

**Neuropsychological symptoms and premorbid temperament traits in
Alzheimer's dementia**

by

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Summary

The aim of this study was to investigate the relationship between noncognitive symptoms and premorbid temperament in a group with Alzheimer's disease. The relationship between premorbid temperament and noncognitive symptoms can be used to understand symptom susceptibility and risk, caregiver burdens, as well as providing insights into the neuroanatomical substrates of temperament and noncognitive behaviour. Sixty-three primary caregivers of Alzheimer's patients fulfilled the eligibility criteria for this study. Information regarding the noncognitive symptoms and premorbid temperament was procured from the primary caregivers. In fifty-one cases, a secondary caregiver also provided information about the premorbid temperament of the Alzheimer's patient. The latter was obtained to enhance the reliability of retrospective data. The Behaviour Rating Scale for Dementia, the Formal Characteristics of Behaviour-Temperament Inventory, and the Blessed Dementia scale were used to elicit data on noncognitive symptomatology, premorbid temperament, and current cognitive status, respectively.

Noncognitive symptoms were grouped into two clusters namely neuropsychiatric and neurobehavioural disturbances. The neuropsychiatric cluster included mood and psychotic symptoms and the neurobehavioural cluster included vegetative and overall behavioural dysregulatory symptoms. Results showed that there is a wide spectrum of noncognitive symptom manifestation in patients' profiles and that the neurobehavioural dysregulatory symptoms are more common than the neuropsychiatric symptoms in this Alzheimer's cohort. With regard to symptom manifestation and cognitive status, a Pearson product moment correlational analysis showed that a lower level of cognitive functioning is significantly associated with aggressive episodes and a higher level of cognitive functioning with manifestations of depressive symptoms.

In terms of interrater concordance on premorbid temperament ratings, intraclass correlations were significant for five of the six temperament domains, thus indicating a reliable estimate of premorbid disposition. Canonical correlational analysis yielded two significant variates. The first variate indicated that Alzheimer's disease patients with a proclivity for aggressive behaviours and general behavioural deregulation but lower depressive profiles, were premorbidly more emotionally reactive, had low sensory thresholds (high sensitivity), and greater cognitive deficit. The second variate showed that patients with Alzheimer's disease who tended to manifest with depressive and dysregulatory behaviour appear to have been premorbidly perseverative in temperament with a low sensory threshold (high sensitivity) and the tendency to maintain and attain a low level of activity (stimulation). Taken together, the significant variates revealed a dimensional relationship between depressive symptoms, aggressive symptoms, and behavioural dysregulation; and sensory sensitivity, emotional reactivity, perseverance, and activity, with cognitive status serving as a moderating variable. In conclusion, the study indicated a dimensional relationship between specific premorbid temperament traits and noncognitive symptoms, thereby highlighting the possible predictive influence of premorbid temperament on noncognitive manifestations in Alzheimer's disease patients.

Keywords

Alzheimer's disease, noncognitive disturbances, premorbid temperament, neurobehavioural symptoms, neuropsychiatric symptoms, neuropsychology, Regulative Theory of Temperament, Behaviour Rating Scale for Dementia, Formal Characteristics of Behaviour-Temperament Inventory, Blessed Dementia Scale.

CHAPTER 1

INTRODUCTION

*"The Brain - is wider than the Sky – For - put them side by side –
The one the other will contain - With ease - and You - beside-."*

Emily Dickinson (1999)

The answers to archaic questions have ebbed and flowed with the tides of changing thoughts and discoveries. The proverbial giant turtle once served as the pivot on which a flat world balanced, until a leap of faith and logic illuminated the void beneath which the giant turtle rested. Notions such as these have their parallels in the progressive history of neuroscience. Some great thinkers were wont to sharing untested and sensational theories whereby they paradoxically devolved to the brain great faculties of thought but judicious responsibility: it was Flourens who proposed that the brain secretes thought as the liver secretes bile (cited in Kandel, 2000). It has been a long path of discovery from the early cephalocentric theories of brain function to the current day notions of functional systems, and many metaphors derived from computer science, mechanics, philosophy, and cybernetics have served as heuristics for understanding functional systems.

Alzheimer's disease, named after Alois Alzheimer who discovered this insidious and progressive degeneration of the brain, by virtue of its neuropathological, cognitive and noncognitive manifestations encompasses the notion of dynamic interacting systems that underlie human thought, emotion, and behaviour. In terms of the neuropathological and cognitive substrates, this disease is imbued with a relative uniformity that expedites classification and diagnosis. The noncognitive manifestations, however, hint at an intricate network of psychological and biological antecedents and disease processes that may confound the occurrence of these manifestations. The latter conjecture is strengthened by illustration; studies have found that neuropathology alone cannot account for the

heterogeneous noncognitive profiles observed in Alzheimer's disease patients. By implication, it illuminates the need to understand the ontology of the antecedents that may colour the neuropsychological profile of an Alzheimer's patient.

In this brief chapter, the problem statement, research questions, aims, and hypotheses are described. Thereafter a chapter-by-chapter synopsis is provided.

1.1 Problem statement

As mentioned above, noncognitive features that accompany Alzheimer's disease are not directly attributable to underlying neural pathology nor are they sufficiently explained as by-products of cognitive impairment. One of the reasons for the limited research interest in noncognitive features pertains to the methodological challenges that face researchers. Firstly, standardised rating instruments for the noncognitive manifestations have only recently been developed, but even these instruments often do not address the gamut of noncognitive features. Secondly, unlike the strong theoretical and experimental paradigms underlying cognitive research, the area of noncognitive Alzheimer's disease symptoms has no comparable epistemology. The consequence of this has been a proliferation of terms that muddy the conceptual waters and discourage comparisons among studies. Moreover, different terms and descriptions of disease symptoms have contributed to the equivocal findings reported by researchers. Thirdly, caregivers serve as collateral sources of information because of the incapability of Alzheimer's patients to provide information. This creates a methodological dilemma that concerns the issue of retrospective bias and caregiver issues influencing the rating of challenging behaviours. Finally, most studies are cross-sectional because of the high attrition rate in the target population and the influence of age-related co-morbid conditions. Cross-sectional studies cannot address the issue of

symptom change in the disease course and is limited to providing insights on symptom manifestation in different age, gender or neurologically impaired groups. The current proliferation of studies, however, attests to the importance of noncognitive symptoms to caregivers and the acceptance of these in the clinical presentation. Caregiver psychological mortality and decisions to institutionalise their wards is usually precipitated by the onset and progression of noncognitive challenging behaviours.

Taken together, the fact that noncognitive symptoms may not entirely be by-products of cognitive decline and they reflect underlying functional and structural mutations, the deliberations provide a motivation for investigating the probable correlates of noncognitive features. One of the dimensions or antecedents of noncognitive manifestations have been identified as premorbid temperament disposition. This possible association arises from: a) the involvement of temperament as a predictor of general psychopathological onset (Andrews, 1996) and, b) the findings that temperament may act as salutogenic factors that protect against psychopathological onset (Cederblad, Dahlin, Hagnell, & Hansson, 1995.). The association between temperament and noncognitive manifestations in Alzheimer's disease is likely on two levels. On a psychological level, the hypothesis states that adaptive responses to the environment are mediated by certain dispositional traits and Alzheimer's disease creates stimuli-response conditions that may cause usually normative adaptation to present as maladaptive, depending on the premorbid disposition of a person. On a neural level, the hypothesis states that the disease alters specific neurochemical and morphological connections and the latter have inherent thresholds and connectivity patterns that are differentially optimal for people with different dispositions. By inference, it would seem that an alteration will influence outcome differentially depending on the inherent threshold levels and functioning of connected systems.

This thesis therefore, investigates the viability and variability of noncognitive symptoms and addresses the relationship between these neuropsychological correlates and premorbid temperament in a cohort with Alzheimer's disease.

1.2 Research questions

The following research questions arise from the above discussion:

- What is the nature and frequency of neuropsychiatric and neurobehavioural (noncognitive) symptom occurrence in Alzheimer's disease?
- What is the relationship between noncognitive symptom occurrence and patient characteristics such as age, gender, education level, and cognitive status?
- How does retrospective bias colour the impressions of caregiver descriptions of premorbid temperament and current ratings of noncognitive disturbances?
- What is the relationship between premorbid temperament and noncognitive symptom profile?
- On what premorbid trait dimensions can one predict the occurrence of specific noncognitive disturbances?

1.3 Research aims

The aims are divided into a primary aim and a secondary aim.

1.3.1 Primary aim

The aim of this study is to elucidate the relationship between noncognitive symptoms and premorbid temperament in a group of people with Alzheimer's disease.

1.3.2 Secondary aim

Measures of temperament and noncognitive manifestations can be utilised as important components for understanding symptom susceptibility and risk, caregiver burdens, as well as providing insights into the neuroanatomical substrates of temperament and noncognitive behaviour.

1.4 Basic hypotheses

- a. There is a significant relationship between primary and secondary informants' ratings of premorbid temperament.
- b. There is a significant relationship between the occurrence of noncognitive symptoms and premorbid temperament disposition in persons with Alzheimer's disease.

1.5 Chapter synopsis

Chapter 2 is an exploration of the neurobiological concomitants of Alzheimer's disease. It delves into the identity of Alzheimer's disease and provides evidence for a disease process separate from normal aging, and utilises principles of dynamic systems to juxtapose deterioration observed in Alzheimer's disease with degeneration observed in

normal aging. The chapter also addresses the aetiology and neuropathology of Alzheimer's disease.

In Chapter 3, the theoretical information and literature review of the neuropsychology of Alzheimer's disease is separated into two parts. Part I of Chapter 3 engages debate on the cognitive bias that accompanies research on brain diseases such as Alzheimer's and the methodological issues that challenge research in the noncognitive domain. Finally, utilising the neurobiological information addressed in the preceding chapter, a case is presented for the amalgamation of noncognitive and cognitive symptoms based on the reciprocal workings of the neural substrates that produce such behaviours. Of note, the term neuropsychology in this thesis refers to both cognitive and noncognitive features, following the idea of reciprocity of function as endorsed by Taylor and Saint-Cyr (1995). The term noncognitive is used to describe specific features, and for descriptive purposes to distinguish them from 'cognitive' aspects. Furthermore, noncognitive alludes to both neuropsychiatric and neurobehavioural symptoms that accompany the disease.

Part II of Chapter 3 provides an extensive literature review on the noncognitive symptoms observed in the disease, and utilises the triadic categorisation of Burns, Jacoby, and Levy (1990a, 1990b, 1990c, 1990d) to illustrate the prevalence, co-morbidity, and phenomenology of various disorders of thought and perception, disturbances of mood, and behavioural dysregulation. The latter symptoms include neurovegetative features, and the disorders of thought and perception and mood that account for the neuropsychiatric symptoms. Chapter 3-I shows that noncognitive symptoms may be related to cognitive impairment not in a causal manner but rather reciprocally if one considers neurobiologic deterioration as malfunctioning of dynamic systems. The reviews in chapter 3-II suggest that although the results of many studies are equivocal, there is consensus among

researchers that noncognitive disturbances do occur and confound the caregiving process. If one accepts the contention that noncognitive symptoms may not be merely by-products of cognitive impairment then by inference one is motivated to better understand the factors or dimensions that may be associated with noncognitive manifestations.

One such factor that is implicated as an antecedent for symptom manifestation is premorbid temperament disposition. Chapter 4 focuses on the biological premise of temperament and elaborates on the various theoretical accounts of temperament as a prelude to interpreting and discussing the relationship between premorbid disposition and noncognitive symptoms.

The above discussions contain the investigative parameters of this thesis and provide the motivation for the operationalisation of noncognitive symptoms and premorbid disposition as the primary variables in this study. Chapter 5 outlines the processes that were followed in the course of the empirical investigation. This includes the procedure followed in obtaining the sample, the design of the study, the instruments used and their relevance to the study, and finally the statistical analyses that were conducted.

The results of the empirical study are presented in Chapter 6 with the aid of figures and tables. The results pertain to the frequency of symptoms that occur, the association between primary and secondary caregiver ratings of premorbid temperament, and finally to the association between noncognitive symptoms and premorbid temperament.

Chapter 7 attempts to interpret and discuss the results with reference to the biological theories of temperament outlined in chapter 4, and the neurobiological theories of

Alzheimer's disease espoused in chapter 2. Finally, the limitations of the study and recommendations for future investigations are provided.

From the preceding synopsis, the chapters are organised in the following manner to enhance the logistical flow:

- Neurobiology of Alzheimer's Disease
- The Neuropsychology of Alzheimer's Disease: Part I & Part II
- Theoretical Foundations of Temperament
- Empirical Investigation
- Results
- Discussion

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).

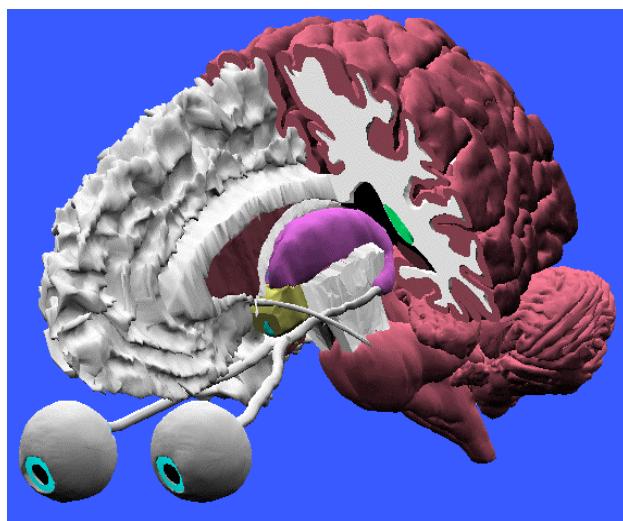


Figure 2-1 An anterolateral view of the brain and underlying white matter (Sundsten & Mulligan, 1998)

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

suberves 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.

