

## CHAPTER 2

### NEUROBIOLOGY OF ALZHEIMER'S DISEASE

*Every mind is a room filled with archaic furniture. It must be moved about or cleared away before anything new can enter. This means ruthless confrontation of the many things we know that are no longer so....my rational mind, who has pestered me since I can remember, escapes into the infinity of imagination...(Hock, 1999, p.7).*

Dementia is the collective reference for a cluster of disorders, which in a typical disease profile, manifests as a global deterioration in cognition and behaviour.

The most common dementia syndrome bears the name of its discoverer, Alois Alzheimer, who described it as a progressive and perplexing condition (Alzheimer, 1907/1977). As an age-related dementia syndrome, the incidence of new cases of Alzheimer's disease increases exponentially with age (Katzman & Fox, 1999). One can predict an ever-burgeoning economic crisis in the health care system on the bases of an increasing life span and a fast growing segment of the at risk population. Current research initiatives therefore, cover the expanse of scientific disciplines and include genetic, preventative, and psychosocial studies, which incorporate the possibilities of pharmacological (genetics and histology) and psychological (behavioural risk factors and care requirements) interventions.

This chapter elucidates the general classification of dementias, addresses the debate on the comorbidity of age-related and Alzheimer's disease symptoms from a neuropathological and connectionist information processing framework, and reviews the field of Alzheimer's disease in terms of aetiology, putative risk factors, and pathological hallmarks. In this light, Alzheimer's disease may be utilised as a metaphor that provides a

heuristic for understanding interactions between the evolutionary process of senescence and disease referents.

## 2.1 Dementia

In the 1800's, dementia pertained to conditions of psychological deterioration related to progressive brain disease and included the gamut of functional psychoses. When dementia occurred in the elderly, 'senile' was the annex to the primary description. The discovery of tangles and plaques consolidated the view that dementia incorporated clinical and neuropathological components (Berrios, 1990). As mortality rates decreased, there was a proportionate increase in dementia in the elderly population. Mortality rates together with new discoveries on cortical ageing prompted investigations and discoveries of distinct brain pathology that subserved the condition of senile dementia. Consequently, the broad defining category of psychological deterioration underwent revision and adopted a cognitive mantle specifically defined in terms of memory.

The clinical presentation of dementia incorporates an assemblage of cognitive and behavioural symptoms, and therefore belies its status as a unitary disease state. Nevertheless, given the cornucopia of terms used, many of the conditions that result in dementia, for example, Alzheimer's disease and Pick's Disease, have been defined in terms of their histopathological criteria, assigned a primary designation, and denote a unitary disease state. However, this procedure serves the interests of clinicians and practitioners because it helps to establish diagnostic consistency.

A reconciliation of the clinical description and the neuropathological definition is possible if one clarifies the contexts of usage. With a diagnostic or categorical connotation, the term dementia applies to a specific disease or group of diseases. Utilising a capacious

description, dementia alludes to a general clinical syndrome. The former is characterised by a progressive deterioration of higher cortical functions that is based on primary neuronal disturbances, while the latter is characterised by a global impairment of mental functioning that may be caused by a wide variety of illnesses (Burns & Levy, 1994). Therefore, a generic definition of dementia would imply certain disease parameters. Hence, brain disorders with variable underlying neuropathologies that prevail in producing acute dissolution of capabilities of intellect, personality, and social function without observable variance in levels of consciousness, qualify for inclusion within the descriptive parameter of dementia.

There are many subtypes and classifications of dementia with the various nomenclatures based on age of onset, aetiology, underlying pathology, and accompanying neurological signs. Some researchers advocate the localisation of atrophy as a classification guide (e.g., Cummings, 1990). Based on this taxonomy the difference between cortical and subcortical dementia is a common and widely drawn demarcation reflected in research and clinical practice. The other known designations in the system refer to mixed dementia and axial dementia (Parks, Haxby, & Grady, 1993). Further recommendations for the diagnostic classification of dementia producing diseases, pertain to the reversibility of the disease (potency of intervention) and the progressive or static pattern of decline (National Institute of Health [NIH], 1987). Diagnostic classification therefore, relies on information about the sites of degeneration, observation of symptom manifestation, and efficacy of treatment outcomes that reflect in essence neurological, psychological, and rehabilitative components.

### 2.1.1. Localisation of atrophy

Alzheimer's disease is a commonly encountered dementia that results from a disease process. Of the most common degenerative dementias, Alzheimer's disease is regarded as a cortical dementia, Huntington's disease and Parkinson's disease are referred to as subcortical dementias, multi-infarct as a mixed dementia and Wernicke-Korsakoff syndrome is classified as an axial dementia. On strictly anatomical grounds, cortical atrophy involves the cerebral cortex (grey matter), which forms the densely convoluted pattern of ridges and furrows, and subcortical atrophy predominantly affects neuronal connections between the cortical areas (gray matter) and structures below the cortex (white matter). In figure 2-1, a portion of the left hemisphere and a portion of the cerebral cortex have been removed consequently revealing the underlying mass of white matter. With an axial dementia, the medial portions of the temporal lobes, hippocampus, fornix, and mamillary bodies are primarily involved (Crossman & Neary, 1998).

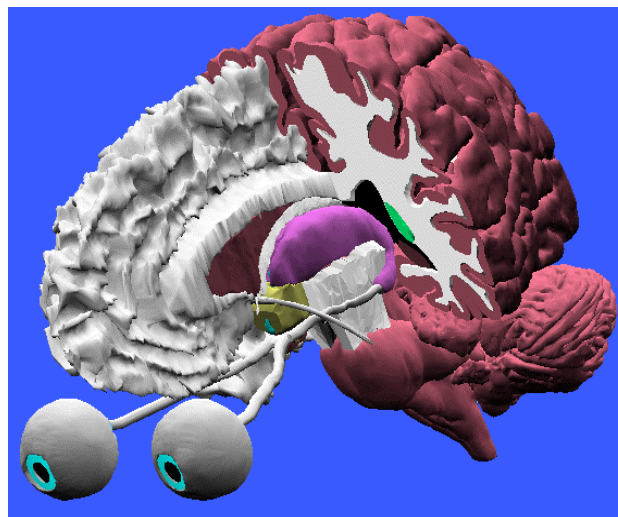


Figure 2-1 An anterolateral view of the brain and underlying white matter (Sundsten & Mulligan, 1998)

Based on the anatomical areas subserving cognitive functions, atrophy associated with cortical dementias produce impairments in learning and memory that result in aphasia,

apraxia, and agnosia. Impairments in learning and memory associated with disturbances in concentration and awareness are manifestations of subcortical atrophy. Considering the nature of these diseases, many researchers (Burns & Levy, 1994; Zillmer & Spiers, 2001) contend that narrow distinctions are inadequate because the anatomical atrophy, which characterises these disorders, is mutually exclusive. To retain the clinical merits of the distinction, researchers suggest that the terms denote a primary area rather than an exclusive area of damage. This is in keeping with current neuropsychological theories that espouse the link between modular functional systems and mental abilities.

To assist diagnosis in instances where localisation of damage is inconclusive, clinicians tend to use states of decline and treatment efficacy as supplementary aids for differentiating disease-producing dementias. These criteria are discussed briefly in the following sections.

### **2.1.2 States of decline**

The progression or pattern of decline or manifestation of symptom profiles delineates dementia types and allows for a differential diagnosis. Disease states diagnosed as Alzheimer's, Huntington's, Pick's, and Creutzfeldt-Jakob are characterised by continuous cognitive and behavioural deterioration. Neurotoxic substances or infection may cause static, steady state patterns of cognitive decline. Vascular dementias (e.g., multi-infarct) produce a stepwise progression of symptoms due to the multiple strokes that occur at different times during the disease. Dementia's arising from disease states tend to manifest as progressive deterioration, whereas the deterioration observed in other dementias tend to be analogous to the severity and frequency of the catalyst (e.g., neurotoxin or strokes). In cases where symptomatic patterns are atypical, the efficacy of treatment outcomes

subverses the clinical distinction between progressive (irreversible) and regressive (reversible) dementias.

### **2.1.3 Treatment efficacy**

The reversible dementias include symptoms that stem from conditions such as nutritional deficiencies (thiamine deficiency), metabolic disorders (hyper- and hypoglycaemia, hypo- and hyperthyroidism), psychiatric disorders, tumours, and drugs (e.g., sedatives, hypnotics, and anxiolytics). When the conditions are treated the symptoms of dementia remit with time (Zillmer & Spiers, 2001). In comparison with the reversible dementias, Alzheimer's disease and Parkinson's disease have no treatment regimens that can reverse the disease process and therefore collate under the label of irreversible dementias.

In sum, brain diseases, illnesses, and many other conditions can cause dementia. The symptom presentation, neuropathological lesions, and the outcome of treatments motivate the classification of the different dementia syndromes. The most common degenerative dementia is Alzheimer's disease, and this condition has been associated with ageing. The following sections elaborate on current research and discourse on the ageing brain and the substantiation of Alzheimer's disease as a separate disease process.

