndal in the sphere of dementia in neuropathology, neurochemistry, neuropsychological examinations and ganglioside investigations. Important to mention for this thesis are the basic ganglioside investigations, ongoing since 1950s [103] and development of the dementia scale, the GBS scale in 1980s [146].

Table 1. Overview of participants and methods in the empirical studies

Paper	Participants	Methods for data collection
I	5 patients with early onset mild-to-moderate AD. Participating of 5 spouses	Neuropsychiatric-psychiatric-neuropsychological examinations, chemical-neurochemical laboratory tests, rCBF, CT, GBS scale, Activity scale, UKU scale, CGI scale, EEG, EKG, Daily Notes, interview
II	5 patients with early onset mild-to-moderate AD (EAD)	Physical, neuropsychiatric-psychological examination, chemical neurochemical laboratory tests, GBS scale, UKU scale, CGI scale, CT, rCBF, MRI, EEG, EKG, interview, clinical observations
III	5 patients with EAD	GBS scale, BAS scale, Activity scale, Norwegian Basic Aphasia test, clinical observations, Daily Notes
IV	5 spouses to patients with EAD	Clinical Global Impression evaluation form, clinical observations
V	5 patients with EAD	Norwegian Basic Aphasia Assessment, clinical observations

3 .1 Subjects and methods in Paper I

Paper I was the first study for intracerebroventricular infusion of ganglioside GM1 including neurosurgical procedures in treatment for patients with early onset AD, in combination with a home based activation programme during one year for each patient. The study was conducted at Department of Psychiatry and Neurochemistry at Sahlgrenska University Hospital - Mölndal (SU/Mölndal).

The procedure before inclusion of the patient in the first study

The patients were referred to the research team at SU/Mölndal (research centre) by general practitioners or other specialists at a distance from the research centre. These patients had met the referred criteria to have probable AD type 1(early onset) [16, 34], to be between 50 and 70 years of age and to have at least 1 relative who was willing to and capable of participating in the training of the patient and in the evaluation of the treatment effect.

These referred patients underwent a physical, psychiatric and neurological examination, a psychometric test, and extensive clinical chemical and neurochemical examinations by the research team (research centre) and computer tomography (CT), electroencephalographic (EEG), and regional cerebral blood flow (rCBF) measurement, in all to be used to baseline data.

Baseline examinations

The neuropsychiatric and neurological signs and symptoms were assessed according to the Stepwise comparative status analysis (STEP). This is a comprehensive observational instrument consisted of 35 items which are relating to various symptoms associated with dementia [36].

The neuropsychological battery comprised MMSE, Fuld's Object memory evaluation, Similarities and Digit Span, Face recognition test and Alzheimer's Disease Assessment Scale (ADAS) assessments [42, 38, 39, 40, 41]. The degree of dementia according to the GBS scale was to be scored at most 4 on items measuring intellectual impairment. The patients were to have moderate intellectual deterioration, to allow for evaluation of the therapeutic effect.

The score according to the Mini Mental State Examination (MMSE) had to be between 10 and 24, preferably closer to 24 than to 10.

Extensive clinical chemical and neurochemical examinations were analysed at clinical chemistry and clinical neurochemistry laboratory, Department of Neurochemistry, SU/Mölndal Hospital. The chemical examination, with use of collected blood sample, included complete haematological status, electrolytes, kidney, liver and thyroid function tests, vitamin B_{12} and folate levels.

The neurochemical examinations, in which samples of CSF was collected by means of a lumbar puncture, were used to determination of proteins in serum and CSF and cytology of CSF. The monoamine metabolites HVA, 5-HIAA, and HMPG [158, 159, 160] was determined in CSF as well as CSF neuropeptides, corticotrophin-releasing factor, DSIP, neuropeptide Y (NPY) and somatostatin [161]. Further, the CSF level of GM1 ganglioside was determined with using a recent developed ELISA method [A. Lekman, unpublished].

Antiganglioside IgG and IgM antibodies were determined with an ELISA method [162] with the following glycosphingolipids antigens: GM1, GA1, GD1a, and GD1b [163]. *SPECT* was used to examination regional cerebral blood flow (rCBF), conducted at the Nuclear medicine section at Sahlgrenska University Hospital, Gothenburg.

Exclusion criteria

Presence of signs indicative of major medical illness or mental disease in addition to Alzheimer's disease, history of inflammatory brain disease, multiple episodes of head trauma associated with sustained loss of consciousness, alcohol or drug abuse, concomitant therapy with CNS-active drugs that might markedly influence brain function were exclusion criteria.

Included patients

The five included patients scored 7-22 on the MMSE and were 54-70 years of age, based on the examinations before entry to the treatment study (base line data). The patients were four men and one woman, lived with their spouse, was Swedes, and had various education years.

The patients had various level of the committed impairment due to AD. The most common impairment was sensory aphasia, visuospatial disturbance and reduced orientation ability. The least common were apraxia, body perception deficits, and loss of power of initiative. The patients were included at different time of the study start year.

The participating spouses

In accordance to the spouses' willing to carry out a home based activation of the patients, an interview was performed including information about documentation of the in real time performance of the practical tasks and activities during the treatment year.

All 5 patients signed a consent form before participating in the treatment project after detailed oral and written information. They were also informed that they could interrupt the treatment at any stage. The relatives who agreed to participate in the training and evaluation of the patient received the information together with the patient, and were also asked to give their written consent. The study was approved by the Ethics Committee, Faculty of Medicine, Gothenburg University, and the Swedish Medical Products Agency.

The start of the one year treatments

The study start was for each patient set to the surgery day (start: Day 0).

All patients was at the study start fully supported by the research assistant from the psychiatric investigation ward at SU/Mölndal Hospital to the end of the surgery day at Sahlgrenska University Hospital, Gothenburg including the surgery aftercare days.

The surgery

Implantation of system for intraventricular ganglioside GM1 was conducted at Neurosurgery division, Sahlgrenska University Hospital. A brain surgery was used to install catheters in both lateral ventricles which were connected to a drug pump in the abdomen for continuous infusion of ganglioside GM1 into the brain.

A craniotomy, including two bore-holes was made and coordinates for the targets in the lateral ventricles were calculated for the localisation of the catheters. Common shunt catheters were implanted and connected to reservoirs which were further connected to the infusion system in the brain. The catheters were connected to a single extension catheter tunnelled under the skin to meet the extension catheter from the drug pump. This was implanted subcutaneous in a pouch in the left fossa iliaca. The programmable pump was a round metal disk about one inch thick (25 mm) and three inches in diameter, weights about six ounces (170 g). The drug pump was filled with 17 ml of ganglioside GM1. The solution used for safe drug was 60 mg/ml in isotonic phosphate-sodium chloride solution, pH 7,4 (Sygen [®])[164]. The initial dose of GM1 was set on the basis of previous rat experiment to 30 mg/24h.

The same neurosurgeon documented and carried out all neurosurgery and surgical treatment involved in the implantation of the infusion system as well as the included neurosurgery care at the psychiatric investigation ward at SU/Mölndal.

The refilling of ganglioside GM1 was subcutaneously timetabled once a month, 30 whole days (based on the rate of 0,5ml/24h). Accordingly there was 2ml of GM1 solution remained in the drug pump and the infusion was then interrupted. For safety reasons, the remaining solution was sent over time for bacteriological cultivation and for endotoxin determinations [162, 163, 164].

The home based programme

Around two weeks after the surgery of the infusion system the home based activation started gently. Daily activities, which were common in each patient's home, was used to an individually adjusting to the patient's need, wishes and field of interest. The patients were activated by the spouses who documented the performances. This was followed up and noted in the Daily Notes. The extended support for 2-4 hours by the research assistant was used to train and activate the patients and to instruct and inspire the spouses.

The Activity scale (constructed by I. Karlsson for this project) was used as an instrument to enable presentation of level of independence/dependency of the patients' performances according to score 0 (independent) - score 4 (cannot accomplish the activity or task). The scale was used by the spouses at home and by the research assistant. In a schema with name of tasks, date and assessment of the quality performances of their partner, the spouses hand over the documented performance at home to the research assistant.

Daily Notes were used to regularly record clinical observations and assessments of the patient's training, motivation and development by the research assistant. All contact between the patients, spouses and the research assistant was regularly documented and followed over time by use of Daily Notes.

Clinical examinations and assessments

An one-year timetable for each patient was used to follow the performed entry examinations (base line data) over time. When combination of examinations had the same day, the patient was inpatient on the psychiatric investigations ward at SU/Mölndal.

Laboratory examinations were used to establish any abnormality and conducted at the research clinic. The chemical and neurochemical laboratory examinations (by blood sample and lumbar puncture), which started before entry study, (see Base line above) were timetabled

from the surgery (Day 0) and on days 30, 90, 180, 270, and 360. Extra determination of CSF level of GM1 ganglioside was to be included if a disturbance of the GM1 infusion was suspected.

Clinical physical, psychiatric and neurological examination went on after the entry study (see base line data above) by the same observation of signs and symptoms associated with dementia following a schedule time tabled on the days 30, 60, 90, 180, and 360 to regularly evaluate disturbance.

The psychometric test was after the entry study time tabled on days 30, 90, 180, 360 and carried out before noon on two occasions with one night's rest between. These were used to assess cognitive functions and treatment response. The GBS scale [46] measure dementia symptoms and was used to examine changes in intellectual and emotional condition and impairment of motor performance (inactivities of daily living/ADL). The GBS scale was used before treatment and every 2nd week for the first 3 months and then every month during the treatment period at home visits or at our research centre.

The CGI scale was used to assess clinical global improvement and the UKU scale [54] to assess side-effect symptom, monthly documented by the research assistant and the psychiatrist.

The examination with SPECT rCBF was used to perform measurements of the blood flow before and immediately after the treatment period and conducted at Sahlgrenska University Hospital. Ten normal subjects with mean age 61 ± 14 (SD) served as controls. Reconstruction was performed as described by Larsson et al. [165] and relative quantification of the rCBF was conducted according to the maximum-minimum method [166].

All these examinations were carried out by the same neuropsychiatrist, psychiatrist, neuropsychologist, research assistant, radiological-imaging experts, during the two year ongoing first study.

Interviews with patients and relatives by an independent researcher were used to capture the experiences of the interviewees during the 1 year of treatment. The results from these interviews were to be use to compare with the research assistant's assessment.

3 .2 Subjects and methods in Paper II

Paper II was a treatment study, based on experiences from preliminary reports from our first study in Paper I, of ganglioside GM1 treatment complemented by a comprehensive training programme.

Procedures before inclusion of the patients

The patients had classical AD based on the NINCDS-ADRDA criteria for probable AD [34, 16]. They were referred to the research team at SU/Mölndal from general practitioners or other specialists nearby the research centre.

Before entry (base line), each patient underwent a physical, neurological and psychiatric evaluation, neuropsychological tests, rating with the GBS scale, clinical chemical and neurochemical examinations, computerized tomography (CT) and/or MRI (magnetic resonance imaging) scans, SPECT to assess rCBF (regional cerebral blood flow) in CSF, and an electroencephalography (EEG) examination.

N*europsychiatric* examination by a STEP protocol was used to evaluate disturbance of mood, emotional function, psychotic or paranoid symptoms, symptoms of delirium, and symptoms related to the frontal lobe [36]. This was together with a neurological examination. A neuropsychiatrist and a psychiatrist carried out the neurological, psychiatric and physical examinations.

The same set of *neuropsychometric tests* as in the Paper I was used to assess the patient's baseline cognitive functions and was carried out by a neuropsychologist. These tests comprised MMSE, Fuld's Object memory evaluation, Similarities and Digit Span, Face recognition test and Alzheimer's Disease Assessment Scale (ADAS) assessments [38, 39, 40, 41, 42]. The GBS scale was used to measure dementia symptom and assessed by the research nurse.

Clinical chemical examinations included complete haematological status, electrolytes, kidney, liver and thyroid function tests, vitamin B_{12} and folate levels. Clinical neurochemical tests included measurement of proteins in serum and CSF. As common decreased monoamine metabolites in AD, homovanillic acid (HVA), 5-HIAA, and HMPG, and of somatostatin in CSF as well as CSF cytology was evaluated as described in Paper I [158, 159, 160].

GM1 levels in CSF were measured by means of resorcinol method [102]. Antiganglioside IgG and IgM antibodies were determined with an ELISA [162] with the following glycospingolipid antigens with 'GM1 epitopes': GM1, GA1, GD1a, and GD1b. The laboratory examinations were analysed at clinical chemistry and clinical neurochemistry laboratory, Department of Neurochemistry, SU/Mölndal.

Exclusion criteria. Presence of signs of major medical illness or mental illness in addition to AD, history of inflammatory brain disease, multiple episodes of head trauma, alcohol or drug abuse, or concomitant therapy with CNS-active drugs that might markedly influence brain function were exclusion criteria.

Entry criteria. The entry criteria were based on the base line examination. The age was set to 50-70 years; the dementia to be mild to moderate dementia (a score of 4 on items measuring intellectual impairment in the GBS scale [46]; the Mini Mental State Examination (MMSE)[42] score to be of 15-25 (preferable closer to 25), and to have at least one relative willing to and capable of evaluating the effect of the treatment.

Included patients

The five included patients (Patient1 - Patient 5) were 54-70 years of age, were four women and one man. The duration of symptoms was 3 - 7 years. The MRI plus CT examination showed for Patient 1, 2, 5 that they had brain atrophy, Patient 4 had widening of lateral ventricles, and Patient 3 had no abnormal findings. Neurological symptom was shown in two patients of whom one had rigidity and subclonus, one patent had gait disturbance with hypokinesia. The MMSE scored 22 - 24.

Before start of the comprehensive training programme, complemented to the GM1 treatment, a home visit was provided by the instructor. This contact with the spouses and the patients was used to give information about this training treatment carried out at a nearby apartment.

The patients lived nearby the research centre, had been married for many years, and were Swedes. The duration of the treatment was one year for each patient, who started at different times during the four years study period.

All patients and their spouses signed consent forms after obtaining detailed oral and/or written information about the treatment. They were informed that they could interrupt the treatment at

any time. The study was approved by the Ethics Committee, Faculty of Medicine, Göteborg University, and the Swedish Medical Products Agency.

The study start

The start of the treatment was set to the surgery day (Day 0). All patients were fully supported by the research assistant from the psychiatric investigation ward at SU/Mölndal to the end of the surgery day at the Neurosurgery ward at Sahlgrenska University Hospital.

The surgery

The surgery procedure was the same as in Paper I. All surgery in the implantation of the infusion system, from a craniotomy to connection with the outflow catheter of the drug pump, was carried out by the same neurosurgeon. This included neurosurgery aftercare, at the psychiatric investigation ward at SU/Mölndal.

The dose of GM1 was set to 30 mg/24 h. When 2ml of GM1 solution remained in the drug pump the infusion was interrupted. For safety reasons, the remaining solution was sent for bacteriological cultivation and for endotoxins determinations [162, 163, 164]. The refilling of ganglioside GM1 was subcutaneously by the same psychiatrist, timetabled to be once a month.