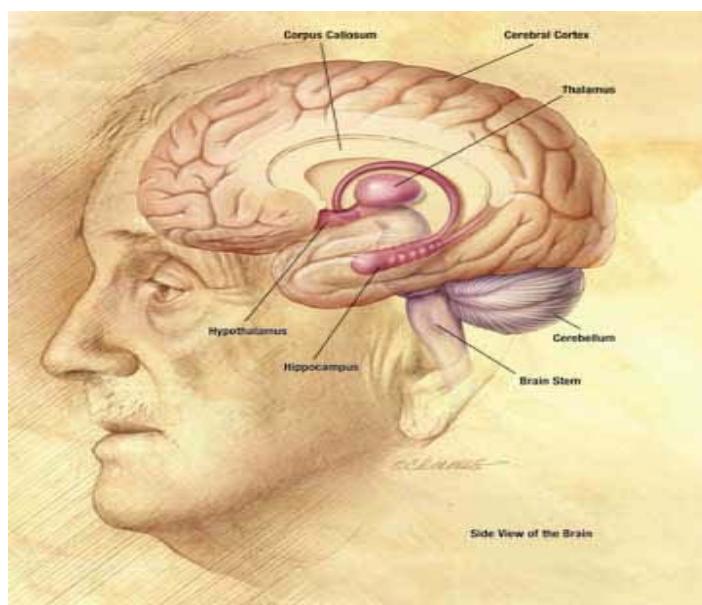


Figure 2-2 Saggital section of the brain with parts of the limbic system (Rogers, 2002)

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 conjunctival 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:

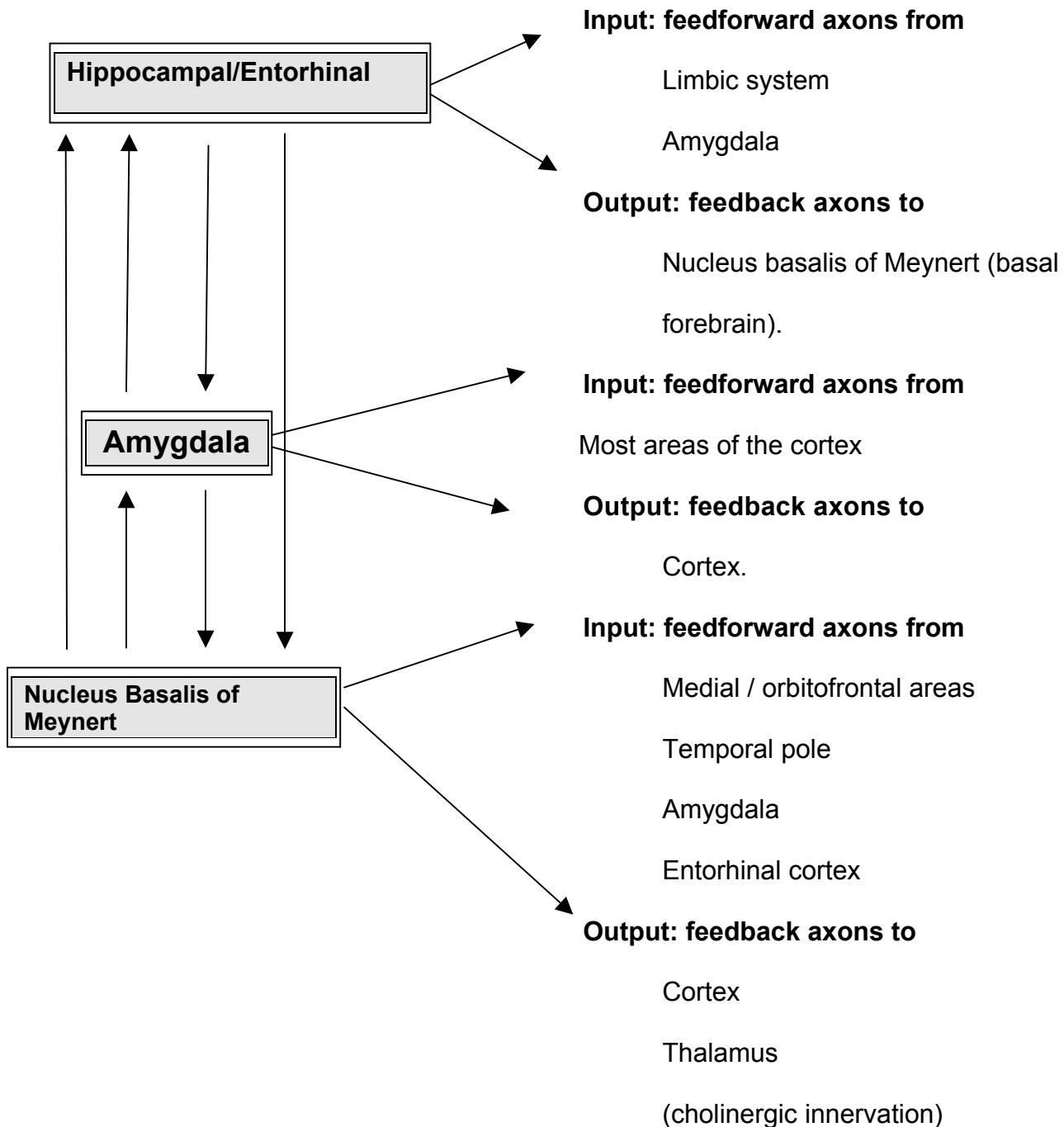


Figure 2-3 Input-output memory pathways

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 21st 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 19th 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 (β -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

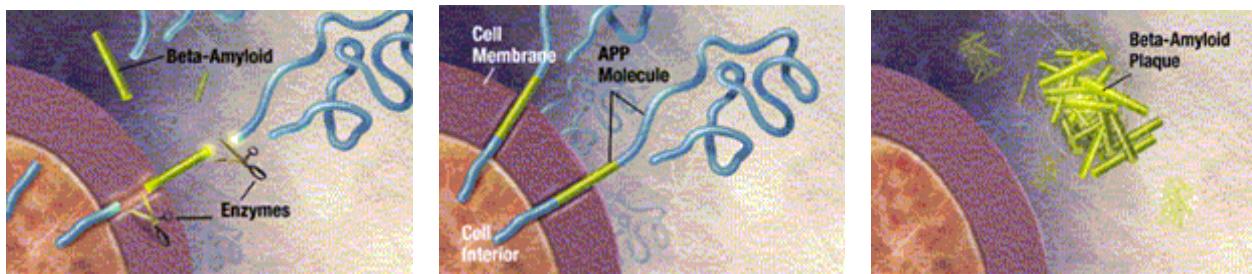
Among the patients with an early disease onset and an inherited autosomal pattern, aetiology has been correlated with a mutation in the amyloid precursor protein (APP) gene on chromosome 21 (Goate et al., 1991). Altered gene sequences on chromosome 21 form the causative link to Down syndrome. By the 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 β amyloid protein, which includes A β 1-40, A β 1-42, and A β 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 β 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 β 1-42 and A β 1-43. According to Price (2000), the neurofibrils observed in the Alzheimer's disease brain are the end products of large deposits of A β 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 β 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 β -apoptists (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 β 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 β 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: ϵ 2, ϵ 3 and ϵ 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 tempoparietal 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 neuofibrils. 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 inchoate 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

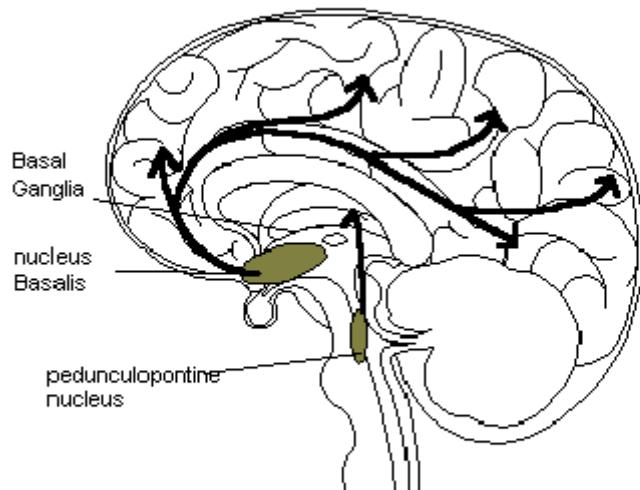
tangles is more closely associated with clinical symptoms than the quantity or dispersion of senile plaques. The presence of these anomalies also affects the neurotransmitter systems, particularly the cholinergic network.

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).

Major Cholinergic Projections



**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.

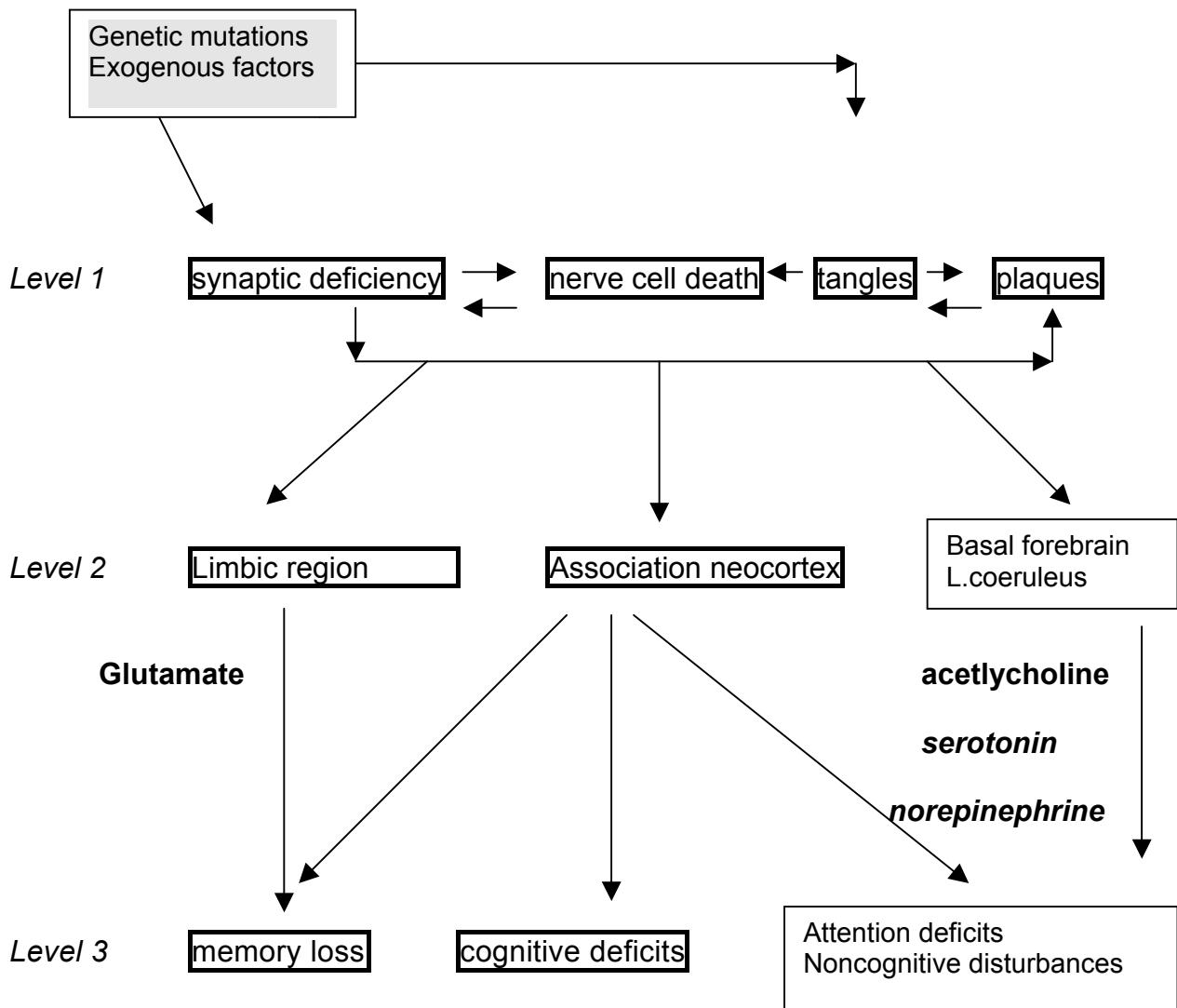


Figure 2-7 Alzheimer's disease: Neurobiological processes and mechanisms

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

CHAPTER 3.1

THE NEUROPSYCHOLOGY OF ALZHEIMER'S DISEASE:

COGNITIVE SUBSTRATES

An acquaintance with these disorders [of mind] unlocks a mine of discoveries with a direct bearing on everything connected with the life of the mind. The study of dementia does not simply uncover a body of general laws; it opens up before us a wealth of profound insights into the history of development of the human mind, both of the individual and of the entire human race.

(Kraepelin cited in Christen & Churchland, 1992, p. vii).

The preceding chapter on the neurobiology of Alzheimer's disease addressed the question of why the disease may arise, not how it manifests in certain individuals. Addressing the latter invokes debate about the functions and interactions of specific neuronal circuits or brain modules.

It is widely known that evolutionary forces have crafted the brain circuitry and encoded the circuits with adaptive algorithmic sequences. Rational output, which ensures timely and appropriate actions, is a derivative of neuronal interactions (responses) matched to environmental demands (stimuli). Dialectical thought, which is a component of rational output, endows humans with the ability to exercise choice and make decisions in forums of ambiguity, which are created by environmental and social interactions. When a brain disease compromises modular interaction, adaptive algorithmic sequences are disturbed, and the cumulative desynchronous mental output reflects an impoverished attempt to apply dialectical thought or personal intelligences in these forums (Stuss, Gow, & Hetherington, 1992). Alzheimer's dementia strips away abilities that have developed over the life span and insidiously allows the devolution of the self. The correlates of this devolution are an inability to maintain complex interactions, regulate emotions, and conform to societal expectations. Although the neuropathology and cognitive symptoms

are relatively homogeneous, this disease manifests with a pleomorphic noncognitive profile that is challenging to both caregiver and patient.

Neuropsychological studies have largely focused on the cognitive aspects of the disease and discounted the noncognitive symptoms that may be associated with the devolution of the self. The following sections incorporate a brief account of this bias and researchers' attempts to stymie this bias by revoking archaic notions of the mind-brain dialectic.

3.1.1 Cognitive morbidity: Necessary or sufficient disease index

The clinical heterogeneity that informs the disease process has been the subject of substantial scientific inquiry. Early studies provided retrospective evidence of a biomedical and cognitive emphasis in descriptions of Alzheimer's disease (Berrios, 1989; Bozzola, Gorelick, & Freels, 1992; Burns et al., 1990a; 1990b, 1990c, 1990d; Donaldson, Tarrier, & Burns, 1998; Stokes, 1996; Ware, Fairburn, & Hope, 1990).

This cognitive accentuation arose from the widely held belief that noncognitive (neuropsychiatric and behavioural) changes were secondary to or a by-product of cognitive deterioration (Fairburn & Hope, 1988). Moreover, with the adoption of the cognitive paradigm, scientists viewed cognitive morbidity (deterioration in memory, attention, language, and executive functioning) as a sufficient index for description and diagnosis, but eschewed the importance of mood and behavioural referents (Berrios, 1989).

This diagnostic emphasis on cognitive dysfunction is traceable to the historical discourse on the emotion-cognition debate espoused by neurophilosophers such as Plato, Aristotle, Descartes, Darwin, and James. Definitions of disease arise from interactions between

descriptive language and observed physical processes, and since the former reflects the “belief of its users, disease creation is also a social phenomena” (Berrios, 1990, p. 356). The vantage point adopted in understanding phenomena determines the utility of certain definitions and the cognitive paradigm dismissed the occurrence of noncognitive features in Alzheimer’s disease. Once a given discourse is subscribed to, certain definitions are promoted, yet the implications of these embedded definitions are often obscured (Foucault, 1975). Thus, the exclusion of noncognitive elements in past studies reflected the underlying prejudice of observers and reliance on the dominant argumentation rather than a change in the disease profile.

A concomitant development from the biased nomenclature has been the widespread administration of pharmacological aids used to impede the progress of cognitive deterioration. A significant side effect of these early interventions was an increased awareness that behavioural and neuropsychiatric symptoms influence presentation profiles and hence, clinical heterogeneity. Furthermore, a pure division between cognitive and noncognitive is unachievable because of the nonspecificity of terms and the considerable overlap in presentation, for example, a demented patient with agnosia may become fearful and anxious (noncognitive) because he/she cannot identify a spouse or family member because of cognitive impairment (Rabins, 1996). Khachaturian (1996) concurred that there is reciprocity between the cognitive and noncognitive and even this division of behaviours into domains should only be done for understanding structural and neurologic circuits.

Alzheimer’s disease provides a suitable model for the deliberations on mind-brain interaction, and on the different features of human thought and behaviour gone awry. In

this light, it serves as a metaphor that provides a heuristic for understanding mind-brain interactions, a theme that will be elucidated in the following subsections.