## **2.2 The ageing brain**

Dementia of the Alzheimer's Type includes cognitive features and behavioural problems endemic to the older adult population. Due to this, it is crucial to qualify the description of Alzheimer's disease in order to distinguish it from neuropsychological and neuropathological changes associated with normal ageing.

Dementia pertains to an atypical loss of mental function and is distinct from the inexorable and noticeable deterioration in specific abilities that accompany advancing age (Villareal & Morris, 1998). The clinical overlap between normal age-related decline and dementia contaminates the true differentiation of this syndrome from normal ageing. At the time of discovery, Alzheimer's disease was regarded as a rare form of presenile dementia with an early-onset presentation. On the other hand, senile dementia was considered a natural consequence of the ageing process because of its late-onset.

After many years it was discovered that the cerebral atrophy described by Alzheimer was present in many of the patients with senile dementia, and the correlation between age of dementia onset and Alzheimer's disease was no longer accepted as a basis for diagnosis (Blessed, Tomlinson, & Roth, 1968). Thus, the juxtaposition of Alzheimer's disease as a true disease and Alzheimer's disease as a natural concomitant of ageing is pertinent because of the overlap between the general consequences of the ageing process and the classical presentation of symptoms at older ages. In younger population groups the manifestations of dementia are more distinct, because of the unique underlying aetiology and the limited influence of age-related comorbidity, in comparison with older groups (Brayne, Dufouil, & McGee, 1999).

There is much debate about the differentiation between the symptoms and underlying neuropathology of ageing and Alzheimer's disease. Research tends to focus on two contentions: firstly, the underlying neuropathological changes, while sharing similarities, are unique to the disease process and secondly, changes in information processing among Alzheimer's disease patients are a function of the disease process and not the consequences of the ageing brain alone. These contentions will be discussed below.

## **2.2.1 Consequences of disease or age? Neurons and thresholds**

On a molecular level, the accompanying circumstances of ageing have been attributed to chromosomal changes that intensify with age, DNA transcript errors resulting from temporal damage, and activation of genetic sequences that are part of the human evolutionary cycle (Price, 2000). The ageing brain also undergoes structural changes and concomitant anatomical and physiological changes. These include brain weight shrinkage of about 20%, degeneration of 5-50% of brain cells, abated enzymatic activity that influences neurotransmitter synthesis, and a loss of 15-20% of synapses particularly in the frontal lobes (Novartis Foundation for Gerontology, 2001).

### **2.2.1.1 Cognition and ageing effects**

A general underlying decline of the brain's compensatory capacity to adjust also reflects alterations related to ageing. The clinical manifestations of ageing (cognitive decline, sleep cycle disturbances, emotional lability, motor and endocrinological functions) are postulated as the behavioural reflections of the underlying abnormalities evident in particular neuronal arteries. In terms of cognition and ageing effects, the decline is not homogeneous. If one considers the hierarchical model of general intelligence as proposed by Cattell (1971), fluid and crystallised intelligence stand out as two subfactors. The latter is defined as stored knowledge and learned skills and the former as the ability to acquire abstract reasoning abilities and understand novel relations and situations (Duncan, Burgess, & Emslie, 1995). Fluid intelligence is more susceptible to the effects of ageing and the influences of biological processes in comparison with crystallised intelligence, but less affected by education and social experience (Zillmer & Spiers, 2001).



### **2.2.1.2 Thresholds of structural degradation**

The presence of senile plaques and neurofibrillary tangles in the ageing brain contributed to the hypothesis that Alzheimer's disease is an acceleration of the general ageing process. At a histological level, the difference between patients with Alzheimer's disease and older individuals is quantitative (frequency of senile plaques and neurofibrillary tangles) and pathology above a certain critical threshold is associated with a dementia syndrome. Unique brain reserves and the compensatory capacity of an individual determine the critical threshold. West, Coleman, Flood, and Troncoso (1997) argue that the quantitative distinction drawn between Alzheimer's disease and the cognitively intact aged population implies that the mechanisms of neurological decline and the processes of structural change are similar in Alzheimer's disease and general ageing. If this contention had gained acceptance, then current research, prevention, and intervention strategies would have focused solely on the processes of general ageing.

There are many detractors, however, who assert that at the critical threshold point, distinct qualitative indicators are associated with degenerative processes of general ageing and with Alzheimer's disease (Berg, 1985; Mayeux, 1999). The qualitative distinctions that characterise Alzheimer's disease include genetic, viral, or environmental risk factors that are likely to induce a pathological change from a subthreshold to a suprathreshold state culminating in Alzheimer's disease onset. Age-related changes according to Mayeux (1999) are clearly recognisable from the pathological changes associated with Alzheimer's disease. Furthermore, although Alzheimer's disease increases relationally with age, causality and consequence is attributable to neither age alone nor the evolutionary ageing process.

West et al. (1997) report on the neuronal loss in the hippocampal area (see figure 2-2), and show evidence of distinctive qualitative patterns of Alzheimer's disease. Its functional association with memory processes and its vulnerability to Alzheimer's disease pathology underscores the importance of the hippocampal area. Utilising a comparative design comprising a control group of healthy aged subjects and a group of Alzheimer's disease patients, West et al. (1997) found a large neuronal loss in the CA1 hippocampal area in 68% of the Alzheimer's disease group. Conversely, the control group revealed no neuronal atrophy in this area.

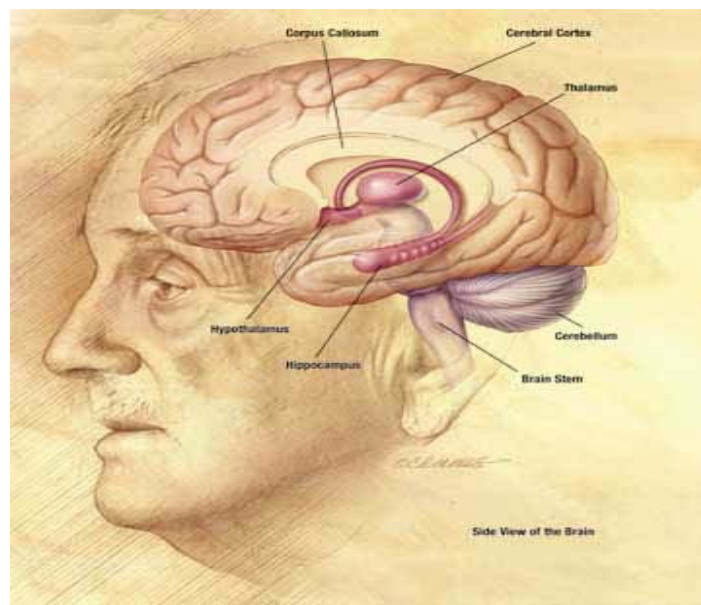


Figure 2-2 Saggital section of the brain with parts of the limbic system (Rogers, 2002)

Other research findings support the notion of differential pathology between Alzheimer's disease patients and normal elderly groups (Gomez-Isla & Hyman, 1997). They report that in parts of the hippocampus (entorhinal cortex-memory-related system) cognitively intact aged persons had approximately 7 million neurons. The clinically mild Alzheimer's disease group had 32% fewer neurons and the severe Alzheimer's disease group had 69% fewer neurons than the controls. The most adversely affected parts were the layers II and IV of the entorhinal cortex whose cells have a known vulnerability for neurofibrillary formation. Therefore, the researchers conclude that Alzheimer's disease reflects brain

degeneration processes that are not characteristic of general ageing and hence it can be classified as “an age-related, but not an age-dependent disease” (Braak, Braak, Bohl, & Bratzke, 1998, p.97).

Conversely, in an autopsy study of 26 cognitively normal elderly, Kazee and Johnson (1998) found the presence of neurofibrillary tangles in the hippocampus but not the neocortex of all subjects, whereas 46% had some senile plaques in the neocortex. Although the mean age of participants was 78 years neither the number of neurons containing neurofibrillary tangles nor the number of senile plaques correlated with age in these subjects. They concluded that either individuals with incipient neuropathology may be a clinically silent Alzheimer’s disease group or that these lesions have a limited effect on cognition within the boundaries of an individual’s reserve capacity. The latter suggests that the neuropathology of the disease is age-related, and the former suggests that it is age-dependent.

Attempts to further understand the processes of brain ageing are underway utilising transgenic mouse models (Treuting, Hopkins, Ware, Rabinovitch, & Ladiges, 2002). The genetic expressions in these mouse models are altered and associated with the neuropathological markers that are accepted as hallmarks for specific diseases namely Alzheimer’s disease and Werner’s syndrome (premature ageing). To date, these attempts have yielded valuable insight into the neuropathological differences underlying ageing and age-related diseases. The transgenic mice, for example, express neuropathological mutations in specific protein depositions that do not parallel the processes in the ageing brain. The studies therefore, indicate that production and deposition of pathological processes are unique to Alzheimer’s disease pathology.