Clinical examinations and assessments

A one-year timetable for each patient was used to follow the entry (base line) examination data during the treatment.

On the day of surgery (Day 0), and on Days 30, 90, 180, 270 and 365 the chemical-, neurochemical laboratory examinations and the neuropsychological assessment were carried out. The clinical chemical and neurochemical laboratory examinations were performed to establish any abnormality. Extra measurement of GM1 levels in CSF was to be on days if a disturbance of the GM1 infusion was suspected. To collect CSF the patients were subjected to lumbar puncture. The neuropsychological examinations assessed cognitive functions and the treatment response over time was carried out before noon on 2 consecutive days by the neuropsychologist.

In combination with these examination and assessments also the neuropsychiatric and psychiatric examination were carried out by the neuropsychiatrist and psychiatrist. Semi-structural neuropsychiatric examinations were used to evaluate disturbances of mood,

emotional function, psychotic or paranoid symptoms, symptoms of delirium, symptoms related to the frontal lobe and a neurological examination [36].

The GBS scale [46] was used to examine intellectual and emotional dysfunction and activities of daily living (impairment of motor performance) before treatment and every second week for the first 3 months and then every month during the treatment by the research nurse. The CGI scale [53] was used to assess clinical global improvement and the UKU scale [54] to assess side-effect symptom, monthly documented by the research nurse and the psychiatrist.

When combination of examinations had to be performed the same day, the patients were inpatients on the psychiatric investigations ward at SU/Mölndal.

The assessment of brain with CT and/or, MRI was done before the study start (base line) and after the one year treatment period to analyse tissue changes. Blood flow, rCBF, was measured with SPECT before and immediately after the one year treatment, conducted at Sahlgrenska University Hospital and data described by experienced appraisers. Ten normal subjects with mean age 61 ± 14 (SD) served as controls. Reconstruction was performed as described by Larsson et al. [165] and relative quantification of the rCBF was conducted according to the maximum-minimum method described by us [166].

All examinations were carried out by the same neuropsychiatrist, neuropsychologist, radiologist, and research nurse during the ongoing four years of the treatment study.

The training programme to assist GM1 treatment

A new developed careful designed programme with Stimulation, Activation and Training (SAT programme), was used to maximizing the use of the patients' identified areas of function and processes that are relatively unimpaired [167]. Cognitive, social and physical activities similar as performed within common daily living were used to be carried out twice a week for 4-5 h/day in an apartment with familiar furniture, objects and material (for details see Paper III).

3 .3 Subjects and methods in Paper III

Paper III described and evaluated a study, a new 12-month training programme, called the

Stimulation-Activation-Training (SAT) programme. It was developed within a dementia care nursing, to be a combined therapeutic treatment for patients with early-onset mild to moderate AD, and to be used when the patients underwent a drug treatment with intracerebroventricular infusion via an implanted infusion system.

The study participants

The patients were the same as in Paper II. They were 54-70 years of age, the duration of symptoms was 3 - 7 years and the MMSE scored 22 - 24. One Patient had rigidity subclonus and another Patient had gait disturbance with hypokinesia. They all had regional cerebral blood flow reduction, three Patients had brain atrophy, one Patient had widening of lateral ventricles, and one Patient had no abnormal findings in the imaging examinations.

The patients, four women and one man, had been married for many years, and lived within a near area of the apartment in which the SAT programme was conducted. They started at different time of the four years ongoing study.

Before participating in the study, all the patients and their spouses signed a consent form after detailed oral and written information about the treatment. The duration of the combined treatment was one year for each patient. The project was approved by the Ethics Committee, Faculty of Medicine, Göteborg University, and the Swedish Medical Products Agency.

The therapeutic treatment

The programme with timetabled cognitive, social and physical activities with stimulation, activation and training (SAT) procedures was used to treat patients with early onset, mild to moderate AD.

A home visit was used before and about two weeks after the conduction of the neurosurgery due to the drug treatment, to supply information about real time home situation conditions. It was also used to give the participants a forward look at the timetabled training day for 4-5 h/twice a week during one year. The start of the training programme with the five native-born Swede patients was set to about two weeks after the neurosurgery.

The milieu and framework of the training programme

A three room homelike, dynamic setting was used to attract the patients to encounter the training surroundings as recommend by Barris et al. [152]. One of the rooms was equipped as

a relaxing room and another as a working room to get privacy and autonomy as stated by Kahana [153]. A step by step demand was used to analysis the tasks/activity performance to correspondence to the patient's real time performance capability [154].

The theory. The focus of the activities in the SAT programme is based on a nursing theory [147] to assist and validate individuals and families to cope with and understand their experience of illness. Communication was used as a process to enable a human-to-human relationship. Continuously dialogue of the contents and results of the training was used to inform the patients and relatives.

The aim. To optimise the patients' best-preserved functions and abilities from their perspective, as regards their quality of everyday life, was the aim to be used in the SAT programme.

The principal strategy: to get the patients to overcome disablement caused by impairment, activity limitations and participation restrictions, was used to plan and design individuality.

The scheduled time for the patients' performance of each activity, 30-60 minutes including breaks, was used to fit a patient group of mostly two patients and the instructor (a RN) and to avoid risk of cumulative stress. A limit of two cognitive activities that can succeed each other was used to give a balance between social and physical training.

The procedures of Stimulation - Activation - Training

For stimulation the verbal and non verbal communication was by the instructor used to:

- maintain the establishing reciprocal relationship during the treatment year;

- repeatedly encouraging patients including to try the use of aids/support;

- awaiting their spontaneous choices and own proposal;

- informing of or actively showing alternative ways of its performance;

- asking for patient's opinions about how a given task should be performed.

For activation all activities making patients actively and passively to take part in activities in a rational way was used to be an act towards achieving the purpose, held by the professional nurse practitioner instructor.

For training, related to AD, was used:

- cognitive support: given both when the patients took in what a certain task involve and

  when they related their experience of the task;

- systematic training: a task was repeatedly performed in the same way and each operation

  had to be completed before next one started;

- continuous plan of action with partial or final goals;

- tests of limitations of individual's optimum capacity to perform and participate in various

  activities while influenced by contextual factors;

  within the process of learning.

The cognitive, social, and physical training

The same activity at the beginning and the same activity at end of the day were used to form a habit of recognition. The different activities and tasks in the SAT programme were interlaced to imitate real time performances at daily life at home.

The cognitive training

Systematic performance of exercises and strategies was used to overcome disablements and to reduce individual difficulties due to AD. Different tool and distinct feature was used as one of the key pathways to assist in developing independent functions. The patient's intact motor skill was utilized to facilitate learning and handle functions of objects.

The orientation sessions involved use of the patient's intact motor skill, ability of visual perception of distinctive features, step by step task-demand analysis, and the instructor being at meeting place until the goal was reach. During all outdoor training, the instructor was in the view of the patients.

The laying table exercises involved use of the patient's spatial and stereognostic ability (the combined use of vision and perceiving and recognizing abilities).

A new tool, a computer with installed language exercises and a printer, was used: to teach the patients to use a new tool; to activate the patient's ability to use required attention, concentration; to use their simultaneous capacity and procedural memory.

Double support at the managing was used to start the teaching of the computer system step by step until the exercises were carried out by the patient's themselves at their own path.

The keyboard was used to writing exercises and the computer program was used to activate the patient's vocabulary. The printer was used to print out their keyboard exercises of different individual decided productions.

In language sessions, oral and writing expression was used to utilize the patient's ability to express themselves. Conversation practice was used to call attention to what had been said. Reading comprehension was facilitated by not asking details of the text. The patients' semantic ability was activated by word-exercises, available both on paper and as computer exercises. Relating the content of read text was used to train working memory.

Guidance in form of tear-off wall calendar was used to make the patients aware of time.

The social training

Conversation sessions with allotted time, was used to get the patients accustomed to participate, start and be active in exchanges of ideas. Allotted time was used to get each patient reasonable time to find words and to interpret what was said.

The household activity was intended to teach the patients all the different tasks involved in a meal in daily life. Systematic training (see above) and step-by-step strategies as well as old habits were used to overcome activity limitations and participation restrictions due to AD.

Dancing, singing, listen to music, watching TV or invite their families to coffee was used to making the patients happy in social togetherness within the quality of everyday life. Instruction was used to make the patient to decide themselves what kind of close social interaction they wanted.

Visit to public places was used to a form of relaxation after two laborious cognitive activities.

The physical training

Walks were regularly used in order to make daily exercise a habit and improve muscle-power functions. A cycle exercises was used as an alternative.

Relaxation in form of muscle relaxation is used to reduce the patients' basic tension. Instructions to be followed on a tape were used to provide five minutes progressive muscular relaxation with the instructor present at the beginning of the exercise.

Tactile ball massage for three minutes was used to strengthen the signals of the patients' sensory receptors and improve the patients' ability to observe and be aware of their body.

The relaxation activities were carried out only at a patient's request during the treatment year.

Table 2. Overview of the contents of the SAT program

Cognitive training	Social training	Physical training
Memory	Conversation	Motor function
learning of new material	experiences	walks
reporting	requests	cycle exerciser
time orientation		
Vision, sensation, perception	Household activities	Relaxation
orientation in the surroundings	shopping	rest
laying-table strategy	cooking	relaxation exercise
reading strategy		tactile ball massage
Language	Social interaction	
usage (pragmatic)	dance music/singing	
content (semantic)	visits to public places	

Assessment instruments

The GBS scale, [46], was used to follow the functional state and symptom during each patient's treatment year with 15 ratings. The rating was carried out before treatment, every second week for the first three months and then monthly during the treatment by the research nurse. The GBS scale has three subscales which measure intellectual impairments (GBS-I with 11 items), emotional impairment (GBS-E with 3 items), motor performance (GBS-M with 6 items), and the symptoms characteristic of dementia (GBS-S with 6 items) [47, 49].

The BAS scale. The bodily symptoms of mental disorders were assessed about every third month on the Body Awareness Scale (BAS) by means of observations during movement tests, which consisted of 37 items [44]. BAS gives important information on the patient's experience of his own body and observations concerning his body management and movement pattern. The evaluator had to be educated in the scale which is reliability and interrater reliability tested [44, 45]. The same physiotherapist carried out all the examinations.

The Aphasia test, the NGA. The language development was observed about every third month by using the Swedish translation of Reinvang's **N**orsk **G**runntest for **A**phasia (NGA)[43]. The Aphasia test is a rating of quality of spontaneous speech and comprehension, repetition, naming, reading, and writing. The Aphasia test is reliability and validity tested. The evaluator had to be educated in the scale [43]. The same speech therapist carried out the examinations.

The Activity scale. All forms of activities were documented in four steps from score 0 "independent performance" to score 4 "not being able to perform the activity". The scale was developed for our studies of AD in Study I, II, III, and V in this thesis [unpublished].

Daily Notes. All documentation was recorded by the research nurse to verify continuous various outcomes and nursing care, during the treatment year of each patient.

3 .4 Subjects and methods in Paper IV

In Paper IV an evaluation form, the Clinical Global Impression, was given to five spouses to patients with early onset mild to moderate AD. On the CGI form an extra space was made for voluntary comments, which constitute the date in this study.

The participants

The spouses were gathered from Study II in which they had been judged willing to and capable of evaluating the effect of the treatment. In that study their husband/wife underwent a one year drug treatment combined with a SAT programme performed 4-5/h, twice a week in a training apartment. The spouses started their one year participating at different time of the four ongoing years.

The evaluation form

The professional person (a RN) at the training apartment monthly handed the CGI form over to the spouses, who, after filling in the form at home, returned it to the nurse in the training apartment. The instructions to the spouses were that the filling in comments was voluntary and also on the form:"The evaluation is valid from the preceding evaluation until today".

A total of 60 evaluation forms (12 forms/per spouse) with extra space for voluntary comments was collected from the five spouses. Seven forms contained no comments. Thus the data consisted of 53 different forms with comments from five spouses. It is the 277 comments on the 53 different forms that constituted the data in this study.

The analysis

The comments were analysed by means of content analysis [168, 169]. The analysis of the content of the comments was performed in four steps.

In the first step, the comments were read and reread several times to obtain an overall picture of the written material. Words, statements, and events, dealing with the related content were grouped into themes, temporarily named according to the content. The analysis continued with reflections on words, statements and events of belonging in existing themes and relevance to the purpose of the study. Any additional units were added to the different themes or, if necessary, further themes formed.

The second step was to establish the themes. Eight preliminary themes emerged from the data and after an inventory a total of four themes were finally established. These themes were named according to their content. It was found that certain areas had more in common with

each other. These areas were called sub themes and were assigned headings based on their content.

In the third step, the analysis was supplemented by a frequency pattern. The frequency of each theme, and each subtheme, was marked for each participant and the sums of the theme groupings were added together to form a total for the whole year.

The fourth step, the interrater reliability was estimated by means of an independent co-examiner [169]. After the independent operation, the examiner and the co-examiner arrived at a consensus as regards the main themes and subthemes by discussing and reflecting on the research question.

3 .5 Subjects and methods in Paper V

In Paper V the Norwegian Basic Aphasia Assessment "**N**orsk **G**runntest for **A**fasi " (**NGA**) was used to examine linguistic development of patients with AD at baseline and over time. This was done when they, during systematically performances of language activities participating one year in a stimulation-activation-training (SAT) programme. The SAT was a therapeutic treatment which was combined to an intracerebroventricular treatment with GM1.

The patients

The patients had early onset form of AD [16, 34], they were 54-69 (m=64) years of age, mild to moderate dementia with intellectual impairment specified as maximum score of 4 on the GBS scale, and a score of 22-24 out of 30 on the MMSE [42, 46]. Education years were 7-10 and two patients had supplementary education. The patients were native Swedish-speaking people, lived at home with a Swedish spouse and started their participating at different time of the four ongoing years of the SAT.

Before participating in the SAT programme study (Paper III), all the patients and their spouses signed a consent form after obtaining detailed oral and written information about the treatment.

The setting and the training

The performances took place in a rented apartment. It had a kitchen, a dayroom, a relax room and a workroom, all looking homelike. The training was carried out by two patients and the

instructor (a RN) for 4-5 hours, twice a week during 12 months for each patient. Each activity, including a break, was scheduled to take 30-60 minutes. The aim of SAT is to optimize the functions and abilities that are important in patients' everyday life [79].

The lots of language performances were parts of the everyday activities in the SAT programme. This comprised language sessions in the cognitive training (which also had memory- and orientation sessions); included regularly held conversation sessions in the social training (which also had housekeeping and social interaction); and the SAT programme encompassed physical training with motor function and relaxation sessions.

The cognitive activities that could succeed each other were limit to two, to balance the cognitive and physical training.

The language activities in the cognitive training

The language activities were used to deal with the usage (pragmatic understanding) and content (semantic understanding) of words and phrases in reading and writing session. To carry out these language activities a personal computer system (new tools for all patients) e.g. a computer, a keyboard, a mouse and a printer was used. Selected mixed 37 exercises, installed and displayed one at a time on the computer screen, was used to activate the patient's vocabulary, which might make them recall previously acquired knowledge of words, the content - semantic ability. The results chart in the computer and same instructions for each exercise was used to standardize the test situation. The short program exercises were used to match the exercises described on paper.