3.1.1.1 Emotion and intellect: Estranged bedfellows

Alzheimer's disease traverses the category of neurological diseases that is typically characterised by the insidious plundering of the incumbent's brain and mind. The faculties of intellect, rational thought, or cognition appear to have a brain base and the vast amount of research on Alzheimer's disease promotes this brain science. Emotion and noncognitive features seem to arise from a mind source with a concomitant intangibility, which renders it partly illusive to scientific scrutiny.

The Cartesian rooted oversight of mind has influenced how certain diseases have been perceived, and in a general sense functional manifestations (psychosis and affective disturbances) have been assigned roles in disease profiles that are secondary to cognitive components. The dualistic paradigm has informed the ranking of intellect as a superior faculty and emotion as its inferior counterpart.

Damasio's (1994) invocation of the philosophies of Descartes led him to the conclusion that the dualistic division of the tangible from the intangible has its parallel in the division and categorisation of neuroanatomical sites responsible for the origination of emotion and intellect. The morphology of the brain includes two primary over-arching structures namely, the neocortex and the subcortex. The former is associated with advanced evolutionary capacities and the latter with primitive repertoires associated with emotion. Although the primary neural sites of processing can be singularly defined in terms of function, it is the manifestations of diseases like Alzheimer's disease that show the integrated workings of both the subcortical and neocortical structures.

The history of neuropsychology mirrors this dichotomy between the elements of reason and affect/behaviour in its parallel contemplation about the neurophilosophy of mind and brain. Neurophilosophers have participated in interminable debates to solve the puzzle of reductionism. They endeavour to map the workings of the mind onto the neuroarchitecture of the brain with the aim of collating psychological abstractions with their neuroscientific mechanisms (Churchland & Churchland, 1992; Rapoport, 1992). Thus far the cognitive domains of language and memory, for example, have been aligned with their neuroanatomical substrates with greater ease than their counterparts of emotion and social conduct. A concomitant bias is observed in the labelling of diseases with observable pathology/lesions as organic, and the labelling of diseases that showed no brain atrophy as functional or psychological (Kandel, 2001).

Together with the advancements in brain science it was more likely then that brain diseases would be conceptualised in cognitive terms. Studies on sensory deprivation and learning have shown that the conceptual boundaries of this distinction, between functional and organic, are nebulous. Advancements in neuroscience have uncovered many of the mysteries of the brain yet Korzybski's notion that the "map is not the territory" hints at the discoveries on emotion and behaviour that are yet to be made (cited in Bateson, 1972, p. 455). What gets onto the map is determined by the protagonists of the time and neuroscientists have now been contemplating descriptions of brain disorders beyond the biomedical fringes, and psychological studies have been moving away from the cognitively dominant trends that prevailed in the field.

3.1.1.2 Psychological states and parallel neural representations

Kitwood (1996) proposes a consolidation of the mind-brain viewpoint that can be applied to understanding dementia. Adopting a monistic outlook, he suggests that long-lasting psychological states have their basis in brain structure. The most perplexing thing about this relationship is the essence of causation. He suggested that long-lasting psychological experience () can be associated with changes in neurophysiology and neurochemistry and can be equated to a brain event/state (b). These neural changes occur within a closed system or structure, which depends on two processes. Firstly, this structure develops through interaction with the environment over the life span (B^d) and secondly, it is vulnerable to disease and age-related neuronal losses (B_p). The equation reflecting the above processes can be stated as:

$$\frac{\text{---}}{B^d, B_p} \approx b$$

Thus, changes that accompany dementia such as cognitive and noncognitive disturbances initially concern changes in b . The plasticity of the brain creates the opportunity for alterations of function to eventually affect alterations in structure. Kandel (2001) affirms this by stating that diseases labelled as functional (psychological) affect the neurons or synapses and culminate in a biological event or process. Hence, a change in B_p follows, and this is observed as gross anatomical lesions on brain scans. One is tempted to conclude that symptoms of dementia can eventually be reduced to neuropathological changes. However, this alteration in B_p (neuropathological) does not address the heterogeneity of the clinical presentations. Neuropathological studies have failed to

account for 80% of the clinical variance when degree of dementia and severity of lesions are compared post-mortem (Kitwood, 1989).

Theories of dementia have neglected issues dealing with the aspects such as learning, experience, temperament, and psychodynamic processes that also appear to determine resilience and vulnerability to pathological brain processes. Including B^d as a component in dementia allows for explanations that may account for some of the variance observed. Therefore, Kitwood (1989, 1996) believes that the mind-brain dichotomy can be overcome if one follows the premise that persisting psychological states have parallel representations in neural structure and the changes in structure are informed by external factors, which determine critical levels of vulnerability and resilience to damage.

This equation was also considered by Humphrey (2002), who aligned mental states (m) with brain states (b). His proposition to solving the mind-brain problem is to define dimensions of mental states, particularly noncognitive elements, as emergent properties that are borne from the collective exploits of brain areas. These attempts at resolving the debate, implicitly guide one's thoughts to the impossibility of disjoining the psychical and physical and disease symptoms and disposition, in other words 'the neural foundations of the self' (Sachs, 1985, p. 10).

3.1.1.3 A symphony of emotion and intellect: Frontal orchestration

Utilising Kitwood's (1996) theory of process, one is drawn to particular functional systems located in the frontal lobes of the brain, which may underlie the amalgamation of mind-brain processes.

The usefulness of Alzheimer's disease in elucidating mind-brain relationships arises from the evidence that in this disease it is the temporal lobes and hippocampal areas that show uniform atrophy, whereas the frontal areas are not "uniformly severely involved pathologically, structurally, or functionally" (Jagust, 1999, p. 110). The randomness of this atrophy, therefore allows for associations between certain anatomical dysfunctions and behaviour and between psychological process (B^d) and brain states (B_P).

The frontal lobes make up about 33% of the entire cortical surface in humans and are considered as the most advanced structure in a phylogenetic and ontological sense. Their importance and complexity is underscored by three anatomical divisions (precentral, prefrontal, and limbic), which produce complex pathways and circuitry to other regions of the brain. For example, circuits from the precentral area directly to the spinal cord are involved in the control of fine hand, finger, and facial movements; circuits from the frontal lobe via synapses in the basal ganglia are involved in the control of gross limb and body movements; and the limbic component has interconnections with limbic and paralimbic structures involved in emotion, mood and motivational outputs (Mega & Cummings, 1994).

The prefrontal area has further histological divisions with extensive connections to the entire central nervous system. The prefrontal cortex mediates higher order processes such as the sequencing and organising of behaviour and thought. Internal representation and temporal organisation are terms used to describe the memory and timing role of the prefrontal cortex, which influences aspects of personality and behaviour.

The prefrontal cortex stands out as the area that co-ordinates many cognitive and noncognitive functions for the purpose of adaptive outcomes (Martin, 1998). For example, the processing of sensory data is handled by its links with association cortices, emotions

and internal states are reflected in the ebbs and flows of neural impulses to the thalamus, limbic system and hypothalamus, and its connection to the basal ganglia sequences motor movement.

The prefrontal cortices are strategic neural circuits that acquire information about all activity occurring at a moment in time (Hasselmo & Linster, 1999). This includes the signals emanating from bioregulatory mechanisms such as the chemical production sites and the areas regulating breathing, hunger, etc. However, one of the most crucial roles of the prefrontal cortex appears to be its “dedication to categorising contingencies in the perspective of personal experience” (Damasio, 1994, p. 182).

The generation of appropriate behavioural actions is controlled by the prefrontal cortex, which holds internal forms of context. Cohen and Servan-Schreiber (1992) define this internal representation of context as “information held in mind in such a form that it could be used to mediate an appropriate behavioural response” (p. 46). The context information drives the response but does not form part of the content thus it is distinguishable from information retained in short-term memory. The prefrontal cortex usually decodes ambiguous stimuli, which are often found in social contexts, and the internal representations held in the prefrontal area frame appropriate responses. The appropriateness or relevance of the response is achieved through the inhibition of prepotent (reflexive or reinforced) actions. It can be hypothesised that behavioural disturbances arising from frontal dysfunction represent responses that are either reflexive or habitually formed.

It would appear that the neural mechanisms underlying social understanding and behaviour reside in the frontal systems generally, and the prefrontal circuitry specifically.

Associated with the idea of neural bases of social conduct is the ‘Theory of Mind’ hypothesis that proposes a relationship between brain atrophy and social dysfunction. Saltzman, Strauss, Hunter, and Archibald, (2000) investigated this relationship in a group of Parkinson’s patients and conclude that the prefrontal cortex orchestrates the reciprocity between theory of mind (social/emotional) and executive (cognitive) functions. In other words, there appears to be a correlation between the appraisal of the nature of the event or situation and the appraisal of types of emotion that have been associated with the event in the past (Damasio, 1994). Perhaps ongoing studies, which highlight the association between emotive and cognitive states and their common neural equivalents, serve as the prism that will modify the mind-brain debate as Newton’s discoveries did for light fractals and Einstein’s equation did for relativity.

In Alzheimer’s disease, the areas of degeneration in the prefrontal cortex correspond with behavioural and psychiatric manifestations at a later stage of the disease. Underlying the adaptive cognitive strategies are somatic/emotional markers that work together to elicit appropriate actions (Damasio, 1994; Saver & Damasio, 1991). It would appear that in diseases affecting frontal areas cognitive features are co-dependent on broad emotional repertoires and these are not secondary to or by-products of cognition.

Echoing these ideas, Adolphs and Damasio (2000) suggest that emotion is interwoven with cognitive processes, and provides the selectivity that enhances the adaptive functioning of humans. In the case of Alzheimer’s disease atrophy, prefrontal systems compound hippocampal and temporo-parietal dysfunction. Thus, associative memory networks and internal representation systems are malfunctioning. Responses to ambiguous stimuli appear as prepotent but unaffected by memory associations. Thus, the

responses may provide some hint of the person's inherent or reflexive tendency, which is a likely reflection of his/her premorbid temperament.

Taken together, this discussion suggests that neuropsychological theories and philosophical debates contributed to the perspective about the relationship between the emotional and cognitive systems. Initially the separation of the two systems was validated by the belief that lesions of the cortical areas disturbed cognitive functions and lesions of the subcortex influenced emotional responses. This was further influenced by the idea that the cognitive system exercised control on overt behaviour by inhibiting the primitive emotional system. A revised approach assumes that emotion and cognition interact in a reciprocal manner with emotions acting as the somatic markers mediating social decision-making (Damasio, 1994; Gianotti, 2000).

Alzheimer's disease provides a valuable model for the amalgamation of mind and brain relations. The disease process influences cortical and subcortical areas and different sectors of the prefrontal lobes that categorise distinct fields of knowledge. The heterogeneous presentation of Alzheimer's disease symptoms and the pathological variance observed post-mortem suggest that brain atrophy and cognitive signs can neither account for nor define the entire disease process. Manifestations of Alzheimer's disease oscillate more comfortably between noncognitive and cognitive referents, and belie its definition solely in terms of disrupted biological processes and its cognitive correlates.

3.1.2 Neuropsychological signs and symptoms

The broad categorisation of Alzheimer's disease symptoms into cognitive and noncognitive domains is the most commonly used classification system. However, the use of a broad categorisation has two disadvantages: the terms are nonspecific and the overlap between

cognitive and noncognitive is not accommodated. Taking the term neuropsychology to allude to cognitive and noncognitive changes, the following sections provide a rationale for the inclusion of noncognitive sequelae as a defining feature of Alzheimer's disease pathology and outline the methodological challenges that arise from this endeavour.

3.1.2.1 Cognitive and noncognitive morbidity

Intellectual or cognitive morbidity specifically in key domains such as memory and executive function delineates the progressive course of dementia of the Alzheimer's type. Several studies have documented the distinct neuropsychological profiles of the dementia types and the characteristic cognitive patterns of change in Alzheimer's disease and these changes have been observed in the domains of episodic memory, language, anomia, visual memory, visual attention, and visuospatial constructional abilities (Razani, Boone, Miller, Lee, & Sherman, 2001; Rizzo, Anderson, Dawson, & Nawrot, 2000; Sevush et al., 1993).

Alluding to the story of Phineas Gage, the phrenologist Sizer (cited in Damasio, 1994, p. 17) concluded that the iron rod pierced in "the neighbourhood of Benevolence and the front part of Veneration." This provided an apt description of the scientific dilemmas pertaining to the categorisation of emotional brain centers, which confronted scientists and practitioners in the 1860's. As a point of departure from the traditional paradigm, contemporary understandings of symptoms of Alzheimer's disease lend themselves to broader definitions, which relate to a hybridisation of cognitive and noncognitive signs and symptoms. This broader conceptualisation has three advantages: firstly, it accounts for the dynamic interaction between thought, emotion, and behaviour. Secondly, it recognises noncognitive correlates as part of the disease presentation and

hence, the clinical picture. Finally, the degree of caregiver burden can be approximated with greater accuracy, and the interventions applied more effectively.

A number of factors contributed to the inclusion of noncognitive features in the area of Alzheimer's disease research. Levels of caregiver burden and psychological morbidity have been associated with non-cognitive disturbances and this usually precipitates caregiver decisions regarding institutionalisation. Rabins, Mace, and Lucas (1982) found that of the seven items of disturbances causing serious carer stress, only one symptom was related to cognitive function (memory). The other disturbances (aggression, catastrophic reactions, and delusions) correlated with non-cognitive sequelae. Pharmacological interventions have also yielded positive results with single treatments improving disturbances with multiple origins and several treatments improving single neuropsychiatric/behavioural symptoms (Rabins, 1996).

Comparative studies between elderly groups with and without dementia showed a higher prevalence of noncognitive disturbances in the former than in the latter group. Näsmann et al. (1993) report a significant correlation between greater noncognitive disturbances and dementia. A recent study confirms this association and reveals that noncognitive features are four times more common in the persons with dementia than in those without (Lyketsos, Steinberg, Tschanz, Norton, Steffens, & Breitner et al., 2000). These disturbances are common in the moderate and severe stages and therefore impact significantly on the burden of care and usually precipitate the caregiver's decision to institutionalise the Alzheimer's disease patient. Whether these occurrences are purely a function of the disease process, social-psychological phenomena in response to the disease or a combination of both are currently the source of many hypotheses and the focus of numerous investigations.

In sum, it is widely accepted that in a progressive dementia such as Alzheimer's disease, noncognitive disturbances are ubiquitous in the clinical presentation of Alzheimer's disease, occur in the early stages of the disease, are not entirely by-products of cognitive decline, and reflect underlying functional and structural mutations produced by the disease course (Petry et al., 1988).

3.1.2.2 Noncognitive conceptual caveats

Unlike the strong theoretical and experimental paradigms underlying cognitive research, the area of noncognitive Alzheimer's disease symptoms has no comparable epistemology. Noncognitive symptoms have been conceptualised as neuropsychiatric and/or behavioural disturbances with the latter pertaining to delusions, hallucinations, and affective disturbances, and the former to changes in psychomotor function and neurovegetative features (Zaudig, 1996). Burns et al. (1990a, 1990b, 1990c, 1990d) applied a more stringent classification and included disorders of mood as a distinct group and separated hallucinations and delusions into disorders of thought and perception, respectively.

The term neuropsychiatric has been used by Cummings and Victoroff (1990) to refer to symptom classification according to psychiatric, mood, personality, neurovegetative, and psychomotor disturbances. Thus, the inadequate specifications for the noncognitive domain result in an inconsistency in the use of terminology due to the difficulty experienced in conceptualising noncognitive symptoms. Furthermore, noncognitive disturbances have until recently elicited little research interest and multiple terms denote similar features.