There is compelling evidence that underlying neuropathological processes differ in normal ageing and Alzheimer's disease. In the following discussion, the debate is addressed from the standpoint of changes in information processing. The motivation for this discussion is derived from assumptions that cognitively intact elderly persons also undergo changes in information processing abilities that may reflect the mechanisms underlying the cognitive changes observed in Alzheimer's disease patients.

## **2.2.2 Consequence of disease or age? Processing capacity**

Applications of the principles of non-linear input-output dynamics and connectionist models, in addition to animal models (transgenic mice), have rendered novel insights into the distinction between general ageing and age-related diseases. The connectionist neural network approach allows for the interpretation of the behavioural and physiologic correlates of Alzheimer's disease from the standpoint of information processing networks. The connectionist network approach and its application to Alzheimer's disease and the ageing processes will be discussed below.

### **2.2.2.1 Basic principles of dynamic systems**

The age-related and disease-related changes in the elderly populations are associated with morphological mutations that underlie the functional disturbances in brain systems. Consequently, these processes create defective adaptive thresholds, and responses to external stressors tend to be unpredictable because of this faulty mechanism. The breakdown of the functional principles of the systems culminates in chaos and produces unpredictable outcomes. Biological systems are stochastic in that they combine random and selective processes in such a manner that only certain random transactions endure

(Perold & Cassimjee, 1999). The purpose of this process appears to involve maintenance of a stable internal state (morphostasis) and development of a complex organisation (morphogenesis), despite variations in the external environment. This state is maintained through feedback principles, which either reinforce (positive feedback) or rescind (negative feedback) a command. Hence, the physiological and behavioural systems of the brain can be classified as dynamic systems containing mechanisms and rules that maintain control functions and perpetuate recurrent outcomes, respectively (Dell, 1982).

Dynamic neural systems are characterised by the complex workings of a number of structural parts and their interactions (couplings) with one another. Neural systems enumerate input-output compatibility through the complex workings of probabilistic pools of neuronal modules, which follow a connectionist pattern of activity. Modules function within specific activity ranges and their interaction is determined by the weights (encoded knowledge) attached to their connections (Plaut & Shallice, 1994).

The optimal functioning of a connectionist system is dependent on “attractors” (Plaut & Shallice, 1994, p. 9). When the processing modules of the network receive input they revise the patterns of activity, and the ultimate activity pattern after revision represents the system’s interpretation of the input. Attractor is the term used for this revised and ultimate pattern of activity. Specific patterns of activity are compatible with specific inputs thereby ensuring that information assimilation (weight changes) in recurrent systems provide predictable outputs to similar inputs. The sensitivity of the system has been demonstrated in healthy young subjects, who encounter difficulty performing a task that requires them to detect change in visual representations (Cassimjee & Maree, in press).

From a connectionist perspective, one can assume that their failure to detect changes results from weight modification flaws that result in defective encoding and reconstruction of output. The inaccurate reproduction and inability to detect gross changes in visual representations indicate the malleability of the weight dependent system. Moreover, subjects showed poorer performance in detecting conjunctural changes when compared to featural changes, thus indicating that the more complex the system interactions needed, the more susceptible the system. Together with the sensitivity of the system, the degeneration of connectionist modules and communication pathways imposed by the disease process may lead to misinterpretations of input and inaccurate outcomes (behaviour). Furthermore, extensive damage to the system could disrupt attractor functioning and the possibility exists that disturbance in the creation of new attractors, distortions of the attractor boundaries, and disappearance of existing attractors would result, and compensatory systems may be rendered ineffectual.

The functional systems of the brain can be regarded as dynamic systems that adhere to the operating principles mentioned above.

#### **2.2.2.2 Brain processes as dynamic systems**

Cerebral cortices with their links to brainstem and forebrain structures control particular distributed neural networks, which in turn modulate higher functions and behaviour. For example, the reticular area called the gigantocellular tegmental field of the midbrain modulates higher brain functions (affect, arousal, vigilance, and memory) in part by controlling the synthesis of acetylcholine (Kandel, 2000). When the levels of acetylcholine drop to a critical point, the presynaptic terminal cholinergic neurons release acetylcholine (exocytosis), which binds to and activates the nicotinic or muscarinic receptors in order to

maintain function at optimal levels. When levels reach their threshold the synthesis is inhibited through the release of the enzyme acetylcholinesterase that hydrolyses acetylcholine into inactive chemicals (Kalat, 2001)

If biological systems function stochastically then the fluctuating levels of acetylcholine would be considered the random component of this stochastic system. The interaction between the regulator (synthesis, release, and response), in this case the gigantocellular tegmental field, and the cholinergic neurons is a selective process that modulates the fluctuation of neurotransmitter levels in a predetermined critical range.

The application of the principles of dynamic systems may enhance the hypothesis that Alzheimer's disease and ageing are distinct, particularly when considering the neurochemical or acetylcholine alterations that characterise the Alzheimer's disease brain. During the disease course, structures such as the tegmental area degenerate and their regulatory processes malfunction, causing a cascade of reactions from a deficiency of acetylcholine levels below the critical range to eventual nerve cell death. The cumulative cell atrophy results in connectivity changes derived from the system's attempts to 'rewire' itself in order to maintain stability, modulate higher functions, and rerun predictable behavioural outcomes.

Thus, random transactions (fluctuating levels of acetylcholine) are allowed to endure and the system progresses to a state of entropy (randomness, non-differentiation, non-organisation) with a compromised ability to adapt to input. This results in more unpredictable outputs and a loss of functional complexity due to changes in the coupling or interaction between nodes, which alters the relationship between the variables and parameters of the system. The clinical presentation of cognitive breakdown is more

profound in Alzheimer's disease than in the normal aging population and may be a derivative of asynchronous systems dynamic that is unique to Alzheimer's disease and observable in the cognitive profile of the disease.

### **2.2.2.3 Brain complexity: Derivative of structure and function**

The heterogeneous clinical profile of Alzheimer's disease is attributable to the complexity of a physiological or behavioural system that requires a number of independent variables to predict the outcome of a system. According to Vaillancourt and Newell (2002), several aspects affect the form of a physiologic or behavioural output. Firstly, there is the functional interaction between variables and this can be mathematically expressed as  $X = f(a, b, c, \dots, k)$  where  $X$  represents the function of many variables. The phenotype of a cognitive ability such as memory is represented by  $X$  and the variables  $a, b, c, \dots$  represent genetic, neuronal, chemical, and exogenous influences on memory. Changing the parameters of these variables would affect the complexity of the system output.

Secondly, to understand the complexity of a mental function (e.g., memory), the anatomical substrates of the input-output pathways have to be conceptualised as an intricate communication network that comprises feedforward and feedback axons, which maintain the integrity of the entire system. The feedback axons travel from the subcortex to the cortex and the feedforward axons travel in the opposite direction from the highly evolved (cortex) to the primitive parts of the brain. Van Hoesen (1997) identifies the following structures (Figure 2-3) that serve as either the source or endstations of feedforward and feedback axons related to memory and other systems:



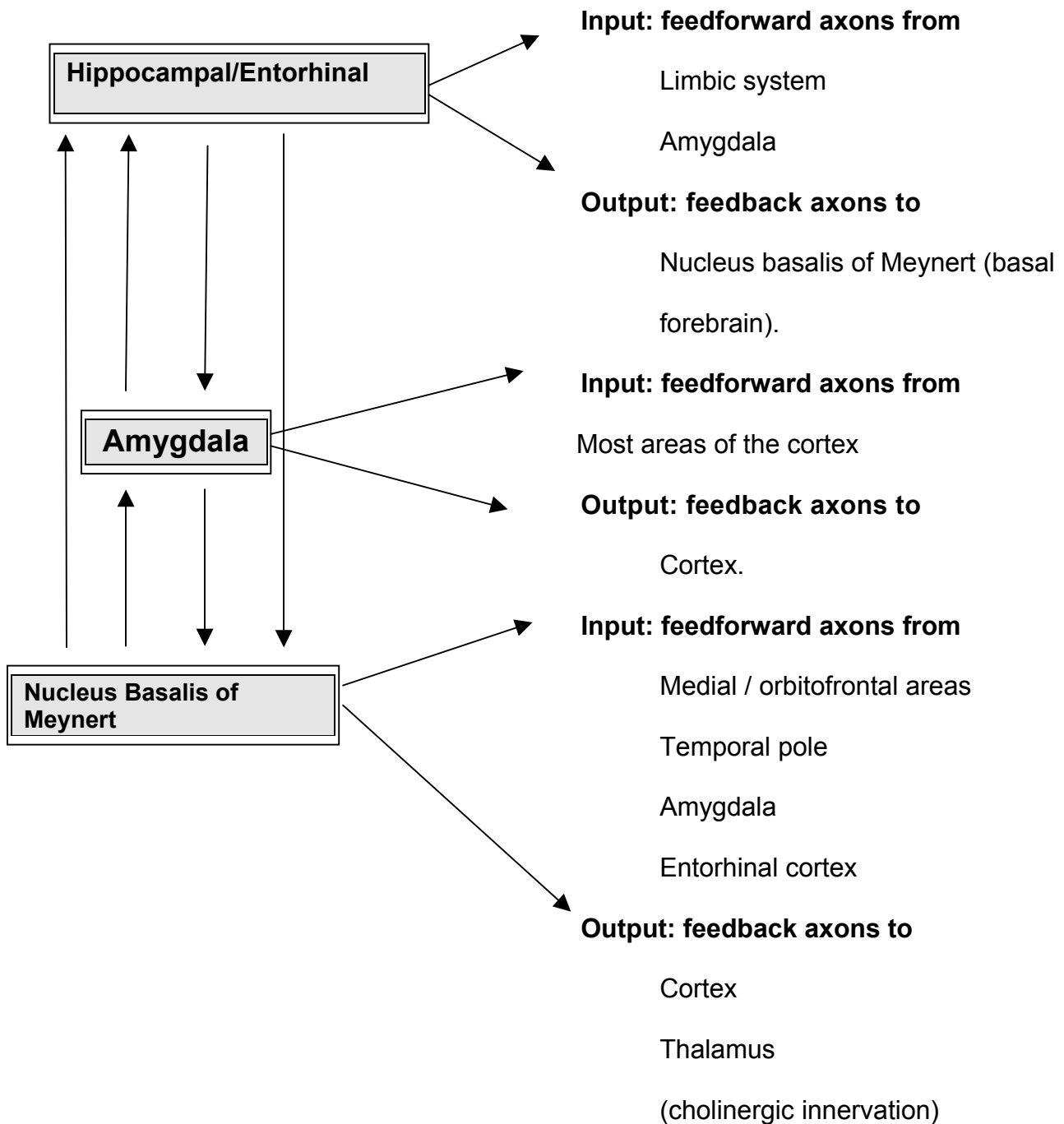


Figure 2-3 Input-output memory pathways

The hippocampus and amygdala are endstations for multisynaptic cortical neurons. The nucleus basalis of Meynert influences the cortex both directly and indirectly via innervation to the cortex and thalamus, respectively. Although the nucleus basalis of Meynert has widespread influence on the cortex, the primary influence is through the cortical

endstations (amygdala and hippocampus) after the sequence of cortical processing is complete.

In Alzheimer's disease, damage is prevalent in the cortical areas that project to the nucleus basalis of Meynert. One of the areas acutely atrophied (50% neuronal loss) is the superior temporal sulcus, which represents the higher association cortex (Gomez-Isla & Hyman, 1997). Furthermore, there is a high density of neurofibrillary tangles many damaged neurons, and low levels of the cholinergic enzyme responsible for acetylcholine synthesis in the nucleus basalis of Meynert. The input/output associations between the amygdala, hippocampus, and nucleus basalis of Meynert are damaged because the endstations of cortical feedforward and feedback axons are destroyed. Thus, the structures degenerate and alterations occur in the connectivity of the couplings and these mutations impact on intrinsic functional complexity and observable cognitive and behavioural output. The nature and extent of structural and functional alterations, according to the neurodynamic approach, is what distinguishes Alzheimer's disease from normal ageing.

Memory problems and the presence of pathological brain markers also qualify as consequences of ageing and not necessarily a manifestation of Alzheimer's disease. According to Van Hoesen (1997), the pronounced deterioration of the limbic system and its connections, tip the balance towards Alzheimer's disease. Destruction of the limbic cortical feedforward and feedback axons is related to executive control problems, which underlie neuropsychological impairments. Pathways from the subcortex to the neocortex, according to Damasio (1994), revive elements in the association cortices and attach them together to create a unified consciousness. The damage to the limbic structures and prefrontal areas, caused by Alzheimer's disease pathology, alters the ability to revive and

recreate associations (attractor function), although much of the cortex may still be undamaged. According to Braak and Braak (1997), streams of data cannot converge on the entorhinal region and the amygdala (afferent leg of the limbic loop) and the projections from the entorhinal region, amygdala, and hippocampus cannot influence the prefrontal area (efferent leg of the limbic loop). The erratic behavioural symptoms of the disease may be partially attributable to the dysfunction of this network of afferent and efferent loops.

The mechanisms of working memory and attention are essential for integrated consciousness, decision-making, and co-ordinated mental activity. Different systems have inherent working memory and attention mechanisms that function as conductors responsible for synchronising disharmonious neural patterns into a readable score. However, the overarching working memory and attention process is driven by the prefrontal cortex and the anterior cingulate that are atrophied by the disease process (Damasio, 1994). The conventional notion of hierarchical processing may account for the cognitive dysfunction but a non-linear model may account for the other symptoms (behavioural/neuropsychiatric) that often accompany this disease and distinguishes it from ageing.

In sum, deterministic and stochastic influences enhance the complexity of physiologic and behavioural systems. In the case of Alzheimer's disease, researchers attempt to identify all the variables that determine a certain outcome and thereafter, identify the random (stochastic) inputs that compromise the recurrent predictable outputs and permit erratic outcomes. The memory impairments and the behavioural manifestations, for example, would translate simplistically as a representation of a system that generates chaotic outcomes. This derives from the system's compromised adaptive ability, which is a

function of the changed structure (cholinergic system) and its altered couplings (nerve cell death). An individual with Alzheimer's disease according to this non-linear dynamic model would then exhibit these symptoms because of the overall lack of adaptability to monitor complex inputs and generate optimal outputs.

Researchers have attempted to translate the theoretical application of non-linear dynamic models to practical predictors and discriminators of Alzheimer's disease and normal ageing.

#### **2.2.2.4 Quantitative indices of chaotic outcomes**

In an attempt to quantify the inequality between chaotic outputs proportional to altered input processing, Lipsitz and Goldberger (1992) applied specific concepts from the field of non-linear dynamics. Fractals and chaos are the two concepts used to quantify the change in physiologic and behavioural complexity associated with age and Alzheimer's disease (Besthorn, Sattel, Geiger-Kabisch, Zerfass, & Förstl, 1995; Jelles, Strijers, Hooijer, Stam, & Jonkman, 1999; Jelles, van Birgelen, Slaets, Hekster, Jonkman, & Stam, 1999; Vaillancourt & Newell, 2002). The term fractal refers to asymmetrical geometric formations that have recurring configurations (e.g. bifurcating nerve systems). Chaos pertains to the erratic outputs that are generated by feedback loops in specific non-linear systems (e.g., damaged cholinergic neural networks).

Through their application of non-linear dynamics to ageing and age-related diseases, researchers generated the hypothesis that ageing and disease alters the complexity of physiologic and behavioural systems, thus resulting in a loss of ability to respond optimally to input. Lipsitz and Goldberger (1992) postulate that a decline in complexity reflects a

malfunction in executable components and a changed non-linear coupling between parts of the system. In addition to a decrease in complexity, Vaillancourt and Newell (2002) postulate that ageing and disease could also cause an increase in behavioural and physiologic complexity. The main argument, in their application of non-linear dynamics, attributes irregular outputs to either an increase or a decrease in complexity. In other words, they contemplate the juxtaposition of forces of stimulation and inhibition that are compatible with the current theories on brain aging and performance.

In terms of noncognitive signs, the hypothesis would state that symptoms result from either an overstimulation of the neuroanatomical sites underlying these behaviours, or an underactivation of neuromodules mediating positive behaviour. The frontal systems in an AD brain may not be able to inhibit prepotent responses (underactivated), alternatively the subcortical neuromodules may be overstimulated due to chemical imbalances and appear to overwhelm the inhibitory mechanisms of the frontal circuits. The former is tantamount to an accident caused by brake failure and the latter is tantamount to an accident caused by a wedged accelerator. These mechanisms cause entropy in homeostatic systems and the end results are similar even though the disruptive mechanisms are different. Another benefit from Vaillancourt and Newell's (2002) stimulation-inhibition hypothesis is that it allows for different behaviours to be investigated as anomalous outcomes of either overactivation or understimulation.

Non-linear EEG studies are one way to measure the neural dynamics in the brain utilising a correlational dimension as a measure of the complexity of brain dynamics, i.e. systems function and coupling. The EEG measure assesses the degree of randomness and the degree of determinism in a signal (Besthorn et al., 1995). In groups with Alzheimer's disease, the use of a correlational dimension is motivated by the knowledge that people

with Alzheimer's disease have a loss of neurons and a depressed overall synaptic response that will most likely reflect less complex dynamics and a lower correlational dimension. Several studies utilising Alzheimer's disease patients and age matched normal controls (Besthorn et al., 1995; Besthorn, Zerfass, Geiger-Kabisch, Sattel, Schreiter-Gasser, & Förstl, 1997; Jelles, van Birgelen et al., 1999;) corroborate the loss of complexity hypothesis on the basis of the following:

1. Alzheimer's disease patients have increased frequency of slow delta and theta waves and decreased frequency of fast alpha and beta waves.
2. Dimensional complexity, Mini Mental Status scores, and dementia rating scale scores are positively correlated.
3. Dynamical changes correspond to brain areas underlying Alzheimer's disease pathology (cholinergic system).
4. Measures of complexity and neuropsychological tests of frontal dysfunction reflect the most correlations.
5. There is an inverse relationship between dementia severity and complexity suggesting that the more severe the dementia the more chaotic the output.