To activate the patients' vocabulary; word comprehension; and understanding of the content of the texts, there were use of paper which had objects and text with one or more questions on the same paper. The answer was given orally or written by hand.

A reading strategy in form of an eye-moving technique was used for patients who had eye problem when following lines in the text e.g. in news paper.

In writing sessions, the keyboard, pen or pencil was used. Keyboard productions were message to someone; timetables of the examinations, various personal notes e.g. telephone numbers with big digits, letters and English words, and family agendas. Support in spelling and word finding was provided by the instructor. Handwriting was used to put their names on sheets, to note down their performances during the day in their pocket diaries, and to enter

personal memos in their binders. The instructor supported, if necessary, the patients in spelling and word finding.

The language activities in the social training

Regularly held conversation sessions to utilize each patient's own vocabulary and counting (mostly used at shopping for lunch in housekeeping) were used to take part in social training.

The conversation sessions were regularly held to form a routine, habit. The sessions were held for 30 up to 60 minutes at start and for a maximum 30 minutes at the end of the day and both the patients and the instructor participated. The subjects of conversation was decided by the patients e.g. own experiences, their proposal of lunch or requests of specific exercise or task to utilize each patient's own vocabulary. Allotted time for all participants was used to give the patients time to find words, to focus on *what* are said and not who said it.

Common general-knowledge words in everyday talk were used to making creative use of: what was left of their previously acquired richness of vocabulary; their knowledge or feelings of knowledge of a topic; and their existing semantic lexicon.

The talking about the same subject of all three participants was used to avoid misunderstanding, which must be semantically relevant. That is because of the connection between question and answer.

Support in word finding, if necessary, was used by the instructor to keep the informativeness high and included the use of eye contact with the patients.

The assessment of the linguistic development

The NGA assessment is a Norwegian standardized test, based on patients with aphasia, for measuring degree and type of aphasic impairment. The test measures fluency, comprehension, repetition, naming, reading and writing. The sum of the total score of the main variables yields the aphasia coefficient, which is a measure of the severity of language impairment. NGA was supplemented with a selected narrative with a good point (length 89 words).

A detailed description of NGA, including its rational, reliability, validity and origins is given by Reinvang [43]. The same speech language pathologist, educated in NGA assessment,

carried out all the assessments at her office. The patients were generally examined on five occasions. The NGA is general used by speech language pathologist [170].

In the present study, the pre-test (at start) and post-test (at 12 months) results was shown.

4 ETHICAL CONSIDERATIONS

Research on persons with diminished judgement ability is ethical problematic and therefore it can be argued that studies should not be made on persons with dementia. However, if dementia is excluded from medical studies, no progress in the treatment could be made. Ethical analyses and ethical restriction have been discussed on this issue [171, 172]. Following the recommendations of the World Medical Association Declaration of Helsinki [173] all patients signed a consent form after detailed oral and written information before participating in the treatment project. They were also informed that they could interrupt the treatment at any stage. The relatives received the information together with the patient, and were also asked to give their written consent.

In addition the degree of dementia according to the GBS scale was to be scored at most 4 on items measuring intellectual impairment, to make it possible for the patients to understand and to give a well-based consent to the study.

In Study III, the caregivers got supplied information of the stimulation-activation-training (SAT) programme information, to help them understand the strategy of the treatment. Further, the content and result of the training were continuously discussed with the patients and relatives, either individually or together at the beginning or end of the day.

In Study IV the spouses are named spouse 1 to 5 to ensure confidentiality and in Study V all the patients are referred to as "she", to give anonymity.

The study was approved by the Ethics Committee, Faculty of Medicine, University of Gothenburg, and the Swedish Medical Products Agency.

5 RESULTS

5 .1 Paper I

In Paper I, the first study, it was evident that there was a need of complex and extensive following ups during the treatment year. There was especially a need to determine the therapeutic dose of GM1, as it was hitherto unknown, and also to follow the performance of the combined home based activation.

The ganglioside dose

The start dose of GM1 during the first three months was 30mg/24 h according to Patient 1. This dose was reduced to 10mg/24 h, however, it was evident that the patient´s function deteriorated. The dose was then changed to 50mg/24h to compensate the low dose. After a few days the Patient 1 developed symptoms of delirium with signs of disorientation and headache. The dose was then reduced to 20 mg/24h and the symptoms of delirium vanished. For Patient 1, a dose of 20 mg GM1/24 therefore appeared optimal.

All four of the subsequent Patients (Patient 2 - Patient 5) received an initial dose of 30 mg GM1/24 h. The dose was reduced to 20 mg/24h, if they showed signs of delirium.

The pre-treatment level of GM1 in lumbar CSF was 11 – 45 nmol/l and in the brain ventricular CSF 10-26 nmol/l.

The steady-state level of GM1 on daily dose of 30 mg/24h was 40-50 µ mol/l, on daily dose on 20 mg/24 h was 18-22 µmol/l; on daily dose on 10 mg/24 h was 5-8 µmol/l.

This means that in lumbar CSF the GM1 concentration rose approximately 1,000 times when the patient received 30 mg GM1/24h.

Adverse events

The following major adverse events occurred:

Patient 2 showed after three months a sign of mild meningitis, which ceased without any treatment. On day 250, the Patient fell and the head was hit. The break in the connection between catheters and pump was not detected until 40 days later.

Patient 3 did not receive adequate GM1 therapy during the first 5 months due to three adverse advents. A break of the connections between catheters and pump was diagnosed on day 30, a subdural hematoma diagnosed on day 47 and evacuated, and a new break was diagnosed on day 90. This had probably occurred a month earlier. It was not possible to reconnect the catheters with the pump until day 152.

Patient 5 had postoperative CSF leakage, which caused moderate pneumocephalus leading to extra-cerebral effusion. This had to be removed via a burrhole and drainage. On day 80, at a routine CT control, bilateral subdural hematoma was found and subsequently evacuated.

The analyses of brain scan and laboratory examinations

The blood flow were analysed with rCBF examinations. These showed at start significantly lower rCBF in the temporoparietal regions in comparison to age matched controls. Further significant reductions were found in the hippocampal, lateral temporal and basal frontal gray matter regions, in comparison to the control persons. No significant changes were seen in the rCBF during the treatment period.

The initial low values for HVA increased significantly in all patients between days 0 and 360, except for Patient 1. Somatostatin increased, especially in Patients 3 and 4.

The analysis of blood chemistry, haematology and urine analysis showed no abnormality at measured during the one year. Two of the patients had slightly increased CSF/serum albumin ratios before treatment, which remained elevated during the whole treatment period. None of the patients had increased antiglycolipid IgG or IgM antibody titers before the treatment. The titers remained low for all antigens tested during the whole treatment period.

Neuropsychological examinations

The neuropsychological assessments (Fuld sum 5 trials, Digit Span, Similarities and Face identity) are summarized in a total score as the patients' cognitive ability. The assessment of *Patient 1, 2 and 4* showed a score indicating improvement of the assessed items on day 90 as compared with the measurement before treatment.

On *Patient 1* and *Patient 2*, the sum of the cognitive scores was increased on day 360 compared with the measurement before treatment, indicating improved ability, ADAS and GBS showed a similar picture.

Patient 4 performances of tests of cognitive ability and of MMSE are missing on day 360.

The level in MMSE showed no increasing values of the five patients at Day 360.

The GBS ratings of intellectual functions for Patient 1 showed continuous decreased score, indicating improvement of the rated items during the whole study period. Assessment scores of Patient 2 and Patient 4 indicate some improve of these performances between days 30 and 360. Patient 3 did not show any change. Patient 5 scores indicated a decline on day 360.

The home based activation

The documentation by the spouses of their partner's performed activities showed less frequently occasions at the end of the year compared at the start of the study. The documentation in the Daily Notes, by the research assistant, showed increase of amount of supply directed to activate the patients as requested by the spouses and the patients. The general impression of the relatives, according to the Daily Notes, was that all 5 Patients showed some improvement. Three of the patients gained weight, while the remaining two showed unchanged weight.

5 .2 Paper II

In the ganglioside GM1 treatment study all patients received an initial dose of 30 mg of GM1/24 h. This dose was based on the preliminary data from the first study (Paper I) of the patients' reaction on the doses given.

The ganglioside doses

Before treatment in the study, the level of GM1 in ventricular CSF and lumbar CSF in this study was varied from 16 to 32 nmol/l.

Treatment with 30mg of GM1/24h increased the concentration about 2,000 times in *lumbar* CSF. The steady-state level of GM1 on this dose varied between 40,000 (means 40 µmole) and 60,000 nmol/l (means 60 µmole).

The concentrations of the other major gangliosides, GD1a and GD1b, did not change significantly during the treatment, thus they were not influenced by the increased level of GM1. Patient 1 had a dose of 30 mg; between days 165 – 210 there was an interruption of the treatment.

Patient 2 showed a slight overactivity after only 2 months of treatment. The CSF GM1 level was over 50,000nmol/l. As this Patient had mild depression at entered the study, this overactivity was regarded as positive, and the dose was not lowered to dose 20mg/24h until the Patient showed signs of delirium on Day 240.

Patient 3 had a dose of 30 mg/day.

Patient 4 had a CSF GM1 level of over 57,000 nmol/l by Day 30, and when signs of delirium was shown by Day 50, the dose were lowered to 20 mg/24 h. The power of initiative based on the spouses observations, gradually diminished why the dose was increased to 25mg/24 h.

Patient 5 had a dose of 30 mg/day.

In this study the GM1 doses variations were: from 30 mg-25-20 mg/24h, which showed a marked narrow therapeutic interval.

The pump was not functioning properly for about 50 days in Patient 1, and the estimation showed that the patient did not receive any GM1 from Day 165 to Day 210. During this period GM1 level dropped from 40,000 to 280 nmol/l, which indicates an interruption in the GM1 treatment.

The change of CSF transmitter metabolites

The CSF sample, which was taken about 25 days after the pump of Patient 1was not working, showed decreased HVA levels and even more marked decrease in the CSF somatostatin concentration. These levels increased when GM1 was re-administrated. This gave ability to evaluate the effect of SAT training without GM1 treatment, which suggests an effect of the GM1 treatment on the concentrations of CSF HVA and somatostatin.

 HVA: The CSF concentration of HVA, the major metabolite of dopamine, was within the normal ranges for healthy persons at start in Patient 1. Values for HVA increased significantly during treatment in Patients 1, 2, 3 and 5 by day 90. The effect of GM1 on dopamine thus remained during the study. **5-HIAA:**The initial CSF concentrations of 5-HIAA, the major metabolite of serotonin, values were low in patients 3, 4 and 5, compared with the normal ranges for healthy persons, and increased during treatment in all patients except Patient 4. **HMPG:** The CSF concentration of the noradrenaline metabolite HMPG was within the

normal ranges for healthy persons and did not change with treatment. **Somatostatin** levels were low in all patients before treatment but increased rapidly after start of the treatment.

Analyses of brain scan and laboratory examinations

The 5 patients had significantly lower rCBF in the basal frontal, frontal association and temporoparietal regions as well as white matter parietal and semi-ovale center regions (p<0.01), indicating reduced blood flow in these areas. Less significant reduction were recorded in the hippocampus, mesencephalon, gyrus singuli, motor cortex, parietal association cortex and frontal white matter (p<0.05). Although the relative blood flow was higher in many regions in four of the five patients after treatment for 1 year, the changes were not significant.

No abnormality was noted in blood chemistry, haematology or urine analysis measured every 3 months. Lumbar CSF cytology, CSF albumin, IgG, and IgM were normal in all samples. Samples of lumbar CSF were taken every 3rd month, except for Patient 3, why these measuring results are missing on Day 180 and Day 270. In serum, none of the patients had increased anti-GM1 or anti-GM1 epitope carrying IgG or IgM reactivity. Bacterial culture and endotoxin determinations of the pump content at each refilling were negative.

Clinical symptoms of the patients

None of the patients showed symptoms of emotional disturbance, psychosis or paranoia. The treatment of Patient 3 with citaloprame (Cipramil®) was continued as before the entry of the study. She showed no symptoms of depression during the study period.

Patient 1 and Patient 4 had mild extrapyramidal symptoms at start of the study which disappeared within the first month.

Neuropsychological examinations

The majority of items in the five patients showed no certain trend. In these items all five patients showed:

- improvement of intellectual functions, according to the GBS scale

- improvement of assessment of prosopagnosia (face identity).

- unchanged score of tactile agnosia (according to Fuld's object memory test).

- kept the same score at assessment of emotional lability, emotional function and of stress

tolerance according to the GBS scale, during the treatment year.

Table 3. Function and/or symptom and neuropsychological tests of 5 Alzheimer patients

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	0	365	0	365	0	365	0	365	0	365
Short-term memory impairment										
(recent memory, item I 4, G scale)	4	3 (+)	4	4 (u)	4	3 (+)	2	2 (u)	3	3(u)
Long-term memory impairment										
(distant memory, item I 5, G scale)	4	2 (+)	2	2 (u)	1	2 (–)	2	2 (u)	2	2 (u)
Personality change										
Emotional function, item E 1, G scale	1	0 (+)	0	0 (u)	0	0 (u)	0	0 (u)	1	0 (+)
Emotional lability, item E 2, G scale	0	0 (u)	0	0 (u)	0	0 (u)	0	0 (u)	0	0 (u)
Emotional function, item E 3, G scale	0	0 (u)	0	0 (u)	0	0 (u)	0	0 (u)	0	0 (u)
Stress tolerance										
(inability to increase tempo, item I 8, G scale)	2	2 (u)	2	2 (u)	3	1 (+)	3	2 (+)	2	2 (u)
Disturbance of consciousness										
(confusion + clinical observation)	1	0 (+)	1	1 (u)	1	1 (u)	1	1 (u)	0	1 (–)
Abstract thinking (similarities)	10	20 (+)	2	6 (+)	8	8 (u)	19	20 (+)	9	12 (+)
Dyscalculia (arithmetic test)	10	8 (–)	8	10 (+)	9	5 (–)	8	7 (–)	5	4 (–)
Sensoric aphasia (ADAS, item 10)	0	0 (u)	0	1 (–)	0	0 (+)	0	0 (u)	0	0 (u)
Episodic memory										
(Fuld's object mem test, tot numb recall, 5 trials)	18	23 (+)	18	20 (+)	13	13 (+)	26	35 (+)	22	20 (–)
Attention (Trailmaking test – part A)	62 s	53 s(+)	39 s	65 s(–)	65 s	95 s(–)	n.t.	305 s(+)	45 s	48 s(–)
Capacity of simultaneous thinking										
(Trailmaking test – part B)	210	235 s(–)	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
Motor aphasia (ADAS, item 9)	1	0(+)	1	1 (u)	2	3(–)	1	1(u)	0	1(–)
Tactile agnosia										
(Fuld's object memory test)	10	10 (u)	10	10 (u)	10	10 (u)	10	10 (u)	10	10 (u)
Prosopagnosia (face identity)	44	57(+)	30	33 (+)	34	35 (+)	31	48 (+)	44	54 (+)
Visuospatial inability										
(Koh's block test)	3	12 (+)	7	8 (+)	0	0 (u)	0	0 (u)	9	6 (–)
Executive functions (ADAS)	0	0 (u)	0	0 (u)	2	3 (–)	2	3 (–)	2	0 (+)
MMSE	22	27 (+)	24	24 (u)	23	18 (–)	23	23 (u)	24	24 (u)
Intellectual functions (G scale)	17	10 (+)	14	13 (+)	19	11 (+)	15	9 (+)	17	9 (+)

Similarities, dyscalculia, Fuld's tests and MMSE [7]: increasing values = improvement (+); (ADAS) [7] and G scale [10]: increasing values = impairment (–); u = unchanged; n.t. = not testable; I = intellectual scale; E = emotional scale.