Some researchers prefer the use of the above mentioned distinction (Burns et al., 1990a, 1990b, 1990c, 1990d; Zaudig, 1996), others use the term 'behavioural' inclusively (Hope,

Keene, Fairburn, McShane, & Jacoby, 1997; Swearer, Hoople, Kane, & Drachman, 1996), and a handful of researchers use the term personality or psychological changes to refer to noncognitive manifestations of Alzheimer's disease (Bozzola et al., 1992; Rubin, Morris, & Berg, 1987). According to Rabins (1996) conceptualisation should include multiple ways of describing Alzheimer's disease symptoms, and the purpose of research should inter alia be to determine the validity of utilising a particular schema. These schemas can be syndromes demarcated in terms of psychopathological clusters (psychosis), function (disorder of eating), or as altered behaviour (aggression) with grouping of these syndromes done according to method of assessment, i.e. interview or observation (Finkel, Costa de Silva, Cohen, Miller, & Sartorius, 1996; Gilley, 1993).

The terminology pertaining to specific behaviours in the noncognitive domain are also vague, imprecise, and stereotypical. These definitions depend on the evaluating criteria, methodologies, and instruments used in the investigations. According to Stokes (1996, p. 602) "terms such as aggression, wandering, and eating disturbance are regarded as incontrovertible behavioural phenomena when they are simply vague descriptors of action". The review that follows will highlight the equivocal results obtained in several studies that are a direct result of the limited operational definitions for behavioural phenomena.

3.1.2.3 Noncognitive methodological caveats

Unlike the cognitive symptoms that follow a linear pattern of decline, behavioural and neuropsychiatric disturbances appear to have both a linear and curvilinear association with dementia severity (McCarthy et al., 2000). The complexity of the relationship between noncognitive symptoms and disease progression is inherent in the different patterns that emerge during the course of Alzheimer's disease. Some behavioural features manifest

early in the disease without a significant alteration in frequency or severity. Inversely, some aspects are initially preserved and may only surface as the disease becomes more severe, and still others may be moderately present in the mild and severe stages only to become challenging in the middle stages.

McCarthy et al. (2000), who report on the patterns of decline in Alzheimer's disease, found that the score on the apathy subscale of the Memory and Behaviour Problem Checklist-Revised follows a linear pattern and the score on the subscale measuring emotional and impulsive behaviours reflect a curvilinear pattern when compared with Mini Mental Status Exam scores. These results support those of Marin et al. (1997), who found that noncognitive symptoms emerge at any stage of the illness and defy a pattern of systematic deterioration over time because of its variable course. These results were found using a different noncognitive assessment scale namely, the Alzheimer's Disease Assessment Scale.

These findings have implications for studies that pool together subjects with different levels of dementia severity. Sampling in this manner may mask the specific patterns of behaviour (increase or decrease) as they emerge during the course of the disease and hinder accurate reflections of prevalence in Alzheimer's disease (Gilley, 1993). Furthermore, these longitudinal studies demonstrate that the positive association between worsening behavioural symptomatology and cognitive deterioration might hold for cross-sectional but not for longitudinal analysis.

Noncognitive disturbances pose different challenges to nurses and caregivers and the evaluation of these as problematic differ according to the settings in which they occur. The surroundings in which the noncognitive symptoms occur are important because the

manifestation only becomes a problem if it disturbs the context. Cooler (1996) isolated problem behaviours in two settings (care-facility and home) and deduced that certain behaviours are labelled as problematic irrespective of context and the labelling of others is more dependent on the surroundings. Wandering, delusions, and sleep disruptions appear to be problematic for the home-based carer, whereas aggression, distraction, and defiance against daily care activities seem to be less dependent on context and is labelled as problematic for both inpatients and outpatients.

There is a vast clinical heterogeneity in the neuropsychiatric and behavioural features observed in Alzheimer's disease patients. The underlying neuroscience cannot at this stage be pinpointed with accuracy. What is known is that these symptoms do occur frequently in Alzheimer's disease with reported occurrence peaking at 98% (Chen, Borson, & Scanlan, 2000). Studies have included community-based samples, population based studies, institutionalised elderly subjects, and multi-ethnic Alzheimer's disease groups (Chung & Cummings, 2000; Lyketsos, Lopez, Jones, Fitzpatrick, Breitner, & Dekosky et al., 2002; Näslund, Bucht, Eriksson, & Sandman, 1993). Moreover, estimates are derived from the use of a wide range of rating scales and interviews with primarily caregivers, and in unique instances with the sufferers themselves.

Although the focus of this study is limited to the noncognitive aspects, a discussion on Alzheimer's disease is incomplete without some reference to memory and executive function. In line with contemporary discourse on Alzheimer's disease, the following discussion will attempt to elucidate the dynamic collaboration between the cognitive and noncognitive domains.

3.1.3 Memory: System or process

Advances in memory research are evident on various levels. On a molecular and cellular level, the discovery of long-term potentiation (LTP)¹ and long-term depression

(LTD)² clarified the role of the synapse and neurochemicals in memory storage. On a neurobiological level, the discovery of the anatomical substrates of memory aroused scientific curiosity about the distinct facets and types of memory. Neuropsychological case studies and cognitive modelling studies are the main source of information about the cytoarchitecture of human memory. The former provided information from lesion studies and the latter from the neural modelling of intact brain processes (Foster & Jelicic, 1999).

Most neuropsychologists follow the systems view of memory, which emphasises the relation between specific memory functions and distinct brain circuits. Conversely, cognitive psychologists espouse a component process view of mnemonic activities, which considers memory as an encompassing function mediated by a general cognitive system. Therefore, the tension inherent in these two approaches stems from the one side advocating the nature of the memory system and the other accentuating the nature of the memory process. Gershberg and Shimamura (1998) and Parkin (1999) state that these views are not necessarily contradictory. The systems proponents focus on the different processes required for memory tasks, whereas the process theorists tend to include both the similarities and differences. A synergy of these views reveals that both local and diffuse activity contribute to general memory functioning. Although evidence from each

¹ LTP derived from the work of Hebb who theorised that reverberations of neural circuits represented the process of memory storage via weighting of synaptic connections.

² LTD is the anti-hebbian process that normalises the weighting of synaptic connections by dampening the reverberating effect.

viewpoint is not completely compelling in isolation, taken together these theories provide convergent views despite different methodological approaches.

The integration of the above discoveries (cellular, neurobiological and psychological) prompted a neuroscientific conceptualisation of memory as a faculty “which under real world conditions, is indissociable from all other components of behaviour, including perception, computation of plans, anticipation of outcomes, attention, motivation, etc.” (Delacour, 1999, p. 239). The faculty of memory appears to be the seer of our psychological evolution: it holds the remnants of the past, blueprints of the present, and the repertoires to deal with future contingencies. These processes are coordinated by the hippocampal system.

3.1.3.1 Hippocampus

The role ascribed to the hippocampus is synonymous with mnemonic functions and processes. This association emanated from the observation of a surgical procedure that resulted in the removal of the medial temporal lobes and inclusive structures (amygdala, hippocampal formation, and associated cortex) in an epileptic patient. An unlikely side effect of this surgery was the diminished memory abilities of the patient known famously as HM. The pathological memory functions included explicit or conscious memory and a severe amnesia (Kolb & Whishaw, 2001). This role ascribed to the hippocampus, however, is an inchoate attribution of function to a structure that is magnanimous in its connections with both neocortical and subcortical structures.

Research has provided the evidence that damage to the hippocampus proper is not related to memory deficits, instead damage to the extra-hippocampal formations that include the dentate, subiculum, entorhinal cortex, fornix, and septal areas disrupt memory

(Gluck & Myers, 1998). In accordance with this premise, Gray and McNaughton (2000) propose that the septo-hippocampal system is a multifunctional unit, which underlies the neuropsychology of memory as well as the neuropsychology of anxiety. Thus, they also argue against the hippocampal system as the sole preserve of mnemonic function and suggest that hippocampal lesion effects observed on memory tests are derived from changes in other processes that are not memory or cognition specific.

Gray and McNaughton (2000) equate septo-hippocampal function to that of a comparator whose primary aim is to reduce and resolve conflict arising from messages in the brain. Furthermore, as part of the behavioural inhibition system, the septo-hippocampal area mediates the inhibition of ongoing behaviour, vigilance, and arousal. When conflicting goals are detected by this system, it enters a mode of control. The information enters the comparator, which contrives an appropriate output. The output is resent to the areas whose activity created the conflicting goal. The purpose of this is to enhance the elective affinity of the negative stimuli and associations of the stimuli (memories). Augmenting the negative weighting causes an increase in bias (suppresses goals) until one of the goals is predominant and the conflict is resolved. The increase in negative bias has two consequences: first, it affects current behaviour outputs directly, and second, it affects future output indirectly through the biasing of associations.

This system also has a role in the neuropsychology of anxiety. According to the proponents (Gray & McNaughton, 2000) anxiety arises from a hyperactive septo-hippocampal system, which is characterised by inordinate functional output. The cognitive basis of anxiety stems from a pathological working memory circuit and alterations in attentional mediation of memory responses to threatening stimuli. Similarly, Damasio (1994, p. 174) suggests that feelings spawned from secondary emotions, function as

“somatic markers” that weigh options and allow for appropriate emotional and sensory output in the realm of personal and social behaviour. He also accentuated that coherent psychical activity sanctions the functioning of somatic markers, thereby contributing to adaptive output. The prerequisites for this psychical stability are working memory and basic attention, which are required for somatic marker functioning and in turn have their operations influenced by somatic markers.

Thus, the septo-hippocampal theory and the somatic marker hypothesis have provided an account of cognitive (memory) function and noncognitive (anxiety and behaviour) capacities, which proposes that the neural substrates required for the former are enmeshed with those required for the latter. This presupposition contributes to understanding the neuropsychological indices of Alzheimer’s disease as complex and dynamically interwoven phenomena, indivisible into absolute cognitive and noncognitive components.

3.1.3.2 Integrated neural systems

Further support for the idea of reciprocity between elements of cognition (working memory) and other correlates of emotion and behaviour, comes from evidence that the similar neural networks underscore both cognitive and noncognitive processes.

Table 3-1.1 (adapted from Delacour, 1999) outlines the cognitive and noncognitive functions and their shared neural substrates.

Table 3.1-1 Reciprocal neural networks

Neuroanatomical substrate	Functional specificity	Noncognitive Correlates	Cognitive function
Modular organisation: Primary sensory/motor areas, Sensory/motor neocortex, Striatum, Cerebellum.	Accurate coding of information.	Perception, Motor activity, Language programming.	Perceptual priming, Procedural/sensori-motor tasks, Language & Motor Programmes.
Reciprocal Organisation. Reticular Formation, Raphe nuclei, Locus coeruleus, Nucleus Basalis of Meynert, Thalamic nuclei, Hypothalamic nuclei, amygdala Hippocampus, Cingulate, Limbic areas	Mediates cell activity and synchrony.	Arousal, Consciousness, Emotion	Declarative memory, Short-term memory, Long-term memory
	Manages planning and output of goal directed activities.	'Voluntary' acts.	Working memory, Metacognition, Strategic memory
Prefrontal Cortex Associated areas			

The three divisions (C, A, and S), as outlined by Delacour (1999) are regarded as systems that carry out general functions and modulate various cognitive and noncognitive features. The relevance of this model to a discussion of Alzheimer's disease is inherent in its parallel and distributed manner of functioning. According to Delacour (1999) there is neither a memory centre as espoused by the localisationists nor is memory directed by a diffuse system that is scattered over the entire brain. Rather the memory circuit comprises an interaction between C, A, and S. This compromise between a localised and distributed organisation has the advantage of accounting for the interaction of memory with other noncognitive correlates.

The characteristic impairments in memory systems observed in Alzheimer's disease patients have been understood using the dichotomy between declarative (explicit) and nondeclarative (implicit) systems (Kolb & Whishaw, 2001; Zec, 1993). Declarative memory includes episodic (memory for events) and semantic (memory for facts) components. The latter degenerates early in the disease course and is linked to atrophy of the medial temporal lobes and the Nucleus Basalis of Meynert and the former displays a pattern of impairment that parallels degeneration of the neocortex.

The destruction of the semantic associative links changes the nature of associations and diminishes the complicity of features representing concepts (Chan, Salmon, & Butlers, 1998). Therefore, an Alzheimer's disease patient would have a distorted cognitive map as represented by his/her impairment on categorisation tasks. Types of nondeclarative memory that are spared include procedural skills (e.g., walking), perceptual priming, and memory that have the basal ganglia as neuroanatomical substrates. However, from the nondeclarative pool, semantic priming (neocortex) and processes of organisation, encoding, and source memory (frontal lobes) decline during disease progression.

Semantic priming relates to contextual memory which seems to be more vulnerable to deterioration than other forms of memory in the elderly because it is associated with age-related changes in frontal lobe functioning and the attendant impairment in working memory circuits (Spencer & Raz, 1994; Yener & Zaffos, 1999).

The prerequisites for the process of working memory are arousal and inhibition. Galvanic skin response studies indicate that autonomic nervous system reactivity decreases significantly with age, while underarousal, which is linked to ANS functioning, contributes to poor behavioural and task outcomes (Woodruff-Pak, 1997). It is worth noting that the ventromedial section of the prefrontal cortex via impulses to the autonomic nervous system can influence neurochemical stimulation linked to emotion. This further supports the idea of reciprocity between elements of cognition (working memory) and other correlates of emotion and behaviour.

3.1.4 Executive functions

Complex goal-directed behaviour and abstract thought fall under the auspices of executive control. The specific referents of these cognitive processes include motivation, planning strategies, output mediation, and volition. As stated previously, the prefrontal area is the primary moderator of executive functions (Chen, Sultzer, Hinkins, Mahler, & Cummings, 1998; Lezak, 1995). In Alzheimer's disease the dissociation between the parietal lobes and the prefrontal cortex fosters desynchronous communication among affected brain regions and causes distorted cognitive patterns by impairing executive processes (Morris, 1999). The dissociation influences the workings of the central executive system (CES), which under normal circumstances assists in keeping information in working memory (Baddeley, 1986).

The CES is essential for synchronising mental activities. Morris (1999) found CES impairment in Alzheimer's disease cases and linked its cortical dissociation to frontal dysfunction. Consequently, general attention and working memory processes are impaired, executive control is minimised, and a brain state exists where congruous mental functions are not possible. In this arena of chaos, emotional and behavioural outcomes are erratic and unstable. Decision making across all contingencies is disrupted because options, meta-options, and outcomes cannot be categorised and applied appropriately to varied situations (Damasio, 1994). This impaired state has been defined as the environmental dependency syndrome, a condition where frontal patients act mechanically or automatically because of a dysfunction in executive modulation (Lhermitte, 1986). Hence, Alzheimer's disease patients are likely to respond erratically because of a breakdown in the interpretation of internal emotional and external cultural social referents.

There is some evidence for the relationship between executive impairment and noncognitive manifestations in Alzheimer's disease. Chen et al. (1998) utilise the Neuropsychiatric Behaviour Rating Scale and a neuropsychological battery of tests that measured executive functions in a cross-sectional study of 31 Alzheimer's patients. The neuropsychological tests included the Controlled Oral Word Test, Wisconsin Card Sorting Test, Stroop, and Trail Making Test, which have touted as sensitive and robust for investigating executive skills (Lezak, 1995). After controlling for cognitive dysfunction (covariance by partial correlation) they found significant relationships between executive dysfunction and agitation/disinhibition, psychosis, anxiety, and depression. Chen et al. (1998) conclude that noncognitive symptoms cannot be merely by products of global cognitive deterioration (as demonstrated after covariance for cognitive scores) and noncognitive symptoms and executive dysfunction are likely to be associated in

Alzheimer's disease because of shared neurobiologic correlates such as the frontal-subcortical circuits.