These results have to be evaluated in the context that the Alzheimer's disease patients participating in the study were moderately demented (Clinical Dementia Rating-2.1) and the mean age ranged from 68-75 years. Although Jelles, Strijers et al. (1999) found a decrease in complexity dynamics in the temporal and frontal areas among their sample of early stage Alzheimer's disease, the significant differences between the demented and control groups were in linear dynamics. Differences in processing capacity between people in the early stages of Alzheimer's disease (younger age) and healthy age-matched

controls indicate that the disease has a causal (linear) as well as a correlational (nonlinear) impact on brain mechanisms independent of the universal markers of senescence.

### **2.2.3 Summary**

The application of the principles of non-linear dynamics to ageing and Alzheimer's disease has theoretical and clinical implications for the field of neuroscience. These applications promote an understanding of cortical dynamics underlying Alzheimer's disease and ageing. Quantifiable measures of complexity (EEG fractal dimensions) can be used to test the negative effects of drugs and stressors on the ageing brain, the efficacy of Alzheimer's disease interventions on neuropsychological and behavioural functions, and the validity of diagnostic tools that distinguish between ageing and Alzheimer's disease.

Although the evidence supporting a distinction between ageing and Alzheimer's disease processes appears compelling on a neuropathological and cognitive level, a caveat against these interpretations is necessary. This necessity derives from: the limited knowledge of the ageing process itself resulting from variability of baseline performances and limited normative population standards, the multifactorial causes of inevitable age-related decline and co-morbidity of conditions amongst the elderly, and moderate scientific capacity for determining the severity and loci of age-related impairments compounded by equivocal findings concerning the effects of ageing on mental ability in longitudinal and cross-sectional research.

From the previous discussions one can deduce that Alzheimer's disease is a disease characterised under the general dementia syndromes, is distinguishable from the processes of normal ageing on a neuropathological level and a cognitive level, and is

characterised by various cytoskeletal (tangles and plaques) mutations and neurochemical imbalances (acetylcholine). The following sections will detail the characteristic neuropathological changes associated with Alzheimer's disease.

### **2.3 Alzheimer's disease**

Alzheimer's disease accounts for over 50% of all dementias and is responsible for a large percentage of morbidity and mortality in older adults (Burns, Byrne, & Maurer, 2002). It is also recognised as a veritable disease qualitatively distinct from the normal ageing process. Almost 95 years ago, this disease was identified by Alois Alzheimer, a psychiatrist, neurologist, and brain pathologist, in a milestone paper that was titled "A characteristic disease of the cerebral cortex" (Bick, Amaducci, & Pepeu, 1987). Alzheimer's disease poses a seminal problem, which in the 21<sup>st</sup> century is compounded by the predicted extension in human longevity.

The first trace of this disease can be found in Alois Alzheimer's detailed observations of a 51-year-old woman named Auguste Deter who was incarcerated with symptoms of dementia (Alzheimer, 1907/1977). During the course of her institutionalisation, he keenly observed signs of swift memory deterioration, disorientation, perceptual disorders, and a general lack of cognitive abilities. On a behavioural level, he recalled that the woman experienced intense feelings of jealousy, paranoia, delirium and hallucinations accompanied by a marked absence of postural and movement disturbances. Her mental and physical demise continued for four and a half years and eventually she ended up being bedridden, incontinent, and totally apathetic. An autopsy of her brain revealed large cerebral vessels, neurofibril mutations, and deposits of an unknown substance. After reflecting on his observations, Alzheimer (1907/1977, p. 3) concluded that



...it is evident that we are dealing with a peculiar, little known disease process. In recent years, these particular disease processes have been detected in great numbers. ...We must not be satisfied to force it into an existing group of well-known disease patterns. ...We must reach a stage in which the vast well-known disease groups must be subdivided into smaller groups, each one with its own clinical and anatomical characteristics.

Studies of the brain pathology accompanying dementia had already begun in the 19<sup>th</sup> century. When Alzheimer described his peculiar case research had already uncovered the presence of neurofibrillary tangles and clinical cases of cognitive and neuropsychiatric disturbances in the elderly. The novelty in Alzheimer's description was neither in the clinical presentation nor in the observation of plaques but rather in the combined presence of cognitive impairment, focal symptoms, and brain pathology. Kraepelin provided the eponym 'Alzheimer's disease' in 1910, and the disease was largely associated with a young onset-age (Burns et al., 2002).

Based on the historical account of the disease, Berrios (1990) argues that at the time Alzheimer's discovery did not warrant a separate diagnostic category, and the cases documented by Alzheimer and his colleagues were not clinically or pathologically pure. Thus, the cases deserved a classification of a severe and atypical type of senile psychosis or senile dementia. Over the years, definitions of Alzheimer's disease and clinical criteria have evolved and these changes have permeated the diagnostic clinical boundaries, descriptions of symptom content, and defining anatomical markers that influence current conceptions of Alzheimer's disease.

Since the time of Alzheimer, many definitions of the disease process have been disseminated across literature. A perusal of these definitions indicates that onset and pathogenesis serve as the essential descriptive referents.

### **2.3.1 Subtypes of Alzheimer's disease**

The general neuropathological and clinical symptoms of Alzheimer's disease are evident in both the early-onset (prior to age 65) and late-onset cases (after age 65). The concept of a unitary disease arose after the 1960's when a diagnosis of Alzheimer's disease was considered independent of the age of dementia onset. However, several researchers (Koss et al., 1996; Lawlor, Ryan, Schmeidler, Mohs, & Davis, 1994; Raskind, Corta, & Bravi, 1995; Roth, 1986; Seltzer & Sherwin, 1983; Sevush, Leve, & Brickman, 1993) found quantitative differences in symptomatology between early-and late-onset patients and argued for the classification of distinct subtypes.

There are four classifications of Alzheimer's disease subtypes as identified by Green (2000). These include the early- and late-onset, visuospatial and verbal, temporal lobe and executive dysfunction, and extrapyramidal motor and non-extrapyramidal motor subtypes. The quantitative differences noted in the majority of research between early- and late-onset Alzheimer's disease pertain to the clinical, histopathological, and genetic variations. The clinical and behavioural symptoms have been linked to particular neurobiological changes documented in the early-onset cases (Lawlor et al., 1994; Nambudiri, Teusik, Fensterheim, & Young, 1997).

Early-onset Alzheimer's disease in comparison with late-onset Alzheimer's disease is characterised by the following:

### **Clinical/Behavioural differences**

- greater apraxia deficits
- greater aphasia deficits
- more malignant and rapid disease progression
- higher rates of institutionalisation
- greater attentional and concentration deficits
- more behavioural disturbances

### **Histopathological differences**

- widespread parietal atrophy
- higher density of neurofibrillary tangles and senile plaques
- greater neurotransmitter abnormalities
- greater norepinephrine neuronal loss and atrophy in locus coeruleus
- more widespread and severe presynaptic cholinergic lesions
- asymmetric cortical glucose metabolism (lower parietal metabolism)

### **Genetics**

- mutations on chromosome 14 ( $\beta$ -APP)
- mutations on chromosome 21 (PS-1)
- mutations on chromosome 1 (PS-2)

Of the differences in clinical (neuropsychological) expressions above, the most contentious pertains to language abilities. Both early- and late-onset Alzheimer's disease patients have shown varying deficits in comprehension, writing, confrontational naming, reading, etc (Green, 2000).

### 2.3.1.1 The subtype hypothesis revisited

There have also been studies that showed no differences in general neuropsychological profiles of patients with early-onset as compared to late-onset (e.g., Swearer, O'Donnell, Drachman, & Woodward, 1992). Green (2000) concurs with Koss et al. (1996) that methodological inconsistencies appear to be responsible for the varying results. The administration of multiple cognitive instruments and the omission of higher-level language assessment in studies of difference appear to have contributed to the inconsistent results. The greater executive deficit in early-onset Alzheimer's disease probably underlies the language disability that researchers have observed. The controversy surrounding subtype classification seems to apply more to the neuropsychological patterns of difference rather than to the histopathological profile and genetic aetiology underlying the disease progression.

Arguments against the 'subtype' hypothesis rely on multiple interpretations of quantitative differences. According to Raskind et al. (1995) and Villareal and Morris (1998), the reserve capacity model can be used as an interpretative tool for the reported differences. The occurrence of more severe atrophy and neurochemical abnormalities are a necessary factor to cause Alzheimer's disease in a younger brain because of the greater reserves available to a younger cortex as compared to the vulnerable aged brain. It is accepted by many researchers (Green, 2000; Radebaugh, Ganguli, & Khachaturian, 1999; Sisodia, 1999; Villareal & Morris, 1998) that Alzheimer's disease is a heterogeneous disease in terms of its clinical and pathological presentation and profile. While Green (2000) argues against a dichotomous classification between disease onsets, she favours the recognition of subtypes to aid with the diagnosis of atypical profiles, prediction of disease progression, and the choice of suitable pharmacological treatments for different pathological lesions.