5 .3 Paper III

The implementation of the content of the SAT program was unquestionably gradually in real time of all performances and caring out with active participating of the patients as shown in the results. No drops out, no sign of cumulative stress was in the results, all tools was used within the SAT programme, and performance goal of all activities during the one year treatment were reaching.

The results on the Activity scale, developed for the combined treatment of patients with early onset AD, showed that all the patients, after a maximum of nine months, had learned to perform a series of all tasks associated with a complex household activity. These comprised eleven tasks from planning a meal to put item back where they belong. These tasks are e.g. plan the meal, write a shopping-list, all tasks involved in shopping, finding the way to and from the shop, cooking, laying the table, and to wash up and put the back the items to their belonging.

The Patients active participating

Making favourite choice:

- four of the five patients chosen singing rather than dancing of the activities in

interaction. One patient did not choose either of these activities.

- all five patients within the free choice activities chose computer programs and writing on

   the keyboard.

- resting in bed was the most common choice of the relaxation activity.

This active participating showed that all patients had learnt to use new tools, a computer with a keyboard, and a printer.

It was also shown that all patients learnt to use a computer programme with its different exercises. Further, the computer chart showed that all five patients did not choose six of the computer exercises which content had maths involvement.

Making requesting preference:

- the activity with instructions for progressive muscular relaxation was more frequently

  requested than tactile ball massage, seen as a group result.

An astonishing outcome was that the patient with severe visuospatial impairment, without assistance, extended his learning by finding the way to the bus stop and going by bus to and from home. The results of that the Patients brought with them material to copy on the computer for printing, CDs and a video cassette containing an amusing film, was an extension of choice to be used within the social relaxing activities.

The examinations with standardized instruments

The results based on examinations with standardized instruments unveil that all patients had shown features of increased maturity. This is based on to the speech therapist's examinations of linguistic performance by the NGA test and the physiotherapist's examinations of the patients' body management and movement pattern by the BAS scale.

Table 4. The change in values as assessed on GBS scale, BAS scale and in Aphasia test

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
The GBS scale					
Intellectual impairment: 11 items					
Max impairment score: **66** Baseline/6 months/12 months	17/11/10	14/14/13	19/14/11	15/11/9	17/12/ 9
The BAS scale					
Observations of symptom: **37**					
Number observations: Baseline/6 months/12 months	14/-/11	10/5/5	16/10/13	12/13/15	8/ 7/ 5
The Aphasia test					
Auditory comprehension					
Subtest: 8 Max score:**71** Baseline/6 months/12 months	71/-/71	✦70/71/71	69/69/69	71/71/71	70/71/71

GBS scale and BAS scale: **decreasing score = improvement**   Aphasia test: **increasing score= improvement** ✦ **Errata in the original**

However, some items did not show clear-cut results. The items in which they all patients reduced their scores of disabilities or kept the same score from the first rate at the last measurement became prominent. This outcome may indicate an improvement which was shown in movement function and movement behaviour assessed by the BAS scale and in auditory comprehension in the NGA test.

The rating with the GBS scale of the 11 items of intellectual impairment showed increased orientation ability in the items space (I:1) and in time (I:2) for all the patients as indicated in accordance of the scale. The GBS scale measured dementia symptoms and decreased score indicated that the Patients improve or had the same ability to perform the item in question, during the treatment year.

5 .4 Paper IV

Paper IV shows the analysis of spouses' depicted 277 *voluntary c*omments from 53 forms monthly filled in a form during one year.

Seven forms, mostly from the first six months, contained no comments due to the spouses claiming difficulty to make comments.

These *voluntary* comments were their views of the content of their jointly life at home and their focus when they made judgments.

These comments are collected in four themes with subgroups, respectively.

The results of the analysis are presented as an overview of frequencies and percentage of the four themes and subthemes and are shown in Table 5.

Table 5. Overview of frequencies and percentage of themes and subthemes

The spouses' view	Sum of the frequency and (%)	Frequency and (%) of each theme and subtheme of the five spouse's comments and the total sum				
Theme and *Subtheme*	of all comments of the spouses	Spouse 1 Male Years of Age 68	Spouse 2 Male Years of age 68	Spouse 3 Male Years of age 67	Spouse 4 Female Years of age 62	Spouse 5 Male Years of age 56
TOTAL a round sum of percentage	**(100%)**					
1. Spouse's view of the partner's activity.	**106 (38%)**	31 (39)	17 (34)	12 (48)	35 (40%)	11 (32%)
activity level		7	9	6	6	5
Housework		17	5	4	23	0
social activities		1	1	2	5	6
selected activities		6	2	0	1	0
2. Spouse's view of the partner's general health conditions and capabilities.	**83 (30%)**	25 (31%)	20 (40%)	4 (12%)	22 (25%)	12 (35%)
health, stress, mood		3, 1, 6	4, 1, 3	0, 0,1,	6, 4, 6	2, 0, 0
self-confidence, awareness		1, 0	1,1	1, 1	0, 1	4, 4
Orientation		3	3	0	4	1
memory function		11	7	1	1	1
3. Spouse's view of influence of the environment.	**15 (5%)**	3 (4%)	1 (2%)	1 (4%)	10 (11%)	0 (0%)
close relatives/friends' opinions		1	1	0	0	0
partner's experiences		2	0	1	10	0
4. Spouses' view of their own responses in relation to the partner.	**73 (26%)**	21 (26%)	12 (24%)	8 (36%)	21 (24%)	11 (32%)
at home, at work, to own health		5, 1, 1	0, 0, 0	1, 0, 0	5, 0, 1	4, 0, 0
behaviour with an obvious cause		3	3	2	4	2
emotional behaviour		3	0	5	10	3
behaviour relating to forgetfulness		8	9	0	1	2
SUM of frequency of each spouse		80	50	25	88	34
Number of CGI form with comments / total number		11 / 12	12 / 12	7 / 12	11 / 12	12 / 12

The original important comments from each theme are illustrated, collected from the spouses comments.

Overview of the original important comments

Spouse's view of the partner's activity showed the highest sum and frequency of the four themes. This theme has four subgroup and the dominating comments showed that all the Spouses focused mainly on *activities* and on *activity levels* performed in their daily life at home. They judged their partner's performance skills without commenting on demands for support or help from the partner.

The theme **Spouse's view of the partner's general health conditions and capabilities** has four subgroups. All Spouses judged the *memory function* in terms of "recent and /or distant memory", especially of patient 1 and patient 2.

The theme **Spouses' view of their own responses in relation to the partner** has four subgroups. In the subgroup *behaviour with obvious cause* showed that all spouses found these in related episodes, in which their partner's manners had an understandable cause.

The comments in the subgroup *behaviour relating to forgetfulness* were often referred to episodes as absent-mindedness and a problem with agreements, especially of Spouse 1 and Spouse 2.

Less frequency and sum was shown in the theme **Spouse's view of influence of the environment** which has two subgroups. The person mentioned was a daughter and good friends. In subgroup *partner's experiences* the comments by the Spouse 4 consisted more of utterances of negative feelings mostly that: "he thinks he can't manage things and I have so much to do" than positive.

5 .5 Paper V

In Paper V, the patients' linguistic development based on 12 months language training is

made by scoring of a standardized test, the NGA. It is also complemented by other assessment which including speech quality.

The results of the NGA assessments made by scoring are presented in Table 6.

Table 6. Degree of language functioning in five patients with mild or moderate AD at start of the study and at 12 months. The scores are the numbers of correct answers to set questions.

Variables	Subvariables	Patient 1 Start/12m	Patient 2 Start/12m	Patient 3 Start/12m	Patient 4 Start/12m	Patient 5 Start/12m
Auditory	Body parts, identify (0- 11)	11 / 11	11 / 11	11 / 11	11 / 11	10 / 11
Compre-hension	Body actions (0-10)	10 / 10	9 / 10	10 / 10	10 / 10	10 / 10
	Objects, actions (0-10)	10 / 10	10 / 10	9 / 9	10 / 10	10 / 10
	Ideas, meaning (0-14)	14 / 14	14 / 14	13 / 13	14 / 14	14 / 14
	Total (max 71)	71 / 71	70 / 71	69 / 69	71 / 71	70 / 71
Repetition	Words (0-20)	20 / 20	20 / 20	20 / 19	20 / 20	20 / 20
	Sentences (0-12)	11 / 11	11 / 11	11 / 10	12 / 12	11 / 11
	Total (max 40)	39 / 39	39 / 39	39 / 37	40 / 40	39 / 39
	Body actions (0-5)	5 / 5	5 / 5	4 / 5	5 / 5	5 / 5
	Objects action (0-5)	5 / 5	5 / 5	5 / 4	5 / 5	5 / 5
	Responsive (0-10)	10 / 10	10 / 10	10 / 10	10 / 10	9 / 10
	Total (max 41)	41 / 41	41 / 41	40 / 39	41 / 41	40 / 41
Syntax	Sentence arr (max 6)	6 / 6	6 / 5	6 / 6	6 / 6	4 / 6
Writing	Total (max 10)	10 / 10	10 / 10	9 / 9	7 / 4	10 / 10
Aphasia coefficient	(Total) (max 217)	216 / 216	215 / 215	212 / 209	214 / 211	212 / 216

The degree of language functioning in each patient is summarized as follows:

- All five patients showed during the whole assessment period maximum scores on reading comprehension and maximum scores on reading aloud.

- Patient 1 and Patient 2 had an aphasia coefficient (total sum score) that did not change from the start to the end of the study.

- Patient 3 showed a decline in scores on repetition and naming but kept the other variable scores for the whole period.

- Patient 4 showed decline in writing but kept maximum score on all the other variables during the whole period.

- Patient 5 had a 4-score improvement

The five Patients reached a maximum score on reading comprehension and on reading aloud from the start to the end of the treatment year.

To established possible changes, an analysis of their performance is needed.

Detailed examination of each patient's performance by the speech pathologist is shown below.

Original excerpts of language functioning

Patient 1, at 12 months. (Conclusion): Her linguistic competence has not become impaired during the last year. If anything, greater certainty is observed in her management of the language. She has improved her reading comprehension of visually presented text. However, her difficulty with retrieval of auditorily presented unrelated words, i.e. her memory reduction, remains. She has pronounced dyscalculia. At the start, the fluency of her spontaneous speech was 117 words per minute and the mean length of her utterances was 7.3 words.

Patient 2, at 12 months. In the introductory conversation, she talks adequate about her own problems. Conclusion: Her greatest linguistic problems are secondary to her reduced memory capacity. At the start, the fluency of her spontaneous speech was 160 per minute and the mean length of her utterances was 6.4 words.

Patient 3, at 12 months. The most prominent features in her spontaneous speech are hesitations and pauses when she describes a course of event. There is latency in her confrontation naming of content, but she can sometimes be helped by prompting. Her reading speed of a connected text is 89 words per minute, which is slow. She has dyscalculia. At the start, the fluency of her spontaneous speech was 64 words per minute and the mean length of her utterances was 4.0 words.

Patient 4, at 12 months. Her reading speed is 70 words per minute (by Swedish standards, the measures range between 121–221 words per minute). Her writing ability is worse; she has more spelling errors: four of 10 words correct, the most pronounced errors being reduplications such as 'clocck'. She has problems with arithmetical tasks. Conclusion: The patient has good linguistic competence, with exception for her reading ability, which is impaired primarily because of reduced memory function but also because of eye problems. Her capacity fluctuates. At the start, the fluency of her spontaneous speech was 95 words per minute and the mean length of her utterances was 5.9 words.

Patient 5, at 12 months. Sometimes she makes a break for word searching, but this hardly disturbs the communication. A few misspellings occur, but her sentence construction is good. She suffers from dyscalculia including both digit calculation and other mathematical operations. Her linguistic test profile has been solid without decline during the year. At the start, the fluency of her spontaneous speech was 112 words per minute and the mean length of her utterances was 7.3 words.

6 DISCUSSION

A cure for AD is unfortunately still a mirage bearing in mind the ongoing increase of amount of people getting AD diagnosis. On the way towards the final goal, all possible reliable pharmacological agents and therapeutic interventions with reasonable treatment technique is crucial, especially since early intervention is important. This thesis will deal with one attempt towards this aim: a therapeutic stimulation of the patient´s cognitive function in collaboration with a neurotrophic agent, which has to be administered directly into the brain. The overall aim is to develop a treatment which could counteract degenerative changes in AD. The focus has thus been to elucidate the possibility of implementation of a therapeutic treatment of various impaired functions of the patients, symptoms which are committed AD combined with gangliosides to stop or slow down the degeneration of neural processes, which are the supposed pathological mechanisms of Alzheimer disease. These studies give information of to what extent we can rely on these therapeutic strategies in AD treatment. The scientific approach is new and focus has been on methodological issues and not the therapeutic results.

6 .1 Methodological and theoretical considerations

The studies in the thesis are open studies and the number of participants small, which makes the use of statistic methods not possible and could be used only for rCBF. A combination of different theoretical approaches and methodologies for evaluation has been done in order to strengthen the obtained results.

The used combination of different methodologies makes it possible to obtain complementary findings and to view the interventions from different perspectives and thus gain a deeper understanding of the topic/subject being studied (cf. [169, 174, 175]). In that way the methodology used may be seen as mixed methods according to methodology and methods in an article by Welford et al. [174]. In according to Burke Johnson et al. [176], definitions on criteria of demarcation of mixed methods is ongoing. However, these methods used gives also possibilities to quantify results and to add clinical observations in the evaluation, to analyse how data can change over the examined time. In language examinations by the Aphasia test [177, 43], the patients reach the maximum score at the first test occasion, but by adding deeper observation, the changes over time could be revealed and provided otherwise hidden

knowledge. This in line found with the highlighting the important of extra-test variables directed to improve the ecological validity of assessment [178].

Study **I** and Study **II** were quantitative in nature. In such research, validity is often defined as the degree to which an instrument measures what it is supposed to measure and reliability as the trustworthiness of the instrument used [169].

All examinations presented in the tables in the original Paper I, II, III and V were tested for validity and reliability and the instruments used are those commonly used to measure patient's cognitive, physical, and language disabilities; together with clinical various laboratory tests and brain imaging.