Apart from the latter explanation, there are two other possible explanations for the results. Firstly, the presence of neuropsychiatric symptoms may influence executive test performance, but may not be etiologically related to executive skills. Secondly, the association may be relevant because the use of executive skill helps maintain conformist behaviour, therefore deficits in these skills of abstraction and inductive reasoning may also be relevant to noncognitive output. Further studies focusing on the reciprocity between symptoms are needed to elucidate the relationship between cognitive and noncognitive deficits.

3.1.5 Conclusion

The first part of this chapter attempted to trace the origins of bias that dictate how brain diseases are conceptualised and defined, and implicitly espoused the principles of dynamic systems that were explained in chapter 2. This section on the neuropsychology of Alzheimer's disease also attempted to utilise neuroscientific knowledge of the fronto-subcortical circuits to demonstrate the neurobiologic correlates that may underscore both cognitive and noncognitive processes. This was done against the backdrop of a brain disease such as Alzheimer's disease that serves as a useful heuristic for understanding the reciprocity between noncognitive and cognitive symptoms because of its underlying pathology.

The purpose of the discussion was to demonstrate that noncognitive symptoms of Alzheimer's disease have been eschewed in research largely because of the conceptual problems and the notion that it is a by product of the cognitive deterioration that

accompanies Alzheimer's disease. The neurobiologic evidence suggests that cognitive deterioration is a necessary but not a sufficient cause of noncognitive symptoms, i.e. the relationship is not causal but assimilates processes that function within sensitivity thresholds and connectivity patterns.

The second part of this chapter provides an extensive review of literature on the occurrence of noncognitive symptoms in Alzheimer's disease.

CHAPTER 3.2

THE NEUROPSYCHOLOGY OF ALZHEIMER'S DISEASE: A NEUROPSYCHIATRIC & NEUROBEHAVIOURAL PERSPECTIVE

Noncognitive is a term that can be used to describe a range of neurobehavioural and neuropsychiatric symptoms that manifest during the dementing process. This section of chapter 3 reviews literature on a spectrum of neuropsychiatric and neurobehavioural disorders. The format follows that of Burns et al. (1990a, 1990b, 1990c, 1990d), who distinguished the various noncognitive symptoms according to a triadic categorisation namely disorders of thought and perception, disturbances of mood, and neurobehavioural dysregulation.

3.2.1 Disorders of thought and perception

According to Burns et al. (1990a), disorders of thought and perception manifest in Alzheimer's disease patients as delusions, hallucinations, and misidentifications.

In his first description of Alzheimer's disease, Alois Alzheimer (1901/1977) alludes to delusions and hallucinations experienced by his 51-year old patient. Since then, many studies have reported on the prevalence of psychotic episodes in Alzheimer's disease. In most studies, the term psychotic incorporated delusional and hallucinatory episodes. Berrios (1990) formulates a summary of the first 15 cases reported after Alzheimer's discovery and reported five patients with delusions and five with hallucinations. In cross-sectional studies, the reported prevalence of psychotic symptoms in Alzheimer's disease ranges from 10% to 84% with the most common frequencies ranging from 28% to 38% (Lopez, Becker, Brenner, Rosen, Bajulaiye, & Reynolds, 1991; Paulsen et al., 2000).

In contrast, longitudinal studies revealed that over 50% of patients with Alzheimer's disease would eventually manifest with psychotic disturbances (Drevets & Rubin, 1989; Zubenko, 1996).

Following the categorisation mentioned above, literature on delusions, hallucinations and misidentification symptoms will be reviewed separately.

3.2.1.1 Delusions

Delusions are described as irrational and inaccurate beliefs pertaining to many situations. Unlike misidentifications that are transient, delusions are characterised by a sustained and fixed belief. Cummings (1985) suggests that patients with organic disease display delusions that are simple persecutory, complex persecutory, grandiose, or linked to underlying neurological impairment (neglect syndrome & Anton's syndrome). Cutting (1987) revises this classification after finding that 18 of his participants had delusions, which did not fit into the system. He labelled the fifth category complex, bizarre, or multiple delusions.

Among patients with Alzheimer's disease, simple persecutory delusions appear to be most common. Burns et al. (1990a) report delusions of theft and suspicion as most common among their sample. Similarly, Deutsch, Byslma, Rovner, Steele, and Folstein (1991) found that 73% of delusions reported in their study warranted a classification of simple persecutory delusions (themes of theft, suspiciousness, abandonment, and threat of harm). In addition to these common delusions, some researchers include the prevalence of symptoms dealing with misidentification in the category of delusion.

The misidentifications include perceiving the spouse as an impostor, the phantom boarder syndrome, misidentification of events/people on television in three-dimensional space, misidentifying one's house as not one's home, and unspecified types (Jeste, Wragg, Salmon, Harris, & Thal, 1992; Lopez et al., 1991; Reisberg, Borenstein, Salob, Ferris, Franssen, & Anastasios, 1987). According to several authors the grouping of misidentification and misrecognition with hallucinations and delusions contaminate the results, and hallucinations and delusions should be the only symptoms that fall under the rubric of psychoses (Burns et al., 1990a; Rubin, Drevets, & Burke, 1988; Zubenko, 1996). Following the categorisation suggested by them the literature on misidentification symptoms will be reviewed separately.

3.2.1.1.1 Prevalence of delusions

Prevalence estimates for delusions in Alzheimer's disease range from 10% to 75% with a prevalence average of one third of patients (Burns et al., 1990a, 1990b; Jost & Grossberg, 1996; Lyketsos et al., 2001; Swearer et al., 1996; Trabucchi & Bianchetti, 1996; Wragg & Jeste, 1988). Hallucinations are also a frequent occurrence in Alzheimer's disease with reported prevalence estimates ranging from 3% to 50% (Lopez et al., 1991). The use of inconsistent definitions of delusions and hallucinations, methods of diagnosis and different population sources account for the variance in estimates.

Delusions and hallucinations often co-occur and in the majority of studies a higher frequency of delusions compared to hallucinations was observed in both clinical and community populations and cross-sectional and longitudinal studies (Assal & Cummings, 2002; Bylsma et al., 1994; Drevets & Rubin, 1989; Jeste et al., 1992; Jost & Grossberg, 1996; Kotrla, Chacko, Harper, & Doody, 1995a; Lopez, Gonzalez, Becker, Reynolds,

Sudilovsky, & DeKosky et al., 1996; Lyketsos et al., 1997; Nambudri et al., 1997; Reisberg et al., 1987; Zubenko, 1996). In the first 15 reported cases of Alzheimer's disease, delusions and hallucinations co-occurred in 80% of the patients (Berrios, 1990).

3.2.1.1.2 Co-occurrence with patient characteristics

Delusions have been associated with a number of clinical characteristics. Significant relationships are noted for delusions and the rate of cognitive decline (Doody, Massman, Mahurin, & Law, 1995; Drevets & Rubin, 1989; Lopez et al., 1991; Jeste et al., 1992); functional impairment (Binetti, Bianchetti, Padovani, Magni, Bianchetti, & Scuratti et al., 1995; Drevets & Rubin, 1989); index age (Nambudiri et al., 1997) and stages of dementia (Drevets & Rubin, 1989; Trabucchi & Bianchetti, 1996). However, the association reported between delusions and rate of cognitive impairment is contentious, because the results of several studies are inconclusive and contradictory (Bylsma et al., 1994; Kotrla et al., 1995a). Bylsma et al. (1994) for example, report no association between delusions and cognitive decline. Their findings are attributable to the distinct manner in which symptoms were defined and the separation of Alzheimer's disease patients into a group with a primary delusion and a group with delusions secondary to hallucinations or affective disorders.

The link between rate of decline, mortality, and psychosis and the presence of dense lesions in areas that are associated with cognitive abilities suggests distinct patterns of atrophy. Zubenko, Moosy, Martinez, Rao, and Claassen (1991) found this difference in neurochemical pathology between nonpsychotic Alzheimer's disease patients and psychotic Alzheimer's disease patients. Drevets and Rubin (1989) suggest that in addition to the pathology, patients with psychotic disturbances appeared to have a lower mortality

level than nonpsychotic patients and attribute this to patients receiving a different quality of care, which may have positive psychological impact and contribute to their longevity.

According to Trabucchi and Bianchetti (1996) the prevalence of delusions remains consistent across mild, moderate and severe stages of the disease. However, some researchers found delusions to be most common in the moderate stage of Alzheimer's disease (Drevets & Rubin, 1989), others show that the prevalence is lower in the severe stages (Jeste et al., 1992), and one study reports no correlation between delusions and disease stage (White & Cummings, 1996). Flynn, Cummings, and Gornbein (1991) support the contention that delusions in Alzheimer's disease are an independent function of underlying brain deterioration.

Since the occurrence of delusions is dependent on the intactness of the neuronal systems of the cerebral cortex and an individual's ability to generate thought, patients in the advanced stages of Alzheimer's disease should have fewer reported delusions because these cannot arise from a grossly lesioned brain (Bylsma et al., 1994; Cummings, 1985). Furthermore, the severity of atrophy influences the contents of the delusions. Patients with neurological impairments that have limited initial cognitive impact, for example Parkinson's, are more likely to manifest with complex delusions. It appears that patients with anosognosia display a greater frequency of delusional episodes. Zec (1993) suggests that an unawareness of deficit, in this case memory, contributes to the false conclusion on the part of the patient that items are stolen, spouses are abandoning them, or people are acting in a threatening manner. On a psychological level, it makes sense to couple the occurrence of delusions with compromised reasoning and poor awareness of impaired cognition (Rubin, 1992).

3.2.1.1.3 Symptom comorbidity

Delusions also share significant associations with other behavioural symptoms. Alzheimer's patients with delusions exhibit more aggressive behaviours and severe activity disturbances (Flynn et al., 1991). Mixed results were found for the increased presence of extrapyramidal signs in Alzheimer's disease groups with psychotic disturbances (Jeste et al., 1992; Stern, Mayeux, Sano, Hauser, & Busht, 1987). Sweet, Akil, Mulsant, Ulrich, Pasternak, and Zubenko, (1998) report that extrapyramidal symptoms are linked to Alzheimer's disease independent of any psychotic or affective comorbidity, whereas Caligiuri and Peavy (2000) show an association between parkinsonism and psychoses and severity of neurobehaviours and parkinsonism. This latter association makes neurological sense because similar subcortical processes are involved in psychoses and extrapyramidal signs (Mega & Cummings, 1994).

A disturbance of personality and mood disturbances in groups of deluded patients have also been reported by Bylsma et al. (1994). Deutsch et al. (1991) found that acts of aggression and a delusional episode was reported to have occurred close together in approximately 90% of the cases they reviewed. Most of these aggressive acts happened during an interpersonal situation with a caregiver implying that the social relationship with the caregiver contributes to these disturbances. The significant association between physical aggression and the frequency of delusions is affirmed by Chemerinski, Petracca, Tesón, Sabe, Leiguarda, and Strakstein, (1998).

The review of several studies has shown that delusions are related to other behavioural disturbances, share comorbidity with hallucinations, do not influence mortality rates, and have a variable effect on cognitive deterioration. However, Trabucchi and Bianchetti (1996) found that a significant number of patients with delusions at baseline were

institutionalised at the end of the 2-year longitudinal study compared with those without delusions. Therefore, in spite of ambiguous prognostic significance, delusions still present a challenge for the caregivers and precede decisions regarding institutionalisation.

3.2.1.1.4 Underlying substrates

Neuroimaging and electroencephalographic studies have shown that there are structural and functional differences in Alzheimer's disease patients with and without psychosis (Lopez et al., 1991; Zubenko et al., 1991). Only a few psychological studies are available for review. These have implicated perceptual and memory deficits and aspects of personality as causative agents for episodes of psychoses in Alzheimer's disease patients.

Psychotic disturbances have been associated with higher density of plaques and tangles in the neocortex and imbalances in levels of norepinephrine and serotonin and dopamine in the cortex and subcortex (Gottfries, 1996; Zubenko et al., 1991). Furthermore, temporo-parietal cortical lesions may disrupt information flow to the limbic system causing disharmonious information channelling, which is linked to delusional and hallucinatory episodes (Lopez et al., 1991).

More specifically, limbic system and basal ganglia dysfunction appears to reflect the underlying structural cause for delusions (Bondareff, 1996; Cummings, 1992). The primary areas in the limbic system that show degeneration are the caudate nucleus and the temporal lobes (Rao & Lyketsos, 1998). The subcallosal gyri, cingulate gyri, parahippocampal gyri, hippocampus, insular, and orbito-frontal region are the cortical representatives of the limbic system. These areas mediate the evaluation of environmental threat and danger, and fearful and anxious responses. Furthermore,

Sultzer, Mahler, Mandelkern, Cummings, and Van Gorp (1995) report a significant correlation between the intensity of delusional thought and lower metabolic activity in the multimodal frontal association areas particularly the cingulate gyrus, dorsomedial prefrontal area, and the anterior frontal pole. This implies that degeneration in the frontal sector contributes to many noncognitive changes and psychotic episodes during the disease process (Assal & Cummings, 2002; Van Hoesen, Parvizi, & Chu, 2000).

Hypoperfusion in the temporal lobes of Alzheimer's patients have also been found in a comparative study between groups with and without delusions (Starkstein et al., 1994). By contrast, Lopez et al. (1996) found that the fronto-subcortical network is not necessarily associated with the manifestation of psychosis in Alzheimer's disease patients. Consequently, they report evidence for a temporo-parietal cortex dysfunction. These findings imply that different areas of the brain may subserve specific types of delusions. Paranoid delusions, for example, are linked to fronto-limbic dysfunction and the structured delusions are linked to temporo-parietal dysfunction (Cummings, 1992; Lopez et al., 1996).

In addition, Jeste et al. (1992) found that patients with delusions perform significantly lower on the neuropsychological test of categorical fluency when compared to Alzheimer's disease patients with no delusions. They relate this to semantic memory and conclude that delusional patients show a disruption in the semantic memory circuits and by association fronto-temporal dysfunction. These varying results suggest that there are various neural circuits that may be involved in thought disturbances. Moreover, Jeste et al. (1992) do not distinguish between types of delusions and neural functioning therefore fronto-temporal dysfunction may underlie a different type of delusional episode.

Cummings (1985) hypothesises that a somewhat intact cortex and cognitive integrity is needed for a psychotic display, which would most likely be activated in the limbic area. In other words, the complexity of the delusions is determined by the intactness of the brain (Cummings, 1992). This is supported by Burns et al. (1990a; 190b) and Förstl, Burns, Levy, and Cairne (1994) who found that Alzheimer's patients with delusions have less brain atrophy and ventricular augmentation than nondelusional Alzheimer's disease groups. Furthermore, subgroups of patients with delusions had higher neuronal counts in the hippocampal structures as compared to nondelusional Alzheimer's disease patients. Taken together, these studies propose that delusions are more likely to occur in the early stages of the disease and may become less complex as the disease progresses.

Contrary to the neurobiological explanation, a dimensional perspective proposes that delusions arise from the interaction between an individual's vulnerability (e.g., cognitive disability or temperament) and his/her maladaption to the current environment. In Alzheimer's disease patients, it is suggested that intact perceptual abilities have to collude with the deviant cognitive processes and this results in the expression of delusions (Bylsma et al., 1994). Part of this anomalous cognition is a severe memory deficit that also appears to produce delusions. Alzheimer's patients often cannot remember where they placed objects and accuse others of theft while displaying behaviour that is perceived as more suspicious.