### 2.3.1.2 A common definition for Alzheimer's disease

In spite of disagreements relating to subtypes, experts agree that in common and scientific parlance, the descriptions suggest that Alzheimer's disease is a progressive, degenerative cortical dementia. The diagnosis of Alzheimer's disease represents three confidence levels based on the premise that there is a deliberate disease progression independent of secondary causes. *Probable* Alzheimer's disease refers to the diagnosis based on the typical profile of the disease, *Possible* Alzheimer's disease is the diagnosis reserved for an atypical disease profile and *Definite* Alzheimer's disease is diagnosed when the neuropathological sequelae are present (Green, 2000; Villareal & Morris, 1998).

This diagnosis criterion follows that of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ARDA) and conforms to the revised DSM-IV standard. The expressions of symptoms are considered stage-dependent. The approximation of stages corresponds with Alzheimer's disease definitions of preclinical, mild/moderate, and severe (figure 2-4a, 2-4b, 2-4c).

In the preclinical stage, atrophy begins in the entorhinal cortex and hippocampus with memory loss the obvious symptom. In the mild/moderate stage larger areas of the cortex begin to shrink and other cognitive and noncognitive signs begin to manifest. Finally, the severe stage is dominated by overall dispersion of tangles and plaques and the person is unable to function and is usually in a vegetative state.

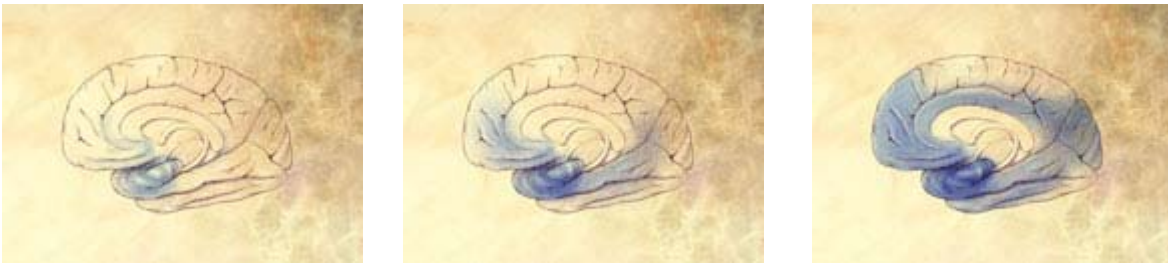


Figure 2-4a, 2-4b, 2-4c Stages of Alzheimer's disease pathology (Rogers, 2002)

Hyman, Duyckaerts, and Christen (1997) suggest the use of the term Alzheimer's syndrome rather than Alzheimer's disease. In their view, this is a better reflection on both the genetic and environmental contributions to pathology. Many factors pre-empt onset age and course of Alzheimer's disease pathogenesis. Genetics, environmental agents, Down syndrome, advancing age, and female gender qualify as risk factors for Alzheimer's disease. Investigators concur (Evans, 1999; Förstl, 1998; Mayeux, 1999; Zec, 1993) that Alzheimer's disease is characterised by a multifactorial aetiology.

### **2.3.2 Theories of aetiology**

Epidemiological and molecular studies have indicated that a small percentage of Alzheimer's patients have a family history of the disorder with an autosomal dominant pattern of inheritance, resulting in what is commonly referred to as familial Alzheimer's disease. The risk of developing this subtype increases exponentially with the number of afflicted immediate family members. Although environmental factors can enhance risk (i.e. shared exposure and acquired behavioural patterns) the contributing aspect is likely to be a genetic polymorphism (Mayeux, 1999).

In the majority of Alzheimer's disease cases, no family history of the disease is evident and these incidences comprise the sporadic cases. A third epidemiological distinction pertains to cases of Alzheimer's disease with a familial aggregation of the disease with an

unknown Mendelian pattern of inheritance. Mendelian genetics refers to the process of inheritance and considers the variability in heredity to be a consequence of discrete factors called genes (Kalat, 2001).

Mendel's work resulted in the theory of chromosomal heredity, according to which each chromosome has a linear pattern of genes, with each gene having a specific location on a chromosome (Gilliam, Kandel, & Jessell, 2000). This also led to the distinction between phenotype and genotype with the latter pertaining to genetic composition and the former to functional expression or appearance. In terms of genetics, large strides have been made in determining the rogue genes located on specific chromosomes that contribute to the onset of Alzheimer's disease pathology (Lautenschlager et al., 1996), and in cases where rogue genes are not implicated, miscellaneous putative risk factors have been named.

#### **2.3.2.1 Rogue genes**

Several genomic research investigations have found mutations or defects in genes localised on chromosomes 1, 14, 19, and 21. The following paragraphs will address research pertaining to mutations on these chromosomes:

- **Chromosome 21**

Among the patients with an early disease onset and an inherited autosomal pattern, aetiology has been correlated with a mutation in the amyloid precursor protein (APP) gene on chromosome 21 (Goate et al., 1991). Altered gene sequences on chromosome 21 form the causative link to Down syndrome. By the age of 40, almost all persons with this

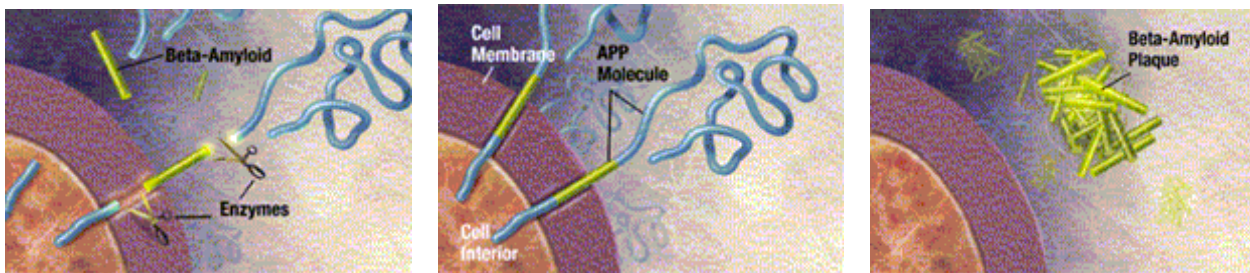
syndrome manifest with the pathological markers of Alzheimer's disease such as APP dysfunction (Brugge et al., 1994).

The A $\beta$  amyloid protein, which includes A $\beta$  1-40, A $\beta$  1-42, and A $\beta$ 1-43, is derived from the APP protein. Structures such as dendrites, cell bodies, and axons have concentrations of APP. People with the gene mutation have concentrations of extracellular A $\beta$  amyloid deposits in the central nervous system. Deposits arise because of a disruption in the amyloid balance due to the mutation, which causes increased secretion of A $\beta$  1-42 and A $\beta$  1-43. According to Price (2000), the neurofibrils observed in the Alzheimer's disease brain are the end products of large deposits of A $\beta$  amyloid (figures 2-5a, 2-5b, 2-5c).

In a milestone study, Yanker, Dawes, Fisher, Villa-Komaroff, Oster-Granite, & Neve, (1989) found evidence that fragments of the amyloid (A $\beta$  1-42) may be neurotoxic and a primary trigger of the neurodegenerative process, thus consolidating its role in Alzheimer's disease pathology. Associated with this hypothesis is the idea that the initial pure memory problems may be the result of synaptic failure, because the earliest symptoms are unaccompanied by obvious brain atrophy. Selkoe (2002) states that in the preclinical stages, the gene mutations may alter and attack the synapses and interrupt transmission of neural impulses before the mutation causes amyloid deposits. Hence, the initial memory symptoms may be attributable to subtle synaptic alterations and research efforts to unravel this mystery at early preclinical phases may elucidate the mechanism of degeneration underlying advanced stages.



Figure 2-5a, 2-5b, 2-5c The process of plaque formation (Rogers, 2002)



The contentious issue arising from the amyloid cascade hypothesis pertains to the identity of the essential ingredient of Alzheimer's disease pathogenesis with the two contenders being amyloid or malfunctioning APP. In a debate defending the two positions (World Events Forum, 2001a), scientists in favour of the amyloid hypothesis argue that the brains of people with Alzheimer's disease always have deposits and the patterns of dispersal parallel other manifestations of neuronal decline. The APP protagonists counter argue that the amyloid hypothesis amounts to tautology. Since amyloid deposits occur in Alzheimer's disease brains, they have a presupposed central role in the pathogenesis of the disease and this correlation has been erroneously attributed to cause neurodegeneration. They proceed further by citing that the most damning evidence against the amyloid hypothesis lies in the discrepancy between clinical and pathological diagnosis. In approximately 20-50% of cognitively intact elderly people, the pathological standard for an Alzheimer's disease diagnosis is achieved, whereas 10-20% of clinically diagnosed probable Alzheimer's disease patients fail to meet this standard.

An extension of this debate involves the  $\beta$ aptists (amyloid scientists) against the tauists (tau protein scientists). The tau proteins form part of the intracellular support structure of neurons and are the constituents of neurofibrillary tangles (Vermersch et al., 1997). The argument encapsulates the deliberations on the central role played by neurofibrillary

tangles (cytoskeletal changes) and synaptic dysfunction (tau protein changes) in the pathology of Alzheimer's disease.