The performances of activities were documented at real time, which is the extent to which a measure measures what it is supposed to measure. Our Activity scale, which was developed for this study to follow and reveal the patient's level of independence in the performance of a task or activity, is, however, not reliability tested. This is a limit but it should also be considered that it assesses the cognitive demands required in the patient's everyday environment, that executive functions are hard to assess and is best done in an actual life situations [178].

The CGI form is commonly used in evaluations in dementia trials [179, 180]. In Study IV, the CGI form was modified by providing space for voluntary comments. The quotes from the spouses' voluntary comments enable the reader to extend his/her knowledge of how and why spouses judged the patient's preserved skills, behaviours, identity and the content of incomprehensive situations. However, another researcher with different pre-understanding might have presented other results [181]. The sample size is small, however, and the aim is not to uncover general facts but rather to provide a perspective or convey possibilities (cf. [182, 169]). Interrater reliability was estimated by means of an independent co-examiner [169]. An attempt was made to give rich descriptions of the steps of each process in the analysis. Credibility is presented and reported in the analysis, and includes supporting quotations taken directly from the data material [182, 169].

To reduce variation in the study, the underlying data in Paper I-V are based on a rather homogenous sample – all the persons are 50-70 years old, living at home. In Paper II, III and V, four out of five of the patient group consisted of females, which is consistent with most studies on care-giving [183]. In Paper I and IV, 4 out of 5 of the patient were male.

Of available nursing theories, which could to be employed as a base in psychiatric-dementia research, the Travelbee's nursing theory was used in Paper III. This theory fits to: the procedures in SAT programme; the approach used to reach the individual's goal; in assisting both individual and family; the use of communication as a process; validation the patients; and include relationships as an integral part of assessment for care.

The patients have in this complex study been involved in a continuous dialogue, especially in the development and implementation of the SAT-programme. The importance to involve the patients in health care has earlier been documented in a thesis by Sätterlund-Larsson [184].

However, the Roy adaptation model [185] would in Alzheimer's disease research also be an alternative nursing theory, if the goal of nursing would be to promote adaptive responses through manipulation of the contextual stimuli [186]. Another approach could be to measure the power for self-care as physical, emotional, social and cognitive factors interact to produce functional patterns for persons of all ages. Orem's self-care deficit nursing theory may then be an interesting intervention of the power of patients' self-care actions [187, 188]. That is, may be, if low self-care ability can be considered as a reason or a consequence of the type of care given by persons in question. Orem's theory has been a well-established base for measuring the power for self-care in several instruments [189]. These two theories do not, however, fit the use of the involved approaches and procedures as well as the theory by Travelbee [147].

6 .2 Medical considerations

The ICV administration of ganglioside GM1 into the brain

In Paper I and Paper II, the IVC infusion with the localization of the catheters bilateral to the frontal lateral ventricles was used as a technically favourable neurosurgical solution. In Paper I, the Teflon tubing connected to the catheters had a tendency to slide as occurred in Patients 2 and Patient 3. On the contrary when the tubing was replaced with a one-pieced extension catheter, the problem was eliminated. This problem has also be seen in other studies, in which a CT brain scan 6 days postoperatively showed that the ventricular catheter had become displaced and required re-site operation of the catheter [190].

Further in Paper I, after the neurosurgeon had contracted the subdural hematoma in two patients, the routine at lumbar puncture was changed to less fluid sampled. The tapped fluid was replaced with physiological saline and this complication was not met in any patient after

changing of the routine. However, the same problems also occurred as in a study with seven patients at different clinical centres in the UK. They assessed effect of continuous IVC infusion of pentosan polysulphate in human prion disease. One patient had an asymptomatic right caudate haematoma which was detected on postoperative imaging. In the study was also documented, that complications of intraventricular catheterization were frequent. Catheters were placed uni- or biventricular. Catheter-site problems occurred in four patients and early complications in two of these four (symptomatic subcortical ischemic stroke and postoperative pyrexia) [191].

Further studies documented in this area is a report of 11 Japanese patients in which subdural fluid collection was observed on CT scans in most cases, meaning in 10 of 11 cases [192].

Lumbar puncture affairs

In Paper II, one patient refused lumbar puncture (LP), a problem seen of different kind in investigations. Other studies have looked into this matter. A study on risk factors at lumbar punctures just for develop Post-Dural Puncture Headache (PDPH) have noted as non modifiable risk factors: age, female gender, low BMI, history of prior PDPH, and history of chronic headache. However, over the age of 60, the PDPH is rare [193]. To determine the frequency and risk factors of PDPH in research volunteers in a large series of LPs, no instances of epidural hematoma, infection, or radiculopathy were identified, and headaches were infrequent (5.6%) [194].

Medical findings

New data are was given of reference of therapeutic levels of ganglioside GM1 in lumbar CSF, which could be used within AD research or other neurodegenerative diseases. The findings in the first study (Paper I) and preliminary study (Paper II) showed that the therapeutic window was between 20 and 30 mg/24h. These also showed that therapeutic levels were not reached in the previous treatment studies. These used the doses of 100-300 mg of GM1/24h as given intravenously, subcutaneously or intramuscularly and are found in large studies of stroke, Parkinson's disease and spinal cord injuries [195]. The therapeutic window is evidently rather narrow for intraventricularly administered ganglioside GM1.

Our studies suggest that the IVC administration of GM1 described here is the method of choice for treatment of brain disorders, with substances which are not passing the blood-brain barrier. In an attempt to overcome those problems, treatment with intravenous doses of 2 g of

GM1 in 3 days a week for 8 weeks of patients with Parkinson's disease were given. They all developed hyperlipidaemia [196].

The biochemical alterations in CSF showed increased values for HVA and 5- HIAA were interpreted as indicative of increased biosynthesis and turnover of dopamine and serotonin. Thus the effect of GM1 on the level of HVA indicates an effect on the dopaminergic function in the brain by GM1. It is in agreement with dopaminergic neurons restoration of function after mechanical or biochemical lessons [195] and beneficial of GM1 effect in Parkinson's disease [197].

In Paper I and Paper II the somatostatin level increased in all patients, which is interesting as the level is reported low in dementia [198]. An increase of somatostatin has also been shown as a result of a caring treatment concomitant with functional improvement [199]. The increased CSF levels of somatostatin thus suggest a relation to improvement in brain function. The somatostatin level has been shown to be related to cognitive function [200].

Cerebral blood flow was slightly increased in 4 of the 5 patients in Paper II, however, not significant. Untreated AD patients show a continuous diminution of the rCBF with time [201]. The results are a further indication of possible positive influence on the brain in our study and suggest that the degenerative process had not accelerated during the treatment year.

The mechanism of action of GM1

It is not known how GM1 acts in the brain. It is suggested that treatment with GM1 would lead to insertion also of those GM1 molecules in the neuronal membrane. The new GM1 molecules would bind Ca^{2+} as counter-ion and increase the inflow of Ca^{2+} during synaptic transmission (efficient communication between these cells is crucial to the normal functioning) and the release of transmitter. Our research team had observed the strong binding of CA^{2+} to gangliosides which several studies had confirmed [202], and also that that the apparent association constant depends on the surrounding ionic strength.

In our research team already in1980 [203] suggested that Ca^{2+} - associated gangliosides on the outer surface of the presynaptic membranes might be replaced by NA^{+} as counter-ion by the action potential (presynaptic is the part of the cell membrane of an axon terminal that faces the cell membrane of the neuron with which the axon terminal establishes a synapse). This would facilitate transformation of the membrane lipid bilayer into a micellar state (a micelle is

an aggregate of surfactant molecules dispersed in a liquid colloid) necessary for the fusion of the synaptic vesicle and the plasma membrane, and release of transmitter. The Ca^{2+}, replaced by Na^+ as counter-ion to <u>gangliosides,</u> would participate in the influx of Ca^{2+} into the synapse.

Beta amyloidad related lesions begin with degeneration of ACh neurone, followed by accumulation of intra neuronal β amyloid ($A\beta$), NFTs , synaptic loss and neuronal death [204]. Ganglioside has later been shown to be involved in the formation of plaques by a combination to $A\beta$ [205]. It is not known how a treatment with very high doses of GM1 will influence $A\beta$. Our findings suggest that there is no acceleration of the disease with such treatment and it is possible that the high concentration of GM1 in the brain protect from the negative effect of $A\beta$ as suggested by Kreutz 2011 [206].

6 .3 Therapeutic treatment considerations

Stimulation influence from milieu or drug treatment

The increase of cerebrospinal fluid levels of monoamine metabolites, neuropeptides and somatostatin in CSF was only seen in connection with the GM1 treatment in Paper II. However, monoamine changes in environmental stimulation of demented persons have earlier been investigated previously [207]. In this study activation was performed in two different long-stay ward hospitals with patients who had a moderate degree of dementia. The evaluation included somatostatin concentrations and monoamine metabolites, which were analysed before and after a programme with intensified intellectual, emotional, emotional and environmental stimulation of one group (n=11) during a two month period. The control group (n=13) had no such environment. Some of the psychological parameters were changed during the study period indicating slight improvement in the activated group and further deterioration in the control group. Although the number of included patients was low, the CSF concentration of <u>somatostatin</u> increased significantly in the activated group during the treatment period and decreased in the control group. It was concluded that the increase in the CSF somatostatin concentration might be a response to the increased environmental stimulation [207]. The next article of this, reported that the <u>HVA</u> (homovanillic acid) concentrations increased in CSF in the treatment group and decreased in the control grope, no change was evident in 5-HIAA or HMPG concentrations in either group. It was suggested that environmental factors can influence biochemical markers of transmitter activity [208]. Another study, with similar design, found that somatostatin in CSF increased by promoting care, concomitant with functional improvement [199].

Findings related to therapeutic treatment

Paper I. In the first study (Paper I), the spouses lost much of their energy before the end of the treatment year. That result may be taken in consideration that the patients really asked for more training and activation of the research assistant. However, there are similar experience from other studies of caregiver's taken care of patients with AD for a longer periods [209], some of these put an importance to including personality of the caregivers of the caregiving process [210]. In this study some respite from homecare through training by professionals outside the home is suggested as long as the patients have mild to moderate AD.

In Paper III (the SAT programme), activities and tasks hard to solve by the patients themselves was successful trained with use of visuosospatial-sterognostic sense strategies to help the patients to overcome great restriction of performance. In another study the use of plenty of memory support was used which was less successful [211].

The strategy to ask each patient to look for feature explicit just for the individual patient to use as a help to find the way to and from the shop, was successful. All patients learn independent to do shopping for lunch. To be lost in the sense of space can evoke feelings of insecurity, which might affect the quality of life for the patient. It is therefore emphasized to include in the education to the caregiver the importance of this kind of supporting from environment, in order to promote the sense of safety and function in daily activities.

Positive experiences of listen to or following audio-taped instructions have earlier been confirmed in Setterlind's thesis regarding progressive muscular relaxation [212] but not hitherto found in dementia studies. This finding in our study, revealed a hidden need of relaxation to be considered as it is based on the patients' own request, within the free choice of activities.

We also found that the implementation of a therapeutic treatment of various impaired functions of the patients, demand comprehensive stimulation, activation and training of all involved in cognitive, social and physical daily life. The theoretical base for this is that each mental function has a specific localisation in the brain, and that there is a need of various strategies to activate these parts of the brain. This therapeutic treatment is important to stimulate impaired brain areas or other to increase function in preserved parts.

The findings in Paper III and Paper V suggest a computer system as an important tool in mild to moderate AD therapeutic treatment, to be used to activate and train the patients' attention, concentration, decision taken, simultaneous capacity and memory. Further, the huge amounts of words in the computer exercise program stimulate the patients to use their preserved language abilities.

Paper IV. Caring is a process and concerns relationships between people. All the spouses arrange social activities and they also paid attention to their partner's need of support in unfamiliar settings. This gave a glimpse of how they viewed their responsibility. Social ties, as has been suggested earlier, diminish the effects of daily negative events [213]. The quality of the relationship between partner and caregiver is important in dementia care giving [214].

All the spouses clearly paid attention to the level of activity and the initiatives taken by the patients themselves. This is contrary to the opinion of professionals, which is contrary to the common opinion, also of professionals. In clinical diagnosis of AD and in studies of motivation it is in terms of the loss of theses abilities [215, 216].

All spouses talked about memory as the only impaired cognitive function. This opinion might have been influenced by the fact that impaired memory function is a characteristic symptom of AD and subjective memory complaints are often found in the population of elderly adults [217].

Paper V. The NGA, generally used by speech pathologists [218] is suitable in this study, as it deals with the complexity of linguistic problems common in patients diagnosed with AD. There is no such test or scale available based on or for patients with AD. NGA is intended to assess impairment; a ceiling effect may occur and did occur in this study. When a patient reaches a maximum score, analysis of their performance is needed to established possible changes. The speech pathologist detailed examination of each patient's performance made this possible and she gave thereby also a 1-year overview.

To take part in everyday talk during one year, like a natural habit was found be well accepted as sometimes they use their pocket almanac to tell what had happen. It is important training as people with languae disorders are significantly disempowered in a culture where oral language skills are highly ranked [219].

A collaborative interchange communication and use of topics with relevance and meaning to the patients in combination with structure, equal power in discourse, is recommended for this patient group as a way to reduce the patients' pragmatic problem.

Difficulty in solving mathematical problems was apparent in both oral and written arithmetic tasks for four of the five patients. This is known to be present early in AD [220]. That one patient had low scores on writing at the start and still lower scores after one year is not surprising, as writing disorder is suggested to be an early manifestation of AD [221].

7 CONCLUSION

This thesis evaluates how a treatment program can be made and used in patients with early onset Alzheimer´s disease of a mild/moderate degree. The addition of a specific stimulation to pharmacologic treatment in dementia adds new knowledge and is a model for test of other substances in Alzheimer´s disease.

The findings in the SAT programme indicate that the complex symptoms in mild to moderate AD need multimodal interventions to utilize all remaining abilities and to cover the patients' capacity of performance of common daily tasks. To improve stabile functional outcomes of the systematic training, the SAT may be continued during 12-months, at least nine months.

The initial finding in Paper II, III, and V support the use of stimulation techniques, visuospatial strategies with utilizing the senses and a nursing process in which the nurse confirms and validates another person. With active participating of the participants in systematic training of cognitive, social, and physical activities and a complex tool as a personal computer system in conjunction with other interventions in everyday activities may help patients to maintain their capabilities and may also offer possibilities of improving. The thesis present novel approaches of procedure in treatment of language dysfunction and in muscular relaxation. These offer possibilities of improving in the linguistic competence and to reduce patients' basic tension and body awareness.

The results of the spouses' comments of their everyday life at home with a partner with AD suggest educational intervention concerning: how to understand and manage healthy emotions created in the life with a patient with AD, and education how to support and manage visually complex symptoms of AD. A respite from homecare through training by professionals outside the home should be considered in planning to ease the strain involved in maintaining the partner's capacity to perform daily tasks of patients with mild to moderate AD.