However, in their investigations, Bylsma et al. (1994) found that patients with delusions of theft show no significant difference from patients with other types of delusions on memory tests. Furthermore, Alzheimer's disease groups without delusions also perform badly on memory tests. They conclude that delusions and cognitive impairment such as memory deficits have no causal relationship. In the light of the latter findings, if noncognitive

symptoms such as delusions are not merely by-products of cognitive deterioration then other possibilities for their occurrence warrant attention. Rao and Lyketsos (1998) offer the hypothesis that two personality features, extroversion-introversion and stability-instability have been correlated with different stress reactions. They contend that patients with premorbid introverted temperaments are more likely to develop delusions in comparison with premorbid extroverted temperaments. The variance arises from a person's internal strength of adaptation to cognitive deterioration and a changing environment. These hypotheses are elaborated further in the next chapter.

The aetiological explanations for neuropsychiatric manifestations are varied. Disorders of thought and perception may arise because (a) patients attempt to understand the environment and act in a manner that they perceive as logical, (b) it is secondary to changes in affect or a direct display of cognitive dysfunction, (c) it is a separate disorder unrelated to dementia, and (d) it is a reflection of underlying neural impairment (Lawlor, 1996; Lazarus, Cohler, & Lesser, 1996; Zubenko, 1996).

Berrios (1989) proposes a varied aetiology linked to the interpersonal state of the patient and to neurological impairment. He suggests that neuropsychiatric manifestations arise from either the dynamic confusional position of a dementing patient, the interposition of premorbid personality and its influence in the clinical expression of dementia, or from neurological impairment, which causes disinhibition and a release of psychotic symptoms.

3.2.1.2 Hallucinations

Alzheimer's disease is characterised by hallucinations of an auditory and/or visual nature. Psychotic episodes (including hallucinations and delusions) are challenging symptoms of Alzheimer's disease that a caregiver has to deal with. However, the challenge is

maximised because psychotic disturbances accompany other behavioural problems such as anxiety, agitation, and aggressiveness (Lopez et al., 1991), influence the severity and intensity at which these occur (Deutsch et al., 1991; Kotrla et al., 1995a), and are associated with behaviours of frontal dysfunction (Paulsen et al., 2000).

3.2.1.2.1 Prevalence of hallucinations

Gilley, Whalen, Wilson, and Bennet (1991) report hallucinations in 29% and misrecognition in 11% of their community dwelling sample ($n=230$) with Alzheimer's disease. Whitehouse et al. (1996) investigated a sample of 556 Alzheimer's patients and report hallucinations in 27% and misrecognition in 25% of the sample. It is important to determine whether these results are obtained because of patient characteristics or methodological deficiencies. Both studies utilised large community based samples and reliable semi-structured instruments. Perhaps the argument concerning the occurrence of hallucinations and misrecognition should focus less on the commonality of one over the other, and more on the co-occurrence. The latter would make sense since both are related to visual perception. Support for the association between hallucinations and misrecognition comes from Whitehouse et al. (1996), who performed a factor analysis on their large data set and found that hallucinations and misrecognition loaded together on a single factor. Due to these varying results and the difficulty in separating hallucinations from misrecognition, it is expected that prevalence estimates would traverse a wide range depending on the classification criteria that researchers endorsed in their studies. Based on data from several studies estimates range from 3% to 55% with many studies reflecting a higher percentage of visual hallucinations compared to auditory distortions (Burns et al., 1990a; Lopez et al., 1991; Reisberg et al., 1987).

3.2.1.2.2 Co-occurrence with patient characteristics

Hallucinations have also been associated with increased rates of cognitive decline, extrapyramidal signs, and other behaviour disturbances (Gilley et al., 1991). Impact and prevalence studies usually group delusions and hallucinations together, however evidence points to different correlates for these symptoms. Burns et al. (1990a, 1990b) found that hallucinations influence the rate of cognitive decline but delusions have no significant effect on cognition. In contrast to delusions, the prevalence of hallucinations increases in the severe stages of the disease (Trabucchi & Bianchetti, 1996). Teri, Larson, and Reifler (1988) show that 10% of the mild (Mini Mental State Exam score >24), 27% of the moderate (10< Mini Mental State Exam score <24) and 30% of the severe Alzheimer's disease group (Mini Mental State Exam score < 10) had hallucinations at different stages of disease severity.

3.2.1.2.3 Symptom comorbidity

Hallucinations and anxiety symptoms seem to occur together because Alzheimer's disease patients who have compromised cognitive integrity (anxiety-inducing) tend to have problems comprehending the information from their internal and external world. Richardson and Divyo (1980) state that in compromised individuals, thoughts that induce anxiety have strong defences that block them from entering conscious awareness, but these thoughts eventually appear as internal vivid images, which the dementing person believes to be a representation of external reality.

3.2.1.2.4 Underlying substrates

Neuroimaging studies implicate parietal lobe hypoperfusion as a cause for hallucinations in Alzheimer's disease patients (Kotrla, Chacko, Harper, Jingran, & Doody, 1995b). One of the roles of the limbic system is to maintain arousal, regulate the adaptation of behaviour to environmental cues, and co-ordinate affect and thought. According to Rubin (1992), dysfunction in this system causes a mismatch between affect (limbic system) and interpretation of input or former memories (temporo-parietal).

Apart from neuroimaging studies, research on the cellular effects of acetylcholine has provided insight into the role of this neurotransmitter in producing hallucinations. Previous research on acetylcholine has focused mainly on mnemonic functions and the role of acetylcholine in learning (Hasselmo & Linstek, 1999). In order to fathom the role of acetylcholine in the pathogenesis of hallucinations, Perry and Perry (1995) suggest that in the context of brain disease, the dual nature of consciousness must be understood.

Hasselmo and Linstek (1999) concur that the focus should be broadened to include the role of acetylcholine in processing of input i.e. extrinsic analysis versus the analysis of information based on prior learning (intrinsic). The dual definitions of consciousness pertain to interacting networks of arousal and content. The former “which is analogous in mechanistic terms to volume control” defines the force of overall neural stimulation, whereas the latter “ which is analogous ...to channel selection” incorporates a unitary wave of present awareness (p. 241). Normal cholinergic functioning enhances neural stimulation and allows for a distinction between specific neural firing and cortical clatter. In other words it maintains the signal to noise ratio. This ratio pertains to mediatory effects

on the dynamics of activity that augments the responsiveness to sensory stimuli relative to background activity.

Disruption of this circuitry can result in hallucinations that are caused by the inefficiency in diminishing internal brain activity during perception. Thus, cortical clatter is augmented and there is a disruption in the streams of consciousness because of the increased noise to signal ratio. Moreover, disruption of cholinergic functions may cause an unusual dominance of sensory input interpretations based on prior representations (top-down activity).

The dominance of top-down or noise processing causes a detour in information flow away from the cortical representations, which act as matching processes with bottom-up sensory input. Thus, the flow of environmental input eludes evaluation against the internally retrieved information (top-down) resulting in a diminished interpretative capacity to handle sensory information (Hasselmo & Linster, 1999). Antimuscarinic actions of drugs (atropine and scopolamine) usually induce visual hallucinations in users because of its antagonistic effect on the dynamics of the neural receptor system. Conversely, cholinergic agents such as physostigmine (cholinesterase inhibitor)³ usually reduce hallucinations and delusions (Cummings, Gorman, & Shapira, 1993).

According to Richardson and Divyo (1980) people who have a predisposition to hallucinate have a greater perplexity in handling the demarcation of their “perceptual-conceptual boundaries” (p. 271). Therefore, they lack sensitivity to their inner source of information and cannot distinguish the source of inner or outer information. A person who fails to acquire this capacity to distinguish during their development would be more susceptible to

³ Cholinesterase reverses the synthesis process and promotes the hydrolysis of acetylcholine into its inactive components (choline and acetate). An inhibitor will prevent acetylcholine from being hydrolysed into inactive components.

external traces, which would extinguish poor internal markers and predispose one to hallucinate. They contend further that the predisposition is a “structural defect in the personalities” (p. 721) and people who hallucinate may have had more persisting and rigid defences premorbidly than those who do not hallucinate.

This account seems to be the psychological equivalent of the Ach (signal-noise ratio) hypothesis. The notion that a more rigid disposition may predispose to hallucinations can be argued utilising Strelau's (1994) notion of high reactives and the Cederblad et al., 1995) personality dimensions. In the former, one can propose that people classified as high reactives would be more sensitive to environmental cues and more susceptible to responding to them because of maladaptive reactions to a stressful environment. In the latter, the authors argue that certain dimensions act as salutogenic factors against psychopathological factors, however, persons classified as ‘sub-valid’ (tense, rigid) are more prone to psychiatric conditions and stress reactions.

An Alzheimer's disease patient who has a particular premorbid disposition is faced with an environment that is perceived as hostile and unfathomable and would likely manifest with symptoms that reflect their particular ‘adaptive’ responses to the environment. Alternatively, hallucinations can be a direct manifestation of Alzheimer's disease pathology and not a consequence of leaky perceptual-conceptual boundaries. Two factors caution against explanations that focus on a single cause: firstly, hallucinations most often occur with other specific behavioural symptoms, suggesting that the structural defects are also responsible for the other symptoms, and secondly hallucinations have a complex neuroanatomic relationship with cognitive performance (Lerner et al., 1994).

Brain deterioration and neurochemical dysfunction may subserve the manifestations of psychotic symptoms but cognitive capacity and temperament, amongst other factors, may have mediating effects on severity, frequency, and content of psychotic episodes.

3.2.1.3 Misidentification

Burns (1996, p. 393) defines misidentification as “misperceptions with an associated belief or elaboration that is held with delusional intensity”. This Alzheimer’s disease symptom is considered distinct from Capgras syndrome, in which the patient has a mistaken belief that an impostor has replaced a specific person even though recognition abilities are intact (Deutsch et al., 1991). However, Burns (1996) considers Capgras syndrome as a form of misidentification and utilises this broad categorisation in his study. Furthermore, he includes two syndromes namely, Fregoli syndrome and intermetamorphosis. The former, which bears the name of an actor who displayed adeptness at altering his appearance, relates to a condition of hyperidentification.

In the case of hyperidentification the patient believes that people are altering their appearance (dress) to represent someone else and the purpose of the disguise is to influence and mislead the observer. Intermetamorphosis pertains to the situation where a person appears to have interchanged their physical countenance and psychological identity with that of another person. Cummings (1992), on the other hand, defines these misidentification symptoms as theme-specific delusions. The lack of a proper operational definition and consensus on symptom content may account for the equivocal findings reported in the literature.

Several researchers hold the opinion that the word syndrome is not applicable to incidences of misidentification (Förstl, Almeida, Owen, Burns, & Howard, 1991). Capgras

and Fregoli are usually characterised by a single feature accompanying many organic disorders and misidentification states. Researchers have used these items to assess signs of misidentification such as: (a) a belief that one's present house is not home, (b) a belief that one's reflection in the mirror belongs to someone else, (c) misidentification of people, (d) misidentification of objects, and (e) a belief that events or people on television are real (Rubin et al., 1987; Tariot et al., 1995).

3.2.1.3.1 Prevalence of misidentification

Researchers have reported misidentification prevalence rates of 5%-50% in Alzheimer's disease patients (Burns et al., 1990b). In a retrospective review, Mendez, Martin, Smyth, and Whitehouse (1992) report that a quarter of their sample had identification disturbances and of these, 16% had transient misidentifications, 5% had Capgras syndrome, 2% had personal misidentifications, and only 1% had prosopagnosia. Furthermore, patients with a personal misidentification were more likely to be paranoid, suspicious and more prone to anger and agitation.

Deutsch et al. (1991) found that misidentifications are significantly associated with hallucinations and Förstl et al. (1991) corroborate these results. Misidentification seems to occur more frequently in moderate stages, with limited reported incidences in the advanced stages (Förstl et al., 1994). This suggests a non-linear association between misidentification and severity of brain lesions. Echoing Cummings' (1992) hypothesis, Förstl et al. (1994) conclude that patients require some atrophy to initiate the psychotic episodes but have to be moderately capable intellectually in order to elaborate on the content of these misrecognitions.

3.2.1.3.2 Symptom comorbidity

Misidentification has led to other behavioural incidences that affect caregivers. The following vignette (Fairburn & Hope, 1988, p. 407) illustrates the association between misidentification and aggression:

A 64-year old man had a 9-year history of progressive cognitive impairment. Aggressive behaviour began about 1 year prior to assessment. It appeared to be precipitated by his misinterpretation of his reflection in mirrors or windows. For example, on one occasion he looked into the kitchen window to see both his wife and his own reflection. He immediately became extremely aggressive towards his wife and accused her of being with another man. In this case, the behavioural disturbance appears to have arisen directly from misinterpretation of stimuli.

3.2.1.3.3 Underlying substrates

Misidentification phenomena have been related to increased degeneration of the right frontal lobe and lower neuronal counts in the CA1 hippocampal area (Förstl et al., 1991).

Studies of children indicate that the frontal lobes are involved in the development of metacognitive skills that result in a theory of mind (Stuss, Gallup, & Alexander, 2001). The ability for self-recognition, which emerges in the early developmental stage, correlates with the rapid development of the frontal cortex, hence this region's association with the Theory of Mind hypothesis. Studies have shown that impaired executive monitoring (frontal activation) disrupts abilities of self-awareness, self-analysis, and reality awareness (Stuss et al., 1992). If the frontal systems are atrophied then Alzheimer's disease patients are likely to have problems of perspectivity in a spatial sense. Furthermore, research on

schizophrenic patients can be used as support for this ‘Theory of Mind’ hypothesis and the occurrence of misidentification because schizophrenic patients share with Alzheimer’s disease patients a disruption in general self-monitoring capacity and by inference a disturbed self-construct.

Hippocampal involvement in misidentification syndromes also implies that certain misidentification features may result from the activity breakdown of memory systems. Misidentifications may arise because patients are unable to update memories and consolidate recent and remote memories (Förstl et al., 1994). Due to this faulty mechanism a person with Alzheimer’s disease may not recognise his/her face or may misidentify a daughter for a spouse. Förstl et al. (1991) demonstrate anatomical evidence for memory dysfunction in misrecognition. In comparison with delusional patients with higher neuronal counts in the parahippocampal area, patients with misrecognition show lower neuronal counts in the CA1 memory region. Organic and functional psychotic states together with underlying cognitive dysfunction (memory) have been associated with people misidentification, whereas place misidentification has been associated with neurological disorders with underlying cognitive impairment (Mendez et al., 1992).

Borrowing a key principle from developmental theory helps to impose a perspective on disorders of thought and perception accompanying Alzheimer’s disease. Such a principle states that actions evolve over time to maximise human adaptive functioning. In most situations, the application of adaptive behaviour to the perceived environment is to fulfil a purpose or achieve a goal thereby allowing for the cessation of that behaviour. Alzheimer’s disease patients observe and analyse the world through anomalous lenses, which project a distorted image and output. These distortions manifest as hallucinations, delusions, and misidentifications.

3.2.2 Disorders of mood

Mood disturbances in Alzheimer's disease have clinical and social implications. There is however, little consensus about its prevalence because of the difficulties experienced in diagnosing this condition in the context of dementia. Mania is often reported as one of the rarest symptoms in Alzheimer's disease, with some researchers reporting occurrence in only 3% of their sample (Burns et al., 1990c; Frisoni et al., 1999; Wragg & Jeste, 1989). Mild forms of depression on the other hand, seem to occur at variable rates throughout the disease process. Depression, anxiety, and emotional lability are discussed under the rubric of mood disorders. The following sections address the prevalence, co-occurrence, and phenomenology of these symptoms in Alzheimer's disease.