- Chromosome 1 and 14

In other pedigrees of familial Alzheimer's disease, chromosome 1 and 14 are identified with the defective genes (Levy-Lahad et al., 1995; Sherrington et al., 1995). The defective gene identified on the latter is presenilin-1 and on the former presenilin-2. Approximately 10% of patients with Alzheimer's disease manifest with a familial early-onset subtype. Thirty to fifty percent of these cases are linked to presenilin-1 mutations and are characterised by a fast and progressive decline (Laws et al., 2002; Price, 2000). Mutations of presenilin-1 and 2 result in higher levels of A $\beta$  1-43 in experimental groups than in unaffected controls (Schellenberg et al., 1992). Two characteristics of the amyloid isoform underscore its importance in Alzheimer's disease pathology: a high level of neurotoxicity and a tendency for rapid nucleation into neurofibrils.

It appears that Alzheimer's disease linked to these causative genes is characterised by an early disease onset, high levels of amyloid depositions, greater neurotoxic forms of A $\beta$  amyloid, and more neurofibrillary formations.

- Chromosome 19

Association studies of loci in the region of chromosome 19 have identified the apolipoprotein E gene (ApoE) as a likely susceptibility area for familial late-onset (Romas et al., 2002; Strittmatter & Roses, 1995) and for sporadic early-onset Alzheimer's disease (Price, 2000). ApoE gene is a polymorphic lipoprotein defined by three alleles:  $\epsilon$ 2,  $\epsilon$ 3 and  $\epsilon$ 4. Whereas the above three mutations (chromosome 21, 3, and 14) are the result of

causative genes, mutation on chromosome 19 is considered a derivative of a susceptibility gene. The most common allele in the general population is  $\epsilon 3$ . ApoE is produced and secreted in the central nervous system (CNS) by astrocytes, which are common types of glial cells (supporting cells) that function as a physical support base for nerve cells (Price, 2000). The support cells are responsible for phagocytosis, the process of expulsion of dead cells, debris, and waste materials. ApoE's presence in senile plaques, neurofibrillary tangles, and cerebrovascular amyloid suggests an important role in the pathogenesis of Alzheimer's disease.

Saunders et al. (1993) report that the  $\epsilon 4$  allele appears more frequently in late-onset familial Alzheimer's disease patients than in cognitively intact individuals in the general population. The  $\epsilon 4$  is present in 60% of the Alzheimer's disease population in contrast to 22% of the total population. This has led to the conclusion that  $\epsilon 4$  contributes to Alzheimer's disease pathology and is responsible for brain toxicity, neuritic spread, and acute behavioural impairments (Pericak-Vance et al., 1991). Researchers have accepted that  $\epsilon 4$  is a neurotoxic isoform but have rejected the other claims because of insufficient evidence (World Events Forum, 2001b). The dissidents reiterate that the presence of  $\epsilon 4$  does not necessarily contribute to Alzheimer's disease pathology, but rather the lack of  $\epsilon 2$  or  $\epsilon 3$ , and suggest that the role of  $\epsilon 3$  is to clear away amyloid deposition and limit any negative consequences of this deposition process. However, in spite of the accepted role of ApoE to Alzheimer's disease pathology the contributions of specific isoforms are still contestable.

The discussion above centred on genetic mutations that are widely accepted as probable causes or susceptibility agents for the development of Alzheimer's disease pathology. Several other gene mutations on chromosome 10, 12, and 17 have been reported in

literature, but their specific contributions to Alzheimer's disease pathology are unconfirmed (Mayeux, 1999). Apart from genetic alterations other risk factors have been cited as probable contributors to Alzheimer's disease onset.

### **2.3.2.2 Miscellaneous putative risk factors**

According to the environmental hypothesis predisposition to Alzheimer's disease is the result of exposure to environmental factors. These include exposure to toxins, dietary habits, transmissible viral infections, and disturbed metabolism.

Results from animal studies show that aluminium is associated with the formation of structures that are similar to the helical filaments of Alzheimer's disease neuritic tangles (Martin, 1998). According to Janson (2001) aluminium appears to accumulate and have adverse effects on the brain particularly during the ageing process. The concentrations of this toxin are 20 times higher in the autopsied brains of the aged than those of middle aged people and aluminium levels correlated with quantity of senile plaques and neurofibrillary tangles.

In a pioneering epidemiological study on diet and Alzheimer's disease, Grant (1997) verifies that diet was a risk factor for Alzheimer's disease pathology. He inferred a positive correlation between fat/calorie intake and frequency of Alzheimer's disease by conducting a meta-analysis of diet studies in several communities across many countries (Grant, 1999; Smith, Petot, & Perry, 1999). Diet appears to play a modulatory role through its association with oxidative injury and inflammation responses, which are pathogenic aspects of Alzheimer's disease enhanced by amyloid deposition.

There is little evidence to confirm the direct link between these agents and the type of brain damage seen with Alzheimer's disease. However, the importance of environmental agents is evident when dealing with cases of sporadic (non-familial) Alzheimer's disease. In the specific case of sporadic Alzheimer's disease, it is difficult to assign exclusive causal roles to either the environment or genes. If a person develops Alzheimer's disease with no known familial genetic influence and this onset is partially attributed to diet then the argument still incorporates the idea of genetic susceptibility (dietary behavioural habits). The favoured conclusion, amongst Alzheimer's disease researchers, is for a combined risk analysis with genetics and environment as co-determinants of Alzheimer's disease onset. Although the risk factors for the disease is open to debate, when a patient is diagnosed with Alzheimer's disease there are specific biological markers that can be identified as unique to the disease process.

### **2.3.3 Biological markers**

Autopsies confirm the clinical diagnosis of Alzheimer's disease in more than 90% of cases. During the course of the disease, nerve cell death appears in distinct areas with other regions relatively unscathed. Furthermore, the degeneration also alters the neurochemical synthesis because sites of damage often include the primary site for acetylcholine release. The following sections delve briefly into the sites of damage and neurochemical changes.

#### **2.3.3.1 Neuropathological features**

The three central areas in Alzheimer's disease pathology are: the frontal cortex that is the most recent phylogenetic development, parts of the limbic system, and the brain stem. A characteristic feature of the disease is enlarged ventricles and pronounced brain atrophy

with a sequential diffusion, which is widespread but not uniform. There are subpopulations of neurons with susceptible architectural areas, which survive the pathological changes accompanying Alzheimer's disease (Gomez-Isla & Hyman, 1997). The path of destruction is sequential in terms of involved areas but is not uniform in terms of the destruction of specific architectonic neuronal units. The neurodegeneration is distinct in the temporoparietal and anterior frontal regions and includes the association cortices, hippocampus (pyramidal cells), amygdala, nucleus basalis of Meynert (cholinergic system), olfactory regions, locus coeruleus, and the raphe nuclei (monoaminergic system). The areas with minimal or no infarction include the primary motor and sensory areas, thalamus, basal ganglia, and cerebellum (Parks et al., 1993). The degeneration of the brain areas corresponds with the clinical signs and symptoms of the disease because the morphological design of the brain system reflects functional capacity. Hence, atrophy will manifest as impairment.

Alois Alzheimer (1907/1977) also refers to the cytoskeleton changes reflected in the presence of neurofibrils. These structures are filaments that collect intracellularly and consist of special proteins including the tau protein. The deposition of proteins leads to the development of two types of substances namely, neuropil threads, and senile plaques. The neurofibrillary tangles emerge because of cytoskeletal alterations in nerve cells. The cytoskeletal abnormalities are constituents of neuritic extensions, which are uncontrollable because of oligodendrocyte (glial cell) dysfunction (Braak & Braak, 1996). Cytoskeletal changes influence cell structure by impeding protein transport and other functions. The compromised viability of transport affects cell functioning by altering synaptic communication. This leads to the eventual death of the nerve cell and the tangles are "left behind as tombstones of the cells destroyed by this disease" (Price, 2000, p. 1154). In an investigation on cytoskeletal alterations and neuropil formations, Braak, Braak, and

Mandelkow (1994) showed that these alterations occur sequentially and form neurofibrillary tangles in the temporal area, amygdala, and hippocampus.

Interestingly, the diffusion of tangles follows a pattern that is opposite to that of brain myelination during development. In other words, the atrophy commences in sparsely myelinated areas and proceeds to areas of dense myelination (Braak & Braak, 1997). The process of degeneration usually begins in the transentorhinal area and progresses to the hippocampus and then to the neocortex. According to Braak and Braak (1997), this sequence of development allows for the distinction of stages of Alzheimer's disease progression. The following six stages are identified by the researchers: (a) transentorhinal I-II, which characterises the preclinical silent stage, with no observable cognitive decline; (b) limbic stages III-IV, which characterises incipient Alzheimer's disease, with hints of cognitive impairment and behavioural change, and (c) neocortical stages V-VI, which correspond to the clinical stage, with a clinical diagnosis of Alzheimer's disease.