This is the first attempt to combine a neurotrophic factor, GM1, and specific therapeutic treatment stimulation programme to activate the brain in early onset Alzheimer's disease (AD). This study involves treatment with a neurotrophic substance administered directly into the brain, hitherto not studied in Alzheimer´s disease, and reinforced with stimulation with an individualized activation programme. It was obvious that no patient found the surgery troublesome and no patient or relative has expressed regret about participating in the study.

This knowledge is important not only for this neurotrophic agent but that assist of the SAT programme can be used for various substances aimed at treatment of neurodegenerative disorders.

Although this is a small and open study, according to a variety of measures there might be a deviation/difference from the general pattern of decline. However, the 5 patients in study II-V did not show deterioration to the extent that can be expected in patients with AD during a 1-year period [222], according to the results of the comprehensive battery of neuropsychological tests showing both increased and decreased scores. The study displays the importance to listen carefully to the opinions of the patients and the relatives both with regard to the training program and the participating in such a long and complex study.

8 FUTURE PERSPECTIVES

It is evident that stimulation, activation and training patients with AD results in positive effects. However, this treatment needs further evaluation to evaluate both degree of improvement and how this is reflected in biologic effects.

The patients suffered from AD, where a brain damage is evident. This will still be there even if the ongoing degenerative process can be stopped. Therefore therapies of AD will be needed to, if possible, improve brain function to the highest possible level, and possibly to overcome the damage. Practical use of the finding in the SAT programme to utilize the senses to successful compensatory other impairment are presented. Also psychophysical studies have shown that performance on perceptual tasks can be improved with training and that improvement in perceptual judgments occurs with practice or training, is evident [226].

The adult CNS retains significant capabilities for structural remodelling and functional adaption. These phenomena depend on the capability of the neurons to modify their functional properties and their connections, which nowadays is defined as plasticity. That environmental stimulation promotes neuronal plasticity in animals has been known since 40 years [227, 228], and is also found in aged animals [229]. There have also come evidence for neuronal plasticity in humans when exposure to an enriched environment [230]. Stimuli coming from the external world have shown to exert a powerful dual influence on plastic processes in both physiological plasticity and injury-induced compensatory processes have been concluded this year [231]. Thus, the SAT programme, performed as in this thesis, can be a tool to induce positive effects on the nerve cells, counteracting degenerative changes of AD.

It is rationale to consider a program as SAT as a base for treatment of AD. However, in earlier studies much more attention has been focused on pharmacologic treatment. The addition of a specific stimulation in a therapeutic treatment to pharmacologic treatment in dementia adds new knowledge, and is a model for test of other substances in AD. Full effect of a pharmacologic treatment in AD should therefore also include the aspect of stimulation of the brain, to evaluate all possible effects of the drug.

The influence on the dopaminergic function and reported beneficial effect in Parkinson's disease (PD) of GM1 treatment, suggest that the presented treatment method will be particularly useful for patients with Parkinson's disease. This has already been tested and results of a five year open study has been published in year 2010 suggesting that long-term

GM1 use by PD patients is safe and results in benefit [223]. Future research with GM1 may be in direction of research of increasing the release of brain-derived neurotrophic factors, which has been reported 2011 [224]. Another possibility may be a protective role for GM1 in betaamyloid-induced toxicity [225].

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REFERENCES

1.   WHO. Executive summary, mental and neurological disorders 1997. Cited, available from http://www.int/whr/1997/media_centre/executive_summary1/en/index14.htlm. Subjectivity in data analysis. Lancet. 1991;337:401-2.

2. Fratiglioni L, Launer LJ, Andersen K, Breteler MMB, Copeland JRM, Dartigues JF, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurology. 2000;54(11)Suppl 5:S10-5.

3. Wimo A, Winblad B, Jönsson L. The worldwide societal costs of dementia: Estimates for 2009. Alzheimer's & Dementia. 2010;6(2):98-103.

4. D´Amelio M, Rossini PM. Brain excitability and connectivity of neuronal assemblies in Alzheimer's disease: From animal models to human findings. Prog Neurobiol. 2012; 99:42-60.

5. Svennerholm L, Gottfries C-G. Membrane lipids, selectively diminished in Alzheimer brains, suggest synapse loss as a primary event in early-onset form (Type I) and demyelination in late-onset form (Type II). J Neurochemistry. 1994;62:1039-47.

6. Hansson H-A, Holmgren J, Svennerholm L. Ultrastructural localization of cell membrane GM1 ganglioside by cholera toxin. Proc Natl Acad Sci USA. 1977;74:3782-86.

7. Mesulam MM. A plasticity-based theory of the pathogenesis of Alzheimer's disease. Ann N Y Acad Sci. 2000;924:42-52.

8. Svennerholm L, Gottfries C-G, Blennow K, Fredman P, Karlsson I, Månsson J-E, et al. Parenteral administration of GM1 ganglioside to presenile Alzheimer patients. Acta Neurol Scand. 1990;81:48-53.

9. Swaab DF. Brain aging and Alzheimer's disease, "wear and tear" versus "use it or lose it". Neurobiology of Aging. 1991;12:317-24.

10. Mirmiran M, van Someren EJW, Swaab DF. Is brain plasticity preserved during aging and in Alzheimer's disease? Behav Brain Res. 1996;78:43-8.

11. Chase TN, Foster NL, Fedio P, Brooks R, Mansi L, DiChiro G. Regional cortical dysfunction in Alzheimer's disease as determined by positron emission tomography. Ann of Neurology. 1984;15:170-74.

12. Cutler NR, Haxby JV, Duara R, Grady CL, Moore AM, Parisi JE, et al. Brain metabolism as measured with positron emission tomography: serial assessment in a patient with familial Alzheimer's disease. Neurology. 1985;35;1556-61.

13. Eslinger, PJ, Damasio AR. Preserved motor learning in Alzheimer's disease: Implications for anatomy and behavior. The J Neurosci. 1986;6:3006-09.

14. Bäckman L. Memory training and memory improvement in Alzheimer's disease: rules and exceptions. Acta Neurol Scand Suppl. 1992;139:84-9.

15. Alzheimer, A. Über eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeitschrift für Psychiatrie und phychish-Gerichtliche Medizin, (Berlin). 1907:64;146-148.

16. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984;34:939-44.

17. Terry RD. Masliah E, Hansen LA. Structural basis of the cognitive alterations in Alzheimer's disease. In: Terry RD, Katzman R, Bick KL, eds . Alzheimer's disease. New York: Raven Press; 1994. p. 79-96.

18. Blennow K, Bogdanovic N, Alafuzoff I, Ekman R, Davidsson P. Synaptic pathology in Alzheimer's disease: relation to severity of dementia, but not to senile plaques, Neurofibrillary tangles, or the Apo E4 allele. J Neural Transm. 1996;103:603-18.

19. Goedert M. Neurofibrillary pathology of Alzheimer's disease and other tauopathies. Prog in Brain Res. 1998;117:287-306.

20. Tomlinson BE, Corsellis JAN. Ageing and the dementias. In: Hume Adams J, Corsellis JAN, Duchen LW, eds. Greenfield's neuropathology, 4th edition. London: Edward Arnold; 1984. p. 951-1025.

21. Armstrong RA. β-amyloid plaques: stages in life history or independent origin? Dement Geriatr Cogn Disord. 1998; 9:227-38.

22. Ferrer I, Blanco R, Carmona M, Puig B, Ribera R, Rey MJ, et al. Prion protein expression in senile plaques in Alzheimer's disease. Acta Neuropathol. 2001;101:49–56.

23. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Klunk WE, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzh & Demen. 2011;7:263-69.

24. APA (American Psychiatric Association): Diagnostic and Statistical manual of Mental disorders, 3rd edn. revised. Washington, DC: American Psychiatric Association; 1987.

25. APA (American Psychiatric Association): Diagnostic and Statistical manual of Mental disorders, 4th ed. Washington DC: American Psychiatric Association;1994.

26. World Health Organization. The ICD-10 Classification of Mental and Behavioral Disorders. Geneva: World Health Organization. 1992.

27. Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. Lancet Neurol. 2007;6(8):734-46.

28. Blennow K, Wallin A, Gottfries C-G. Presence of parieto-temporal symptomatology distinguishes early and late onset Alzheimer's disease. Int J Geriatr Psych. 1991;6:147-54.

29. Tomlinson BE. Ageing and the dementias. In: Hume Adams J, Duchen LW, eds. Greenfield's Neuropathology. 5th edition. London: Edward Arnold; 1992.

30. Sjögren T, Sjögren H, Lindgren Å. Morbus Alzheimer and morbus Pick: A genetic, clinical and patho-anatomical study. Acta Psych et Neurol Scand. 1952;Suppl 82:1-152.

31. Blennow K, Wallin A, Gottfries CG. Confusional symptomatology distinguishes early- and late-onset Alzheimer's disease. Aging (Milano). 1990 Dec;2(4):395-401.

32. Svennerholm L, Gottfries C-G. Membrane lipids, selectively diminished in Alzheimer brains, suggest synapse loss as a primary event in early-onset form (Type I) and demyelination in late-onset form (Type II). J Neurochemistry. 1994;62:1039-47.

33. Blennow K, Wallin A, Uhlemann C, Gottfries CG. White matter lesions on CT in Alzheimer patients: relation to clinical symptomatology and vascular factors. Acta neurol Scand. 1991; 83(3);187-93.

34. Wallin A, Blennow K, Scheltens P. Research criteria for the clinical diagnosis of pure Alzheimer's disease. Drugs of Today. 1994;30(4):265-73.

35. Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. AM J. Psychiatry. 1982;139:1136-39.

36. Wallin A, Edman Å, Blennow K, Gottfries C-G, Karlsson I, Regland B et al. Stepwise comparative status analysis (STEP): A tool for identification of regional brain syndromes in dementia. J Geriatr Psychiatr Neurol. 1996;9:185-99.

37. AAN. American Academy of Neurology. Assessment: neuropsychological testing of adults. Neurology. 1996;47(2):592-9.

38. Fuld P. Guaranteed stimulus-processing in the evaluation of memory and learning. Cortex. 1980;16:255-72.

39. Wechsler D. Manual for the Wechsler Adult Intelligence Scale. New York: Psychological Corporation; 1955.

40. Lezak MD, ed. Neuropsychological Assessment. New York: Oxford University Press; 1983.

41. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psych. 1984;141:1356-64.

42. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res. 1975;12:189-98.

43. Reinvang I. Aphasia and Brain organization. New York: Plenum Press; 1985.

44. Roxendal G. Body awareness therapy and the body awareness scale. Treatment and evaluation in psychiatric physiotherapy [dissertation]. Göteborg University; 1985.

45. Maltesson C, Persson I. Utvärdering av interbedömar reliabilitet vid användandet av Body Awareness Scale. Sjukgymnasten. 1993;2:40-5. Swedish.

46. Gottfries CG, Bråne G, Gullberg B, Steen G. A new rating scale for dementia syndromes. Arch Gerontol Geriatr. 1982;1:311-30.

47. Bråne G. The GBS scale – a geriatric rating scale- and its clinical application [dissertation]. Vasastadens Bokbinderi: Göteborg University; 1989.

48. Bråne G, ed. Att bedöma demens med GBS-skalan. Stockholm: Natur och Kultur; 1997. Swedish.

49. Bråne G, Gottfries CG, Winblad B. The Gottfries-Bråne-Steen scale: validity, reliability and application in anti-dementia drug trails. Dementia and Geriatric Cogn Dis. 2001;12:1-14.

50. Dencker K, Gottfries CG. Activities of daily living ratings of elderly people using Katz' ADL Index and the GBS- M scale. Scand J Caring Sci. 1995;9(1):35-40.

51. Wippold FJ 2nd, Gado MH, Morris JC, Duchek JM, Grant EA. Senile dementia and healthy aging: a longitudinal CT study. Radiology. 1991;179:215-9.

52. Kantarci K, Jack CRJr. Neuroimaging in Alzheimer disease: an evidence-based review. Neuroimaging Clin N Am. 2003;13(2): 197-209.

53. Guy W, ed. ECDEU assessment manual for psychopharmacology. Revised 1976. In: Clinical Global Impressions (028 - CGI). Rockville, Maryland: Public Health Service. Rockville; 1976; 217-222. Available on line: http://ia700103.us.archive.org/10/items/ecdeuassessmentm1933guyw/ecdeuassessmentm1933guyw.pdf

54. Lingjaerde O, Ahlfors U, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treatment patients. Acta Psych Scand Supplementum. 1987; 334:76:1-96.

55. Morris R. & Kopelman M.D. The memory deficits in Alzheimer-type dementia: A review. The Quaterly J Exp Psych. 1986;38A:575-602.

56. Tulving E, ed. Elements of episodic memory. Oxford: Oxford University Press; 1983.

57. Becker JT, Lopez OL, Butters MA. Episodic memory: differential patterns of breakdown. In: Morris G, editor. The Cognitive Neuropsychology of Alzheimer-type. Oxford: University Press; 1996; 71-88.

58. Bäckman L, Andersson JLR, Nyberg L, Winblad B, Norberg A, Almkvist O. Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. Neurology. 1999; 52(9):1861-70.

59. Karlsson T, Bäckman L, Herlitz A, Nilsson L-G, Winblad B, Österlind P-O. Memory improvement at different stages of Alzheimer's disease. Neuropsychol. 1989;27(5):737-42.

60. Herlitz A, Adolfsson R, Bäckman L, Nilsson LG. Cue utilization following different forms of encoding in mildly, moderately, and severely demented patients with Alzheimer's disease. Brain and Cog. 1991;15:119-30.

61. Heller RB, Dobbs AR, Rule BG. Communicative function in patients with questionable Alzheimer's disease. Psychol. Aging. 1992;7(3):395-400.

62. Emery VOB. Language functioning. In: Morris RG, editor. The cognitive Neuropsychology of Alzheimer-type dementia. Oxford: Oxford University Press;1996.

63. Nicholas M, Obler LK, Au R, Albert ML. On the nature of naming errors in aging and dementia: a study of semantic relatedness. Brain and Language. 1996;54:184-95.

64. Bayles KA, Tomoeda CK. Confrontation naming impairment in dementia. Brain and Language. 1983;19:98-114.

65. Cummings JL, Benson F, Hill MA, Read S. Aphasia in dementia of the Alzheimer type. Neurology. 1985;35:394-97.

66. Henderson VW, Mack W, Freed DM, Kempler D, Andersen ES. Naming consistency in Alzheimer's disease. Brain and Lang. 1990;39:530-8.

67. Perkin L, Whitworth A, Lesser R Conversing in dementia: A conversation analytic approach Journal Neurolinguistics. 1998;11 nos 1-2: 33-53.

68. Mathias J.L. Reading disorder in Alzheimer-type dementia. In: Morris RG, editor. The cognitive neuropsychology of Alzheimer-type dementia. Oxford: Oxford University Press; 1996.

69. Faber-Langendoen K, Morris JC, Knesevich JW, LaBarge E, Miller JP, Berg L. Aphasia in senile dementia of the Alzheimer type. Ann Neurol. 1988:23;365-70.