3.2.2.1 Depression

Merriam, Aronson, Gaston, Wey, & Katz (1988) raise the important issue concerning the conceptual similarity between depression in an Alzheimer's disease patient and depression expressed in a cognitively functioning individual. They found that distracting Alzheimer's disease patients with tasks and stories, had a positive influence and alleviated the 'depression' even when patients were most despondent. The individuals seemed to display a less pervasive and more alterable 'depression' and therefore warrant a conceptually different classification.

Several researchers agree that most Alzheimer's disease patients are not syndromically depressed, but exhibit depressive symptoms, which are transient rather than continuous because they arise from frustrated responses pertaining to diminished abilities (Burns et

al., 1990c; Cummings & Victoroff, 1990; Green, 2000). Further support for this conjecture is derived from findings obtained for anosognosic Alzheimer's disease patients. This group of patients has an unusually low incidence of depressive symptoms, which suggests a link between observed depressive symptoms and awareness of declining functional abilities (Zec, 1993).

Irrespective of the variable rate of depression reported in Alzheimer's disease groups and the debate over the absence of syndromic depression, the impact on quality of care is tangible. Patients with depressive profiles increase the perceived burden and psychological morbidity of caregivers, thereby precipitating placement decisions (Donaldson et al., 1998).

3.2.2.1.1 Prevalence of depression

Sixty three percent of Alzheimer's disease patients report on average one depressive symptom (Burns et al., 1990c). Helplessness, sadness, and hopelessness are some of the depressive features reported by 41% of the sample investigated by Mendez, Martin, Smyth, and Whitehouse (1990). Prevalence rates according to Reifler (1996) range between 25% to 33%, whereas Cummings and Victoroff (1990) report rates of 0% to 87%. Zubenko (1996) agrees with the high prevalence rates (86%) of mild to moderate depressive symptoms in Alzheimer's disease patients. Conversely, Knesevich, Martin, and Berg (1983) report no significant rate of major depression in their mild Alzheimer's disease sample.

A perusal of the literature on depression and dementia provides some explanations for the disparity in prevalence figures. Firstly, investigators use different inventories such as the

Hamilton Rating Scale for Depression, DSM criteria, Neuropsychiatric Inventory, Cornell Scale for Depression, BEHAVE-AD, and Behaviour Rating Scale for Dementia (Chen et al., 2000; Donaldson et al., 1998; Lyketsos et al., 2002; Ross, Arnsberger, & Fox, 1998). Secondly, different information sources (independent observer, caregiver, or patient) are tapped to elicit information on mood status (Burns et al., 1990c; Jost & Grossberg, 1996; Merriam et al., 1988). Thirdly, assessment occurs at different stages of the disease with diagnoses based on different criteria (Cummings & Victoroff, 1990). Lastly, samples are drawn from different population sources namely, research clinics, communities, or care facilities.

The frequency of depressive symptoms tend to vary depending on the setting, for example, primary care settings may have a biased representation of patients with depressive symptoms (Burns et al., 1990c; Chen et al., 2000; Merriam et al., 1988; Ownby, Harwood, Barker, & Duara, 2000). Wragg and Jeste (1989) also note higher prevalence in psychiatric wards or hospital clinics (55%), whereas outpatients and research participants show lower prevalence (17%).

3.2.2.1.2 Co-occurrence with patient characteristics

The classification of Alzheimer's disease depression into mood and motivational dysfunction permits clarity on the actual signs and symptoms manifested (Eikelenboom, Hoogendoijk, Jonker, & van Tilburg, 2002). Moreover, complex associations with age, disease severity, and cognitive functioning warrant delineation into two clusters. For example, mood disorders (dysphoria, hopelessness, guilt feelings and suicidal thoughts) are more common in mild than severe dementia, whereas motivational disturbances (loss of initiative, psychomotor retardation, attention disturbances) are positively linked to

dementia severity. According to these clusters, the depressive symptoms most common in Alzheimer's disease patients are motivational disturbances, which are also likely to be present in the preclinical stage of the disease (Cummings, Miller, Hill, & Neshlces, 1987; Eikelenboom et al., 2002; Jost & Grossberg, 1996).

The existence of mood disturbances in the early phases as opposed to later stages implies that the complicated emotions and abstract thought processes required to experience some of these symptoms in the later stages are dysfunctional because of greater brain atrophy (Burns et al., 1990c). Therefore depression in Alzheimer's disease seems to be linked to an increased mortality rate but not to the rate of cognitive decline (Burns et al., 1990c; Lopez et al., 1991; Reifler, Larson, & Harley, 1982).

Merriam et al. (1988) found support for an inverse relationship between cognitive functioning and depressive symptoms using informant-rating scales, and Burns et al. (1990c) replicated these results using self-report instrumentation. Thus, these studies imply that irrespective of the information source depression occurs more frequently in mild/moderate Alzheimer's disease cases. Furthermore, the existence of depressive symptoms early as opposed to late in the disease course suggests that this is a reactive response to awareness of one's declining abilities. Insight and awareness diminishes with disease severity, thus the reactivity to declining abilities also diminishes. This contention provides a psychological substrate for the occurrence of depressive symptomatology.

Although the evidence exists for a relationship between functional impairment and depression in cognitively intact persons, Harwood, Barker, Ownby, and Duara, 2000) found no significant relationship between these two variables in their Alzheimer's disease sample. Alternatively, Payne et al. (1998) show that the risk for depressive symptoms

increases in Alzheimer's disease patients with mild cognitive impairment and greater functional deficits. According to Payne et al. (1998) functional deficits are either part of the depressive clinical picture (neurobiological) or contribute to the occurrence of depression in less cognitively impaired individuals. In the latter case, these individuals would still have a significant level of insight and awareness of their deficits and functional impairment could contribute to depressive symptomatology. Functional impairment can be the result of the depressive symptoms or a cause of the depressive symptoms.

An explanation for the discrepant findings in both studies could lie in the different definitions attributed to depression and the instruments used to assess these symptoms in both studies. Payne et al. (1998) used the Cornell Scale for Depression in Dementia (CSDD) as opposed to the BEHAVE-AD, and the Psychogeriatric Dependency Rating Scale (PGDRS-P) as opposed to the Blessed Dementia Scale (BDS). The CSDD and the PGDRS-P are more extensive measures of depressive disorders and functional status than the BEHAVE-AD and the BDS, respectively.

Ross et al. (1998) argue that the lack of association found between cognitive functioning/functional impairment and frequency of depressive symptomatology results from small sample sizes, lack of diversity in the sample, and limited assessment of range of cognitive functioning in these studies. Using an ethnically diverse sample, they found a significant relationship between depressive symptoms, cognitive impairment, and functional deterioration. It is important to note that most studies use a composite global score as a simple indicator of disease severity. Results from studies using specific domain deficits usually yield more robust associations between cognitive processing and behavioural symptomatology (Gilley, 1993).

3.2.2.1.3 Symptom comorbidity

Correlates of apathy have often been mistaken for those of depression in Alzheimer's disease patients. Diminished interest, initiative, and psychomotor deceleration can manifest as either depression or apathy (Webster & Grossberg, 1996). However, apathy seems to manifest without the dysphoria and vegetative signs that accompany depression. Consequently, it is important to maintain a distinction between apathy and depression because of the choices for a proposed course of intervention. In a cross-sectional study including patients with Alzheimer's disease, fronto-temporal dementia, supranuclear palsy, Parkinson's, and Huntington's disease this distinction between apathy and depression was affirmed. Levy et al. (1998) found that in these different groups apathy did not correlate with depression but emerged as an independent neuropsychiatric feature, which unlike depression correlated significantly with declining cognitive abilities.

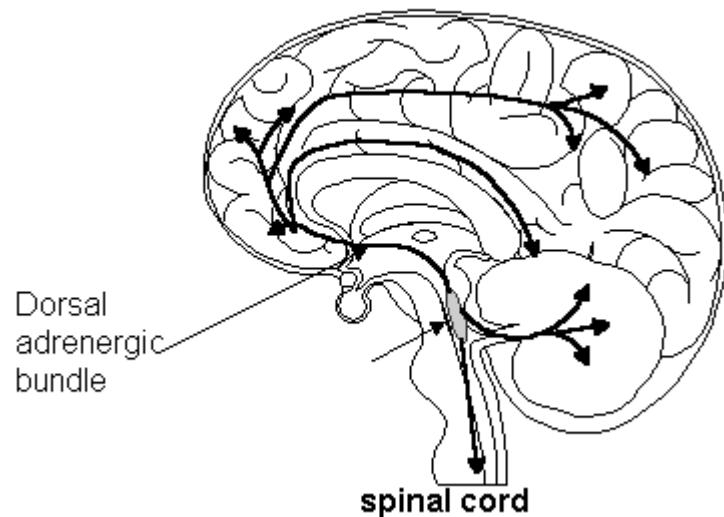
3.2.2.1.4 Underlying substrates

The brain atrophy associated with depression in a group without dementia is specific to the brainstem regions that regulate the various neurotransmitters such as norepinephrine, serotonin, dopamine, and acetylcholine (Lopez et al., 1996). Figures 3.2-1, 3.2-2, 3.2-3 show the specific nuclei and neural pathways of norepinephrine, serotonin and dopamine and Figure 2-6 (p. 53) elucidates the acetylcholine nuclei. Groups with a primary dementia with depression showed more acute damage in these areas and in limbic and frontal areas in comparison with a nondementing group with depression (Zubenko, 1996). This would account for the lower responsiveness to pharmacotherapy (antidepressants) in Alzheimer's disease patients.

In comparison with degeneration seen in psychosis, depressive Alzheimer's disease patients have degeneration in the substantia nigra, raphe nucleus, and the locus coeruleus. These are the production sites for dopamine, serotonin, and norepinephrine, respectively. Thus, the neurochemical correlates of depression in Alzheimer's disease would include lower serotonin, and norepinephrine levels in the cortical and subcortical areas and by association imbalances in the dopamine levels.

Of note, Cummings and Victoroff (1990) suggest that a deficit in acetylcholine (hallmark of Alzheimer's disease) might protect against depression. Support for this hypothesis comes from treatment studies that show a link between anticholinergic administration and elevated mood (Cummings & Black, 1998). Further evidence for a neurochemical basis for depression comes from studies comparing the clinical profiles of late-onset Alzheimer's disease patients with early-onset Alzheimer's disease patients. Lawlor et al. (1994) found that early-onset age predicts the development of severity of depression. Several studies have shown that dementia onset at an early age is accompanied by more widespread atrophy and neurochemical disturbances (eg., Green, 2000). It follows that depression in these cases is more likely initiated because of disruptions in the monoaminergic systems.

Locus coeruleus projections



Locus coeruleus projections

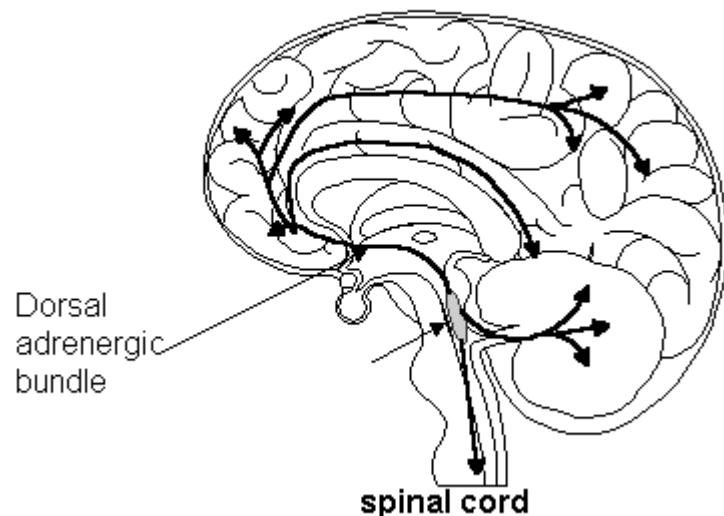


Figure 3.2-1 Norepinephrine pathways (Schatz & Chute, 2000)

Dopaminergic projections

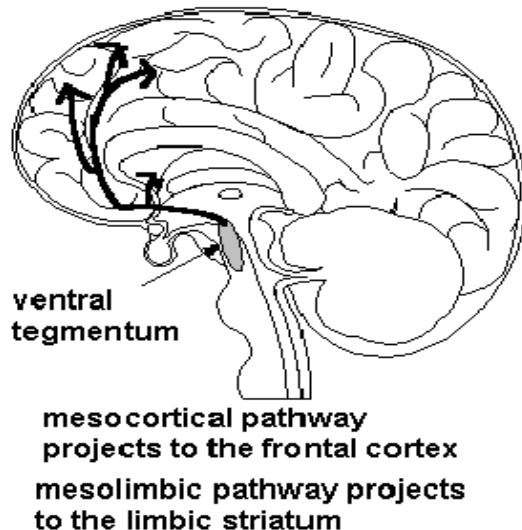


Figure 3.2-2 Dopamine pathways (Schatz & Chute, 2000)

Serotonin projections

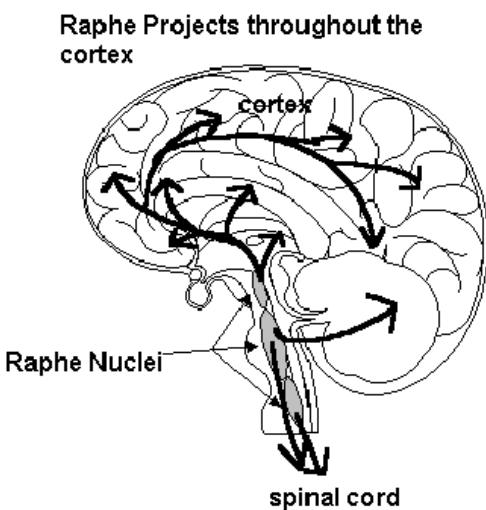


Figure 3.2-3 Serotonin pathways (Schatz & Chute, 2000)

Hope et al. (1997) examined the behavioural disturbances of 97 Alzheimer's disease patients and used component factor analysis to determine the existence of behaviour syndromes in Alzheimer's dementia that might have common aetiology. They found that

psychosis, over-activity, and aggressive behaviour emerge as robust clusters, whereas depression is independent of and separate from the other clusters. In their study, Frisoni et al. (1999) assess the frequency of occurrence of disturbances that clustered together. The factor analysis also yielded three robust clusters namely, psychotic, frontal and mood (depression and anxiety) syndromes. The independence of the mood syndrome from the other syndromes was affirmed when the analysis revealed an inverse relationship between depression and psychoses in Alzheimer's disease. These studies imply that the underlying aetiology for depression appears to be distinct from the other disturbances.

There have been a few studies examining the association between premorbid personality and risk of behavioural disturbances in Alzheimer's disease. These investigations have yielded equivocal data. According to Zubenko (1996) Alzheimer's disease patients with depression appear to have some premorbid affective lability and a family history of affective disorders. Another study confirmed an association between premorbid neuroticism and current depression in Alzheimer's disease patients (Chatterjee, Strauss, Smyth, & Whitehouse, 1992).