The dispersal and density of senile plaques is less consistent in comparison with tangles, and seem to be a weaker predictor of clinical symptoms. These histopathological features also occur in the general ageing population, however they are more numerous in Alzheimer's patients. In comparison with age-matched controls, patients with Alzheimer's disease have a higher density of senile plaques in the neocortex. The plaques predominate in the neocortical layers, parts of the dentate gyrus, and amygdala. Their presence has been observed in the primary sensory and motor cortex, which even at advanced disease stages, may remain clinically silent (Arriagada, Growdon, Hedley-White, & Hyman, 1992). Gomez-Isla and Hyman (1997) found a correlation between the frequency of tangles and dementia severity, but no correlation between the number of plaques and disease progression. They concluded that the presence of neurofibrillary

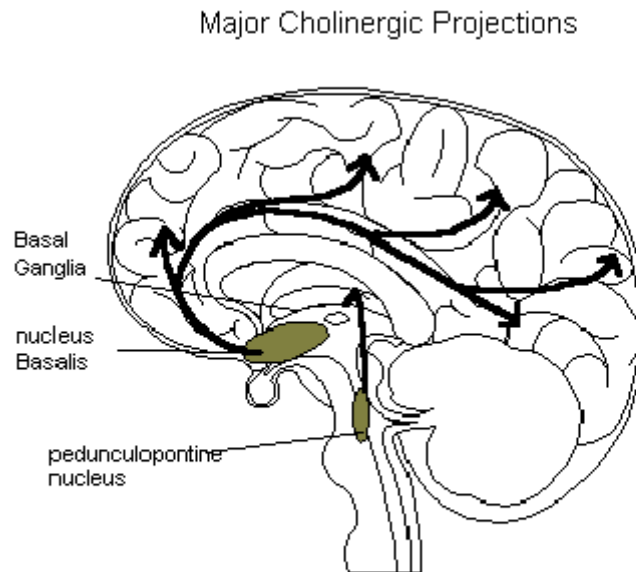
tangles is more closely associated with clinical symptoms than the quantity or dispersion of senile plaques. The presence of these anomalies also affects the neurotransmitter systems, particularly the cholinergic network.

### **2.3.3.2 Neurochemical features**

The histological changes mentioned above are concentrated within the cholinergic neuronal circuitry. The cholinergic pathways linking the nucleus basalis of Meynert the cerebral cortex and those linking the septum to the hippocampus are both functionally compromised in Alzheimer's disease (Schatz & Chute, 2000). The cholinergic projections to the cortex and hippocampus arising from these basal forebrain and septal areas contain neurons that produce primarily acetylcholine (figure 2-6). The areas incorporated in this pathway are involved in the mediation of different behaviours. In the cortex, acetylcholine mediates cognitive functioning, in the hippocampus, it correlates with memory and learning, and in the amygdala, it influences processes involved with emotional behaviour. Its association with brain signal to noise ratios may also indicate some contribution to mediating temperament thresholds (this will be discussed in the following chapters).

The nucleus basalis of Meynert branches into all parts of the cortex but receives afferents only from multimodal frontal and temporal association cortices. Being the source of cholinergic influence on the cortex and thalamus, this structure exerts direct and indirect influences on all tiers of cortical processing. In Alzheimer's disease, the axons of the cortex (endpoint) and the axons of the nucleus basalis of Meynert (root) are destroyed and the cortical feedback and feedforward loops are rendered ineffective (Van Hoesen, 1997).





**Nucleus basalis projects to the neocortex**  
**PPN projects to the thalamus**

Figure 2-6 Acetylcholine projection pathways destroyed in Alzheimer's disease (Schatz & Chute, 2000)

Damage to the afferent and efferent branches lead to many cascading events of which the low level of acetylcholine in Alzheimer's disease autopsied brains is one. Cholinergic destruction is also responsible for disrupting glutamate, GABA, serotonin, and norepinephrine levels (Cohen & Servan-Schreiber, 1992). Whereas, the cholinergic effects tend to be cognitive (memory), the other neurotransmitters influence the neuropsychiatric and behavioural profile of the disease. Thus, the emerging clinical profile parallels the neurochemical and functional systems abnormalities that arise from structural atrophy.

## **2.4 Alzheimer's disease in perspective**

This degenerative disease of the brain is poised to become the seminal consequence of human longevity. To counter this, research initiatives have probed for causes and cures from many perspectives in order to unravel the mystery of this brain disorder. These initiatives have uncovered a real disease distinguishable from normal ageing, complicated by patterns of genetic inheritance and environmental input, and characterised by a heterogeneous clinical profile. As a neurodegenerative disease, it commands special interest from neuroscientists because of its clinical course and patterns of degeneration. It starts out as a disease of memory impairment with a concomitant loss of limbic and associative functions, and ends with the insidious dissolution of the abilities to encode, retrieve, and reason.

Figure 2-7 (adapted from Masliah, Mallory, Alford, de Teresa, Iwai, & Saitoh, (1997) is a graphical synopsis of discussion in this chapter.

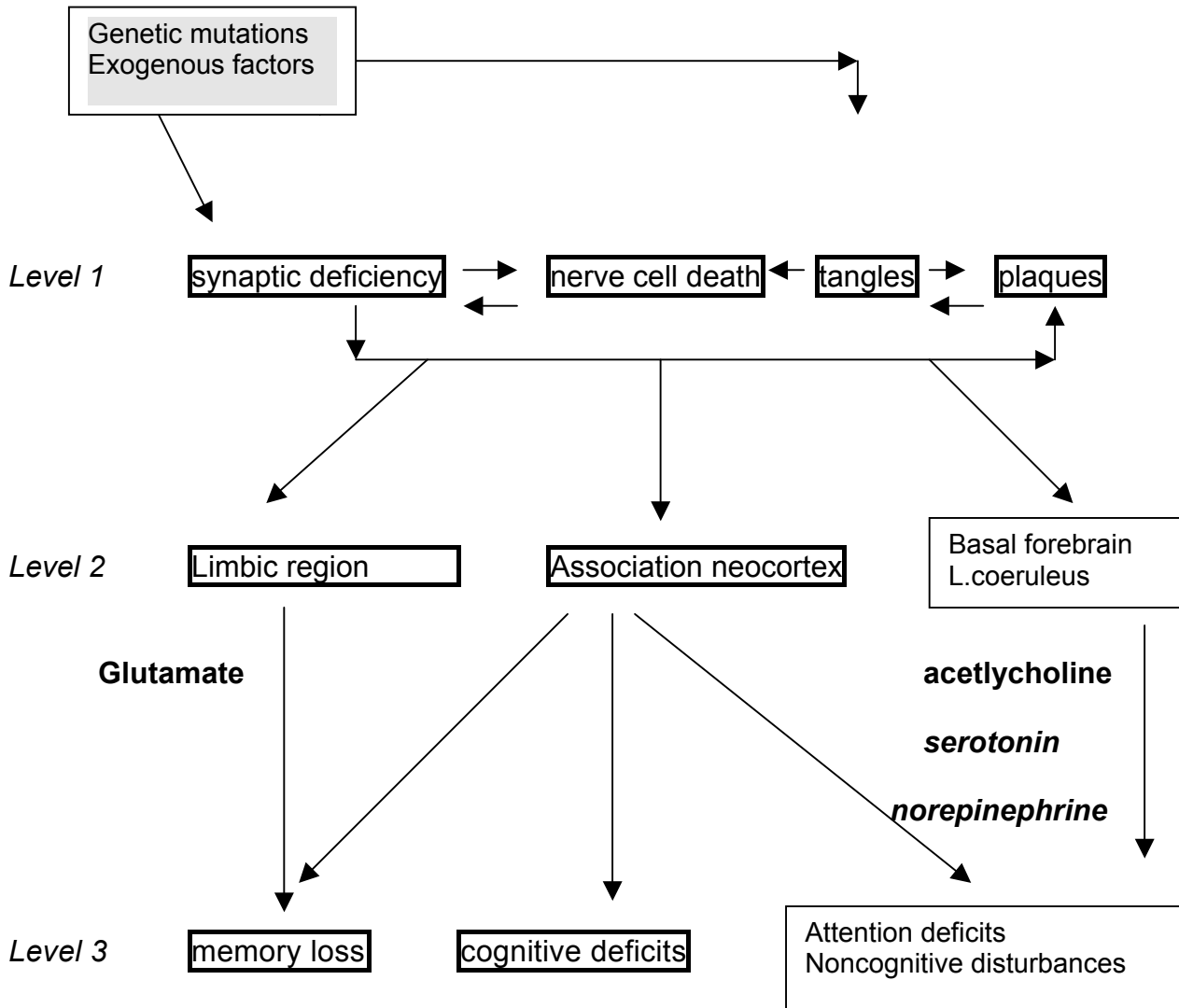


Figure 2-7 Alzheimer's disease: Neurobiological processes and mechanisms

The following chapter addresses the cognitive and noncognitive symptoms (characteristic neuropsychological profile) associated with the neurobiological markers outlined in this chapter.