70. Croisile B, Brabant M-J, Carmoi T, Lepage Y, Aimard G, Trillet M. Comparison between oral and written spelling in Alzheimer's disease. Brain Lang. 1996;54:361-87.

71. Mantovan MC, Delazer M, Ermani M, Denes G. The breakdown of calculation procedures in Alzheimer's disease. Cortex. 1999;35:21-38.

72. Norman DA, Shallice T. Attention to action: willed and automatic control of behavior. In: Davidson RJ, Schwarts GE, Shapiro D, eds. Consciousness and Self-Regulation: Advances in Research and Therapy. New York: Plenum; 1986;1-18.

73. Fuster JM, ed. The Prefrontal Cortex. 3rd ed. Philadelphia, Pa: Lippincott-Raven; 1997.

74. Lafleche G, Albert MS. Executive function deficits in mild Alzheimer's disease. Neuropsychol. 1995;9:313-20.

75. Collette F, Van der Linden, M, Salmon E. Executive dysfunction in Alzheimer's disease. Cortex. 1999; 35: 57-72.

76. Pettersson AF, Engardt M, Wahlund L-O. Activity level and balance in subjects with mild Alzheimer's disease. Dementia and Ger Cogn Dis. 2002;13:213-16.

77. Edwards DF, Deuel RK, Baum CM, Morris JC. A quantitative analysis of apraxia in senile dementia of the Alzheimer type: Stage-related differences in prevalence and type. Dementia. 1991;2:142-9.

78. Travniczek-Marterer A, Danielczyk W, Simanyi M, Fischer P. Ideomotor apraxia in Alzheimer's disease. Acta Neurol Scand. 1993;88:1-4.

79. Ramström I. Stimulation-activation-training in early-onset Alzheimer's disease: a pilot study. J Chinese Clin Med. 2010:5(7);425-32.

80. Pettersson AF, Engardt M, Wahlund L-O. Activity level and balance in subjects with mild Alzheimer's disease. Dementia and Ger Cogn Dis. 2002;13:213-16.

81. Richards M, Folstein M, Albert M, Miller L, Bylsma F, Lafleche G. et al. Multicenter study of predictors of disease course in Alzheimer's disease (the 'Predictors Study'). II. Neurological, psychiatric and demographic influences on baseline measures of disease severity. Alzheimer Disease and Ass Dis. 1993;7:22-32.

82. Mendez MF, Martin RJ, Smyth KA, Whitehouse PJ. Disturbances of person identification in Alzheimer's disease. The J Nerv. Mental Dis. 1992;180:94-6.

83. Parasuraman R, Haxby JV. Attention and brain function in Alzheimer's disease: a review. Neuropsychology. 1993;7:242-72.

84. Morris RG, ed. Neurobiological correlates of cognitive dysfunction. In: The cognitive Neuropsychology of Alzheimer-type dementia. Oxford: Oxford University Press; 1996.

85. Henderson WW, Mack W, Williams BW. Spatial disorientation in Alzheimer's disease. Arch Neurol. 1989;46:391-94.

86. Kaskie B, Storandt M. Visuospatial deficit in dementia of the Alzheimer type. Arch Neurol. 1995;52:422-25.

87. Coslett HB, Saffran EM. Visuospatial functioning. In: Morris RG, ed. The cognitive Neuropsychology of Alzheimer- type dementia. Oxford: Oxford University Press; 1996;193-205.

88. Frith CD. Consciousness information processing and the brain. J Psychopharmacology. 1992;6:436-40.

89. Trick GL, Trick LR, Morris P, Wolf M. Visual field loss in senile dementia of the Alzheimer's type. Neurology. 1995;45:68-74.

90. Mendez MF, Mendez MA, Martin R, Smyth KA, Whitehouse PJ. Complex visual disturbances in Alzheimer's disease. Neurology. 1990;40:439-43.

91. Kiyosawa M, Bosley TM, Chawluk J, Jamieson D, Schatz NJ, Savino PJ. Alzheimer's disease with prominent visual symptoms. Clinical and metabolic evaluation. Ophthalmology. 1989;96(7):1077-85.

92. Cronin-Golomb A, Corkin S, Rizzo JF, Coen J, Growdon JH, Banks KS. Visual dysfunction in Alzheimer's disease: Relation to normal aging. Ann Neurol. 1991;29:41-52.

93. Bassi CJ, Solomon K, Young D. Vision in aging and dementia. Optometry Vision Sci. 1993;70(10): 809-13.

94. Svennerholm L. Structure and biology of cell membrane gangliosides. In: Ouchterlony Ö, Holmgren J. eds. Cholera and Related Diarrheas. 43rd Nobel Symposium, Stockholm 1978. New York, NY: S Karger AG; 1980. p. 80-7.

95. Svennerholm L, Boström K, Fredman P, Månsson J-E, Rosengren B, Rynmark B-M. Human brain gangliosides: developmental changes from early fetal stage to advanced age. Biochimica et Biophysica Acta. 1989;1005:109-17.

96. Suzuki K, Katzman R, Korey SR. Chemical studies on Alzheimer's disease. J of Neuropathol Exp Neurol. 1965;24:211-24.

97. Ando S. Gangliosides in the nervous system. Neurochem Internat. 1983;5:507-37.

98. Ledeen, R. Gangliosides of the neuron. Trends in Neurosci. 1985;8:169-74.

99. Hakomori, SH, Igarashi Y. Functional role of glycosphingolipids in cell recognition and signaling. J Biochem. 1995;118:1091-1103.

100. Ledeen RW. Biology of GangliosidesLe: Neuritogenic and neuronotrophic properties. J Neurosci Res. 1984;12:147-59.

101. Ariga T, Wakade C, Yu RK. The pathological roles of ganglioside metabolism in Alzheimer's disease: Effects of gangliosides on neurogenesis. Int J Alzheimer's Dis. 2011; volym 2011:193618 -14. DOI: 10.4061/2011/193618.

102. Svennerholm L. Quantitative estimation of sialic acids. II. A colorimetric resorcinol-hydrochloric acid method. Biochimica et Biophysica Acta. 1957;24:604-11.

103. Svennerholm L. Quantitative estimation of gangliosides in senile human brains. Acta Soc Med Upsaliensis. 1957;62:1-16.

104. Svennerholm L. Chromatographic separation of human brain gangliosides. Journal of Neurochem. 1963;10:613-23.

105. Sabel BA, Slavin MD, Stein DG. G_{M1} ganglioside treatment facilitates behavioral recovery from bilateral brain damage. Science. 1984:225;340-42.

106. Sofroniew MV, Pearson RCA, Cuello AC, Tagari PC, Stephens PH. Parenterally administered GM_1 ganglioside prevents retrograde degeneration of cholinergic cells of the rat basal forebrain. Brain Res. 1986;398:393-96.

107. Sabel BA, DelMastro R, Dunbar GL, Stein DG. Reduction of anterograde degeneration in brain damaged rats by GM_1-gangliosides. Neurosci Letters. 1987;77: 360-66.

108. Toffano G, Savoini G, Moroni F, Lombardi G, Calza L, Agnati LF. GMI ganglioside stimulates the regeneration of dopaminergic neurons in the central nervous system. Brain Res. 1983;261:163-66.

109. Hadjiconstantinou M, Mariani AP, Neff NH. GM1 ganglioside-induced recovery of nigrostriatal dopaminergic neurons after MPTP: an immunohistochemical study. Brain Res. 1989;484:297-303.

110. Lazzaro A, Seren MS, Koga T, Zanoni R, Schiavo N, Manev H. GM1 reduces infarct volume after focal cerebral ischemia. Exp. Neurol. 1994;125; 278-85.

111. Samson JC. GM_1, ganglioside treatment of central nervous system injury: clinical evidence for improved recovery. Drug Dev Res. 1990;19:209-24.

112. Bassi S, Albizzati MG, Sbacchi M, Frattola L, Massarotti M. Monosialoganglioside therapy in Stroke. Stroke. 1985;16: 899-900.

113. Argentino C, Sacchetti ML, Toni D, Savoini G, D'Arcangelo E, Erinio F, et al. GM1 ganglioside therapy in acute ischemic stroke. Stroke. 1989;20(9):1143-49.

114. Schneider, JS, Roeltgen DP, Rothblat DS, Chapas-Crilly J, Seraydarian L, Rao, J. GM1 ganglioside treatment of Parkinson's disease: an open pilot study of safety and efficacy. Neurology. 1995; 45(6):1149-54.

115. Ala T, Romero S, Knight F, Feldt K, Frey II WH. GM-1 treatment of Alzheimer's disease. Arch Neurol. 1990;47:1126-30.

116. Flicker C, Ferris SH, Kalkstein D, Serby M. A double-blind, placebo-controlled crossover study of ganglioside GM_1 treatment for Alzheimer's disease. Am J Psychiatry. 1994;151:1126-129.

117. Augustinsson L-E, Blennow K, Blomstrand C, Bråne G, Ekman R, Fredman P et al. Intracerebroventricular administration of GM1 Ganglioside to presenile Alzheimer patients. Dement and Geriatr Cogn Disord. 1997;8:26-33.

118. Oikawa N, Yamaguchi H, Ogino K, Taki T, Yuyama K, Yamamoto N, et al. Gangliosides determine the amyloid pathology of Alzheimer's disease. Neuroreport. 2009;20(12):1043-6.

119. Ariga T, McDonald MP, Robert K. Yu RK. Role of ganglioside metabolism in the pathogenesis of Alzheimer's disease - a review. J Lipid Res. 2008;49:1157-75.

120. Carpenter PA, Just MA. Modeling the mind: very high-field functional magnetic resonance imaging activation during cognition. Top Magn Reson Imaging. 1999;10(1):16-36.

121. Kandel ER. The brain and behavior. In: Kandel ER, Schwartz JH, Jesell TM, eds. Principles of neural science, 4th edition. New York: McGraw-Hill; 2000;5-18.

122. Bäckman L, Andersson JLR, Nyberg L, Winblad B, Nordberg A, Almkvist O. Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. Neurology. 1999;52:1861-70.

123. Becker JT, Lopez OL, Butters MA. Episodic memory: differential patterns of breakdown. In: Morris G, editor. The Cognitive Neuropsychology of Alzheimer-type. Oxford: University Press; 1996.

124. Almkvist O. Functional brain imaging as a looking-glass into the degraded brain: reviewing evidence from Alzheimer disease in relation to normal aging. Acta Psychol (Amst). 2000;105:255-77.

125. Schultz D, ed. Sensory restriction: Effects on behavior. New York: Academic Press; 1965.

126. Breuil V, De Rotrou J, Forette F, Tortrat D, Ganansia-Ganem A, Frambourt A. et al. Cognitive stimulation of patients with dementia: preliminary results. Int J Ger Psychiatry. 1994;9:211-17.

127. Quayhagen MP, Quayhagen M. Differential effects of family-based strategies on Alzheimer's disease. The Gerontol. 1989; 2(29);150-55.

128. McKitrick IA, Camp CJ, Black FW. Prospective memory intervention in Alzheimer disease. J Gerontology. 1992;47(5):337-43.

129. Zanetti O, Binetti G, Magni E, Rozzini L, Bianchetti A, Trabucchi M. Procedural memory stimulation in Alzheimer's disease: impact of a training programme. Acta Neurol Scand. 1997;95:152-57.

130. Hutchinson SA, Marshall M. Responses of family caregivers and family members with Alzheimer's disease to an activity kit: an ethnographic study. J Advan Nurs. 2000;31(1):44-50.

131. Hofmann M, Hock C, Müller-Spahn F. Computer-based cognitive training in Alzheimer's disease patients. Ann the N.Y. Acad Scien.1996;777:249-54.

132. Cochrane. Cochrane Library. Available from: http://www.thecochranelibrary.com/2012.

133. SBU. The Swedish Council on Technology Assessment in Health Care. Dementia-Caring, Ethics, Ethnical and Economical Aspects. A systematic Review.[In Swedish: SBU · Statens beredning för medicinsk utvärdering]. Stockholm: Elanders Infol.Väst AB. 2008 Jun:3.

134. Spector A, Davies S, Woods B, Orrell M. Reality orientation for dementia: A systematic review of the evidence of effectiveness from randomized controlled trials. The Gerontologist. 2000;40:206-12.

135. Lai CKY, Chi I, Kayser-Jones J. A randomized controlled trial of a specific reminiscence approach to promote the well-being of nursing home residents with dementia. Intern Psychoger. 2004;16:33-49.

136. Forbes D, Forbes S, Morgan DG, Markle-Reid M, Wood J, Culum I. Physical activity programs for persons with dementia. The Cochrane Library. 2008;8 Oct. Issue 4. DOI: 10.1002/14651858.CD006489.pub2.

137. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. Arch Phys Med Rehabil. 2004; 85:1694-704.

138. Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. BMJ Open. 2012;2(3):1-8.

139. Lopez OL, Becker JT, Wahed AS, Saxton J, Sweet RA, Wolk DA, et al. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. J Neurosurg Psychiatry. 2009;80(6):600-7.

140. Woods B, Aguirre E, Spector AE, Orell M. Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database of Systematic Reviews. Online EISSN 1469-493X. 2012; Volym 2: p. CD005562. Also available from Art. No.: CD005562.DOI.10.1002/14651858.

141. Onor ML, Trevisiol M, Negro C, Alessandra S, Saina M, Aguglia E. Impact of a multimodal rehabilitative intervention on demented patients and their caregivers. Am J Alzheimer's Dis & Other Dem. 2007;22(4):261-72.

142. Cipriani G, Bianchetti A, Trabucchi M. Outcomes of a computer-based cognitive rehabilitation program on Alzheimer's disease patients compared with those on patients affected by mild cognitive impairment. Arch Gerontol Geriatr.2006;43:327-35.

143. Giordano M, Dominguez LJ, Vitrano T, Curatolo M, Ferlisi A, Di Prima A et al. Combination of intensive cognitive rehabilitation and donepezil therapy in Alzheimer's disease (AD). Arch Gerontol and Geriatr. 2010; 51:245-49.

144. Arkin, S. Language-Enriched Exercise Plus Socialization Slows Cognitive Decline in Alzheimer's Disease. Am J Alzheimer's Dis and Other Dementias. 2007;22: 62-77.

145. Fawcett J, ed. Analysis and Evaluation of Conceptual Models of Nursing. 3rd edition Philadelphia: Davis Company; 1984;1-36.

146. Brenner P, Wrubel J, editors. The Primacy of caring. Stress and coping in Health and Illness. California: Addison-Wesley Publishing Company;1989.

147. Travelbee J. Interpersonal aspects of nursing, 8th print. Philadelphia: Davis cop.; 1977.

148. Rangel S, Hobble WH, Lansinger T, Magers JA, McKee NJ. Joyce Travelbee. Human-to-human relationship model. In: Tomey AM, Alligood MR, eds. Nursing theorists and their work. St. Louis: Mosby-Year Book Inc; 1998;364-374.

149. Tronto JC, ed. Moral Boundaries. A political argument for an ethic of care. NewYork: Routledge; 1993.

150. De Graaf KR, Marriner-Tomey A, Mossman CL, Slebodnik M. Florence Nightingale. Modern Nursing. In: Marriner-Tomey A, ed. Nursing theorists and their Work, 2nd edition. St Louis: Mosby Company; 1989;65-79.

151. King I.M. Heath as the goal for nursing. Nurs Sci Quarterly.1990;3:123-28.

152. Barris R, Kiehlhofner G, Levine RE, Neville AM. Occupation as interaction with the environment. In: Kielhofner G, ed. A model of human occupation. Theory and application. Baltimore: Williams & Walkins; 1985. p. 42-62.

153. Kahana E. A congruence model of person-environment interaction. In: Lawton MP, Windley PG, Byerts TO, eds. Aging and the environment: Theoretical approaches. New York: Springer Publishing Company; 1982. p. 97-121.

154. Czaja SJ, Weber RA, Nair SN. A human factor analysis of ADL activities: A capability-demand approach. J Gerontol. 1993;48:44-8.

155. Frings S. Chemoelectrical signal transduction in olfactory sensory neurons of air-breathing vertebrates. Cell Mol Life Sci. 2001;58:510-19.

156. Frings S. Primary processes in sensory cells: current advances. J Comp Physiol A. 2009; 195:1-19.

157. Nordenfelt L. On the nature of health. An action-theoretic approach. Second revised and enlarged edition. Dordrecht: Kluwer Academic Publishers; 1995.

158. Blennow K, Fredman P, Wallin A, Gottfries CG, Skoog I, Svennerholm L, et al. Protein analysis in cerebrospinal fluid. II. Reference values derived from healthy individuals 18-88 years of age. Eur Neurol. 1993;33:129-33.

159. Blennow K, Rybo E, Wallin A, Gottfries C-G, Svennerholm L. Cerebrospinal fluid cytology in Alzheimer's disease. Dementia. 1991;2:25-9.

160. Lekman A, Witt-Engerström I, Holmberg B, Percy A, Svennerholm L, Hagberg B. CSF and urine biogenic amine metabolites in Rett syndrome. Clin Genet. 1990;37(3):173-8.

161. Edvinsson L, Minthon L, Ekman R, Gustafson L. Neuropeptides in cerebrospinal fluid of patients with Alzheimer's disease and dementia with frontotemporal lobe degeneration. Dementia. 1993;4:167-71.

162. Fredman P, Lycke J, Andersen O, Vrethem M, Ernerudh J, Svennerholm L. Peripheral neuropathy associated with monoclonal IgM antibody to glycolipids with a terminal glucuronyl-3-sulfate epitope. J Neurol. 1993;240:381-7.

163. Svennerholm L. The gangliosides. J Lipid Res. 1964;5:145-55.

164. DiMartino A, Safar J, Ceroni M, Gibbs CJ Jr. Purification of non-infectious ganglioside preparations from scrapie-infected brain tissue. Arch Virol. 1992;124:111-21.

165. Larsson A, Bergh A-C, Bilting M, Ärlig Å, Jacobsson L, Stephensen H, et al. Regional cerebral blood flow in normal pressure hydrocephalus: Diagnostic and prognostic aspects. Eur J Nucl Med. 1994;21:118-23.

166. Ärlig Å, Larsson A, Bergh A-C, Jacobsson L, Wikkelsö C. A new method for the relative quantification of rCBF examined by [99]Tc[m]-HMPAO SPECT. Nucl Med Commun. 1994;15:814-23.

167. Richards M. Neurobiological treatment of Alzheimer's disease. In: Morris RG, editor. The Cognitive Neuropsychology of Alzheimer Type Dementia. Oxford: Oxford University Press; 1996. p. 327- 42.

168. Morse JM, Field PA, editors. Nursing research: the application of qualitative approaches. 2nd ed. London: Chapman and Hall; 1996.

169. Polit DF, Hungler BP, editors. Nursing Research. Principles and Methods. 6th ed. Philadelphia: Lippincott; 1999.

170. Laska AC, Hellblom A, Murray V, Kahan T, von Arbin M. Aphasia in acute stroke and relation to outcome. J Int Med. 2001;249:413-22.

171. Cuénod M, Gasser J. Research on the mentally incompetent. J Med Ethics. 2003;29:19-21.

172. Baldwin C, Hughes J, Hope T, Jacoby R, Ziebland S. Ethics and dementia: mapping the literature by bibliometric analysis. Int J Geriatr Psychiatry. 2003;18:41-54.

173. World Medical Association (WMA). Declaration of Helsinki. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended the latest by the: 59th WMA General Assembly, Seoul, Korea, October 2008.

174. Welford C, Murphy K, Casey D. Demystifying nursing research terminology. Part 1. Nurse Researcher. 2011;18:38-43.

175. Welford C, Murphy K, Casey D. Demystifying nursing research terminology: Part 2. Nurse Researcher. 2012;19; 29-35.

176. Burke Johnson R, Onwuegbuzie AJ, Turner LA. Toward a definition of mixed methods research. J of Mixed Methods Research. 2007;1:112-33.

177. Reinvang I, Sundet K. The validity of functional assessment with neuropsychological tests in aphasic stroke patients. Scand J Psychology. 1985;26:208-18.

178. Chaytor N, Schmitter-Edgecombe M, Burr R. Improving the ecological validity of executive functioning assessment. Arch Clin Neuropsych. 2006;21(3):217–27.

179. Rogers SL, Friedhoff LT. The Efficacy and Safety of Donepezil in Patients with Alzhemeir's disease: Results of a US Multicentre, Randomized, Double-Blind Placebo-Controlled Trial. Dementia. 1996;7(6):293-303.

180. Agid Y, Dubois B, Anad R, Gharabawi G. Efficacy and tolerability of Rivastigmine in patients with dementia of the Alzheimer type. Curr Therapeutic Res. 1998;59:837- 45.

181. Dahlberg K, Drew N, Nyström M, editors. Reflective lifeworld research. Lund, Sweden: Studentlitterature; 2001.

182. Patton MQ, ed. Qualitative evaluation and research methods. London: Sage Publications; 1990.

183. Hooyman NR, Gonyea JG. A feminist model of family care: practice and policy directions. J of Woman & Aging. 1999;11:149-69.

184. Sätterlund Larsson. Being involved. Patient participation in health care [Dissertation]. Linköping University: Linköping University, Sweden; 1989.

185. Roy SC, ed. Introduction to nursing: An adaptation model. New Jersey: Prentice-Hall Inc; 1976.

186. Thornbury JM, King LD. The Roy adaptation model and care of persons with Alzheimer's disease. Nurs Sci Q. 1992;5:129-33.

187. Orem DE, ed. Nursing: concepts of practice. 4 th ed. St. Louis: Mosby-Year Book; 1991.

188. Orem DE, ed. Nursing. Concepts of practice. 5th ed. St Louis: Mosby Year Book; 1995.

189. Gast HL, Denyes MJ, Campell JC, Hartweg DL, Schott-Baer D, Isenberg M. Self-care agency: conceptualizations and operationalizations. Adv Nurs Sci. 1989;12(1):26-38.

190. Parry A, Baker I, Stacey R, Wimalaratna S. Long term survival in a patient with variant Creutzfeldt-Jakob disease treated with intraventricular pentosan polysulphate. J Neurol Psychiatry. 2007;78:733-34.

191. Bone I, Belton L, Walker AS, Darbyshire J. Intraventricular pentosan polysulphate in human prion diseases: an observational study in the UK. European J Neurol. 2008;15:458-64.

192. Tsuboi Y, Doh-ura K, Yamada T. Continuous intraventricular infusion of pentosan polysulfate: clinical trial against prion diseases. Neuropathol. 2009;29:632-36.

193. Bezov D, Lipton RB, Ashina S. Post-dural puncture headache: Part I diagnosis, epidemiology, etiology and pathology. Headache. 2010;50:1144-52.

194. de Almeida SM, Shumaker SD, LeBlanc SK, Delaney P, Marquie-Beck J, Ueland S, et al. Incidence of Post-Dural Puncture Headache in Research Volunteers. Headache 2011;51:1503-10.

195. Svennerholm L. Gangliosides: A new therapeutic agent against stroke and Alzheimer's disease. Life Sci. 1994;55:2125-34.

196. Roberts JW, Hoeg JM, Mouradian MM, Linfante I, Chase TN. Iatrogenic hyperlipidaemia with GM1 ganglioside. The Lancet. 1993;342:115-115.

197. Schneider JS, Roeltgen DP, Mancall EL, Chapas-Crilly J, Rothblat DS, Tatarian GT. Parkinson's disease: Improved function with GM1 ganglioside treatment in a randomized placebo-controlled study. Neurology. 1998;50:1630-1636.

198. Bissette G, Widerlöv E, Walléus H, Karlsson I, Eklund K, Forsman A, et al. Alterations in cerebrospinal fluid concentrations of somatostatinlike immunoreactivity in neuropsychiatric disorders. Arch Gen Psychiatry. 1986;43(12):1148-51.

199. Widerlöv E, Bråne G, Ekman R, Kihlgren M, Norberg A, Karlsson I. Elevated CSF somatostatin concentrations in demented patients parallel improved psychomotor functions induced by integrity-promoting care. Acta Psychiatr Scand. 1989;79:41-7.

200. Epelbaum J, Guillou J-L, Gastambide F, Hoyer D, Duron E, Viollet C. Somatostatin, Alzheimer's disease and cognition: An old story coming of age? Prog Neurobiol. 2009; 89(2): 153-61.

201. Weih M, Degirmenci U, Kreil S, Suttner G, Schmidt D, Kornhuber J, et al. Nuclear medicine diagnostic techniques in the era of pathophysiology-based CSF biomarkers for Alzheimer's disease. J Alzheimers Dis. 2011;26 Suppl 3:S97-103.

202. Thomas PD & Brewer G. Gangliosides and synaptic transmission. Biochim Biophys Acta. 1990;1031: 277-89.

203. Svennerholm L. Gangliosides and synaptic transmission. Adv Exp Med Biol. 1980:125:533-544.

204. Mesulam MM. A plasticity-based theory of the pathogenesis of Alzheimer's disease. Ann N Y Acad Sci. 2000;924:42-52.

205. Yanagisawa K. Role of gangliosides in Alzheimer's disease. Biochim Biophys Acta. 2007;1768(8):1943-51.

206. Kreutz F, Frozza RL, Breier AC, de Oliveira VA, Horn AP, Pettenuzzo LF, et al. Amyloid-β induced toxicity involves ganglioside expression and is sensitive to GM1 neuroprotective action. Neurochem Int. 2011;59(5):648-55.

207. Karlsson I, Widerlöv E, Melin EV, Nyth A-L, Bråne GAM, Rybo E, Rehfeld JF, Bissette G, Nemeroff CB. Changes of CSF neuropeptides after environmental stimulation in dementia. 1985;39(Suppl.11):S75-81.

208. Karlsson I, Bråne G, Melin E, Nyth A-L, Rybo E. Effects of environmental stimulation on biochemical and psychological variables in dementia. Acta Psychiatr. Scand. 1988;77:207-13.

209. Parks SH, Pilisuk M. Caregiver burden: Gender and the psychological costs of caregiving. Amer J Orthopsychiatr. 1991;61(4):501-09.

210. Hooker K, Monahan D, Shifren K, Hutchinson C. Mental and physical health of spouse caregivers: The role of personality. Psychol Aging. 1992;7(3):367-75.

211. Josephsson S, Bäckman L, Borell L, Bernspång B, Nygård L, Rönnberg L. Supporting everyday activities in dementia: An intervention study. Int J Geriatr Psychiatry. 1993;8:395-400.

212. Setterlind S. Teaching relaxation in school. A survey of research and empirical studies [dissertation]. Allfoto AB: Göteborg University; 1983.

213. Okun MA, Melichar JF, Hill MD. Negative daily events, positive and negative social ties, and psychological distress among older adults. Gerontologist. 1990;30:193-99.

214. Sprutte N, van Audenhove C, Lammertyn F, Storm G. The quality of the caregiving relationship in informal care for older adults with dementia and chronic psychiatric patients. Psychol Psychother. 2002;75:295-311.

215. Lisman WA. Senile dementias, presenile dementias and pseudodementias. In: Lisman WA, ed. Organic psychiatry. Oxford: Blackwell Science; 1998. p. 428-450.

216. Thomas P, Clement JP, Hazif-Thomas C, Leger JM. Family, Alzheimer's disease and negative symptoms. Int J Geriatr Psychiatry. 2001;16:192-202.

217. Jonker C, Launer LJ, Hooijer C, Lindeboom J. Memory complaints and memory impairment in older individuals. J Am Geriatr. 1996;44:44-9.

218. Laska AC, Hellblom A, Murray V, Kahan T, von Arbin M. Aphasia in acute stroke and relation to outcome. J Int Med. 2001;249:413-22.

219. Armstrong E. Language disorder: A functional linguistic perspective. Clin Linguistics & Phonetics. 2005;19:137-53.

220. Martin RC, Shannon M, Darling LZ, Wadley V, Harell L, Marson DC. Loss of calculation abilities in patients with mild and moderate Alzheimer disease. Arch of Neurol. 2003;60:1585-89.

221. Croisile B. Agraphia in Azheimer's disease. Dementia Geri Cogn Dis. 1999;10:226-30.

222. Nyth AL, Gottfries C-G, Blennow K, Bråne G, Wallin A. Heterogeneity of the course of Alzheimer's disease: A differentiation of subgroups. Dementia. 1991;2:18-24.

223. Schneider JS, Sendek S, Daskalakis C, Cambi F. GM1 ganglioside in Parkinson's disease: Results of a five year open study. J of the Neurol Sci. 2010; 292:45-51.

224. Lim ST, Esfahani K, Avdoshina V, Mocchetti I. Exogenous gangliosides increase the release of brain-derived neurotrophic factor. Neuropharmacol. 2011;60:1160-67.

225. Kreutz F, Frozza RL, Breier AC, de Oliveira VA, Horn AP, Pettenuzzo LF, et al. Amyloid-β induced toxicity involves ganglioside expression and is sensitive to GM1 neuroprotective action. Neurochem Int. 2011;59(5):648-55.

226. Gibson EJ. Improvement in perceptual judgments as a function of controlled practice or training. Psychological Bull. 1953;50(6);401-31.

227. Diamond MC, Johnson RE, Ingham C. Brain plasticity induced by environment and pregnancy. Int J Neurosci. 1971;2(4):171-8.

228. Diamond MC. Response of the brain to enrichment. An. Acad. Bras. Ciênc. 2001;73(2):211-20.

229. Diamond MC, Connor JR. Plasticity of the aging cerebral cortex. Exp Brain Res. 1982; Suppl 5:S36-44.

230. Foscarin S, Ponchione D, Pajaj E, Leto K, Gawlak M, Wilczynski GM, et al. Experience- dependent plasticity and modulation of growth regulatory molecules at central synapses. PLos ONE. 2011;(6);1-24.

231. Foscarin S, Rossi F, Carulli D. Influence of the environment on adult CNS plasticity and repair. Cell Tissue Res. 2012;349:161-67. DOI 10.1007/s00441-011-1293-4.