Expanding on the neuroticism trait, researchers also established a significant correlation between low level of premorbid frustration tolerance and depressive symptoms (Meins, Frey, & Thiesemann, 1998). In the latter study, the authors used the Munich Personality Scale, which had an additional component to the neuroticism scale used by Chatterjee et al. (1992). The results obtained by Meins et al. (1998) would therefore link to neuroticism, albeit on a more specific aspect of this dimension and endorse the link between premorbid neuroticism and Alzheimer's disease depressive symptoms. Further support for the association was obtained when Meins et al. (1998) found that the correlation was still robust even after controlling for disease duration. A related study, focusing on a person's

psychological history, found that high percentages (92%) of Alzheimer's disease depressed patients had a premorbid history of depression when compared to a nondepressed Alzheimer's disease sample (Ross et al., 1998). On the other hand, several studies found no evidence of predisposition to depression or behavioural disturbances in general (Strauss, Lee, & DiFillipo, 1997; Swearer et al., 1996).

3.2.2.2 Anxiety

Anxiety is one of the neuropsychiatric features of Alzheimer's disease that has limited exposure to systematic investigations although it is a frequent liability accompanying the aged. This paucity of research is partly due to methodological constraints imposed by overlapping rating scale definitions of anxiety and agitation in dementia. However, some prevalence estimates have been reported and causes of this symptom in Alzheimer's disease have been linked to emotional memory processing.

3.2.2.2.1 Prevalence of anxiety

Prevalence estimates of anxiety in Alzheimer's disease are difficult to ascertain because of the methodological pitfalls. On the other hand, the prevalence of agitation, which includes aspects of anxiety, is well documented (Reifler, 1996). Studies often report on these disturbances in two ways: either as anxiety representing a mild form of agitation that is eventually defined as agitation and reported as such, or as distinct features that occur during the disease course with separate prevalence estimates.

In one of the few studies focusing on anxiety, 29% of dementia patients with multiple aetiologies reported anxiety symptoms on a standardised questionnaire, and these symptoms were associated with a younger age ($Z=0.15$, $p<0.88$) (Ballard, Boyle, Bowler &

Lindsay, 1996). Utilising odds ratios (OR) with a 95% confidence interval (CI), they found that anxiety was not associated with either Alzheimer's or vascular type of dementia (OR 1.08, 95% CI 0.21, 3.71) but with a higher level of insight (OR 2.86, 95% CI 0.97, 8.41). The anxiety symptoms in these 158 clinic patients were also associated with a thought and mood disorder and were categorised as depression induced anxiety, psychosis induced anxiety, and contextual anxiety.

Reporting on the nature and incidence of behavioural disturbances, Reisberg et al. (1987) found anxiety symptoms in 12% and fearfulness in 9% of their sample. Mendez et al. (1990) undertook a retrospective review and revealed that 31% of the outpatients studied had anxiety symptoms. In a recent study, Ownby et al. (2000) evaluated the noncognitive symptoms in 133 ethnically homogeneous outpatients from a memory clinic. Data from the 25-item Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) shows that 62 % of patients experienced some form of anxiety and 35% expressed the fear of abandonment.

This high prevalence rate was also endorsed in a multi-ethnic community sample of 125 Alzheimer's disease patients who reported anxiety symptoms on the BEHAVE-Alzheimer's disease (Chen et al., 2000). Furthermore, logistical regression analysis shows that anxiety symptoms are predicted by the aggressiveness score and the activity disturbances score (wandering or purposeless activity) but are not related significantly to age, cognitive impairment or insight.

Frisoni et al. (1999) studied the occurrence of behavioural clusters in a cross-section of Alzheimer's disease patients (162) who attend an Alzheimer's clinic. Using the Neuropsychiatric Inventory, they identified anxiety symptoms in 35% of their sample and

identified three robust noncognitive syndromes in Alzheimer's disease. The psychosis syndrome is represented by agitation and disturbances of perception and thought, the frontal syndrome loads on inhibition and euphoria, and anxiety together with depression represent the mood syndrome. In the latter case, the comorbidity implies that either one of these symptoms is secondary to the other or that they share similar underlying atrophy and neurochemical imbalances. A recent study confirms that anxiety is common among Alzheimer's patients and a difficult symptom for caregivers to contain. (Porter et al., 2003).

3.2.2.2 Underlying substrates

In Alzheimer's disease pathology, the amygdala is one of the primary sites of acute atrophy. Mori, Ikeda, Hirono, Kitagaki, Imamura, and Shimomura, (1999), highlight the role of the amygdala in emotional memory using a sample of Alzheimer's disease patients. Thirty-six Alzheimer's disease patients were interviewed using the 1995 Japan (Kobe) earthquake as an index of emotional memory. The index comprised a semi-structured interview with three items dealing with patient recollections of the earthquake, three items dealing with the depth of emotional memories, and three questions focusing on nonpersonal factual knowledge of the earthquake. Memory was assessed using the Japanese version of the Wechsler Memory Scale, and MRI scans were used to ascertain the amygdala and hippocampal volumes in these patients. They found that impoverished emotional memories in these patients positively correlate with the amount of amygdala damage and lower amygdala volume ($r=0.52$, $df=34$, $p=0.001$) and hippocampal volume ($r=0.49$, $df=34$, $p=0.002$).

Consistent with this study, Hamann, Monarch, and Goldstein (2002) report impairment in the processing of emotional information and fear conditioning in a group of Alzheimer's disease patients. The importance of these results lies in its association with pathological

features especially anxiety symptoms induced by dysfunctional emotional memory and impaired fear conditioning.

In a longitudinal, prospective study, Hope et al. (1997) identified three behaviour syndromes among patients with Alzheimer's disease and vascular dementia. Contrary to Zubenko's (1996) features of psychosis (delusions and hallucinations), they found evidence for the inclusion of anxiety symptoms in the psychosis syndrome. They justify the inclusion of anxiety on the suggestion that delusions and hallucinations create anxiety in a person or alternatively, that anxiety leads to the delusions and hallucinations. Richardson and Divyo (1980) explored the latter idea and concluded that in persons with a predisposition to hallucinate, anxiety is the key that unlocks repressed thoughts and allows them to manifest as vivid images, which the person attributes to the external world. If anxiety is associated with psychosis then these symptoms may share common aetiologies.

3.2.2.3 Emotional dysregulation/affective lability

Sudden changes in mood states and emotions have been observed, with studies showing mood fluctuations in approximately 30% to 74% of Alzheimer's disease patients (Haupt, 1996; Tariot et al., 1995). These expeditious changes tend to lean more towards the depressive side than the manic side of the mood continuum. Therefore, more incidences of anxiety, fear, and sadness in relation to feelings of hopefulness or enthusiasm would be expected.

In some instances the emotional lability results in displays of aggressive or rage behaviours. The behavioural disturbances significantly associated with affective lability include anxiety, depressed features, aggressive actions, and increased activity. Age, cognitive deficit, and functional impairment seem to have no significant association with

affective lability (Haupt, 1996). The rage reactions accompanying emotional lability often have a classification pertaining to catastrophic behaviours such as emotional outbursts and physical violence. Haupt (1996) reports catastrophic behaviour in 38% of his sample and identifies misperceptions, hallucinations, and delusions as antecedents for catastrophic behaviour.

Patients with hypothalamic lesions appear to demonstrate higher incidences of rage reactions, whereas the other organic pathological factors for catastrophic behaviours include damage to the amygdala, temporal lobes, and hypothalamus, with lower serotonin serving as the neurochemical correlate (Webster & Grossberg, 1996). Apart from this, the underlying brain mechanisms of affective lability are currently unknown. However, many symptoms share common traits with this behaviour and their underlying atrophy may contribute to the genesis of affective oscillations.

Apart from brain atrophy, situational stress can also place overwhelming demands on the limited cognitive repertoire of Alzheimer's disease patients. These patients are likely to react in a catastrophic manner because of their inability to cope with the demands of the environment. Furthermore, premorbid emotional instability may predispose certain individuals to react in inappropriate ways and this together with the cognitive impairment can influence the lability of mood states.

Haupt (1996) in accordance with a more dimensional perspective, identifies the following psychological variables causing catastrophic reactions:

- Encountering an unfamiliar place.
- Insight into one's deteriorating abilities.
- Impoverished ability at communicating.

- Acting out psychotic distress.
- Accentuation of premorbid traits.
- Premorbid patterns of interaction with carer.

The psychological variables he identified deal with the interpersonal, intrapersonal, and maladaptive reactions to diminishing abilities and these multifactorial correlates can become the antecedents of rage reactions with accompanying neurological confounds.

3.2.3 Summary of neuropsychiatric disturbances

An extrapolation from the review above suggests that neuropsychiatric features (disorders of thought perception, and disturbances of mood) have a strong neurobiological basis, whereas neurobehavioural features may have a greater association with cognitive impairments. Furthermore, the relationships found between psychoses and acetylcholine depletion and depression and acetylcholine preservation together with the occurrence of these symptoms in separate individuals, hint at the complex nature of the relationship between noncognitive disturbances and aetiology (Harwood et al., 2000).

Following the triadic categorisation of Burns et al. (1990a, 1990b, 1990c, 1990d) neuropsychiatric symptoms of Alzheimer's disease have been discussed as disturbances of thought and perception and disturbances of mood. To complete the triadic categorisation the spectrum of behavioural disorders accompanying Alzheimer's disease will be discussed below.

3.2.4 Disorders of behaviour

Caregivers frequently report behavioural disturbances during the tenure of caring. This is expected because Alzheimer's disease patients, due to frontal dysfunction, display an inability to interpret and interact appropriately in the social milieu (Teri, Edwards, & Saul, 1999). Several studies show that approximately 60% of Alzheimer's disease patients exhibit some problematic behavioural feature. Reisberg et al. (1987) report on the nature and incidence of behavioural disturbances amongst patients with a primary dementia. They found that apart from delusions, agitation, psychomotor overactivity, and aggression were the most commonly endorsed items.

Tariot et al. (1995), using a reliable rating scale (Behaviour Rating Scale for Dementia), confirms these results. They state that the most common behavioural disturbances were apathy, agitation, and wandering. In comparison with fronto-temporal dementia, Alzheimer's disease patients exhibit lower scores on apathy, disinhibition, euphoria, and aberrant motor behaviour (Usman, Franzen, & Hahner, 1997). This is consistent with the pattern of neuropathology that characterises these dementias. When Alzheimer's disease patients are compared to a cognitively intact elderly control group, behaviours such as agitation/irritability, psychomotor restlessness, and tiredness are reported more frequently by the Alzheimer's disease group (Tractenberg et al., 2000). Therefore, behavioural pathology in Alzheimer's disease is distinguishable from mental health problems of normal ageing and other dementias.

In institutional settings, prevalence of behaviour anomalies appears to be consistent. However, in community studies reports of prevalence rates differ greatly. Table 3.2-2 shows the rate variations in community samples (Ritchie, 1996).

Table 3.2-2 Behavioural disturbances in community samples

Behavioural symptom	Prevalence
Activity disturbance	9%-44%
Agitation	9%-48%
Aggression	8%-60%
Wandering	3%-60%
Restlessness	36%-45%
Sleep disorder	19%-44%

From Table 3.2-2 it can be deduced that some estimates differ by as much as 57% (aggression). Others such as restlessness have a shorter range of incidence. The latter can be attributed to studies that do not differentiate between verbal and physical aggression and studies that impose a more stringent definition criteria. Restlessness on the other hand can be classified as observable behaviour encompassing more specific behaviours and estimates would likely reflect the unambiguity in judging such behaviours. In the following sections the neurobehavioural symptoms of Alzheimer's disease will be outlined. In each discussion the difficulties that researchers face when estimating these will be weighed against the particular behaviour i.e., is a caregivers response based on the presence of some behaviour (e.g., aggression or activity disturbance) or on the absence of behaviour (e.g., apathy). In the latter case, caregiver estimates are likely to be less accurate.

3.2.4.1 Apathy

Apathetic Alzheimer's disease patients reveal a lack of initiative or interest in activities, diminished spontaneous initiation, poor grooming, asocial behaviour, and impoverished emotional responsivity. According to Gilley (1993), the apathy–hypokinesis syndrome stems from a diminished sentience of outer and inner stimulation and hence, an impoverished affective and behavioural responsivity to the environment. This syndrome is

relevant to Alzheimer's disease because of the involvement of the prefrontal areas and basal ganglia.

3.2.4.1.1 Prevalence of apathy

Burns et al. (1990d) report apathetic behaviour in 41% of their subjects. Several recent studies have confirmed the prevalence of this behavioural symptom in Alzheimer's disease. In comparison with the other reported behavioural problems (20%-50%), apathy was present in 70% of the participants (Frisoni et al. 1999). Starkstein, Petracca, Chemerinski, and Kremer (2001) observed apathetic behaviour in 37% of their Alzheimer's disease sample compared to 0% in a healthy sample. The highest frequency and severity score for a behavioural disturbance is reserved for apathy in comparison with the other behavioural disturbances (Benoit et al., 1999). The significant correlates of apathy appear to be functional impairment, poor insight, age, cognitive dysfunction, and wandering behaviour (Starkstein et al., 2001).

3.2.4.1.2 Co-occurrence with patient characteristics

Apathy tends to be more common in severe dementia with some studies revealing increases from 70% in mild/moderate cases to approximately 93% in severe cases (Gilley, 1993; Mega, Cummings, Fiorello, & Gornbein, 1996; Webster & Grossberg, 1996). Rubin et al. (1987) affirm this association between apathy and disease severity and found that approximately 90% of their subjects displayed some form of passive behaviour and this increased with the severity of dementia.

Of note, unlike the studies mentioned above that used standardised rating scales, Rubin et al. (1987) assess noncognitive changes using open-ended questions and the personality items from the Blessed Dementia Scale (protocols like the BEHAVE-AD, and the CERAD battery were not yet developed). Inspite of the use of different assessment techniques, taken together these studies affirm the presence of apathetic behaviour in the more advanced stages of the disease. Furthermore, several studies have reported a correlation between apathy and declining functional abilities that enhanced the need for care (Webster & Grossberg, 1996).

3.2.4.1.3 Symptom co-morbidity

Apathy is often misdiagnosed or reported as depression because carers infer that a loss of interest in hobbies or activities is comparable to symptoms of depression (Green, 2000). However, the distinguishing criterion appears to be an increase in the dysphoric disturbances (vegetative symptoms) commensurate with the prevalence of depression and not apathy. Levy et al. (1998) hypothesise that if apathy and depression are the same they would manifest together in different cortical and subcortical dementias and at different stages of the disease. They observed that there was no significant association between apathy and depression in the different dementias, and apathy unlike depression shared a significant relationship with disease severity.

The difficulty in assessing the presence of apathy-hypokinesis in Alzheimer's disease patients lies in the manifestation of this symptom. Caregivers often have minimal problems ascertaining the presence of the other discrete features that tend to be hyper forms of behaviours. With apathy, caregivers have to pay attention to behaviours that are

not occurring and distinguish whether this is due solely to cognitive deterioration or from diminished awareness of a stimulus (Gilley, 1993).

3.2.4.1.4 Underlying substrates

Prefrontal dysfunction correlates with symptoms of apathy in a primary dementia. Neuroimaging studies have also shown that the anterior cingulate or anterior temporal region is linked to abnormal behaviour changes such as lack of initiative and drive (Assal & Cummings, 2002; Benoit et al., 1999; Craig et al., 1996). The cingulate forms part of the prefrontal limbic cortex and limbic lobe, with the latter structure containing primitive tissue that encloses parts of the prefrontal cortex, brainstem, hippocampus, and amygdala. The cingulate, because of this association, is involved in the cortical representation of emotional memory and the perception of feeling (Kandel, 2000).

The link between frontal dysfunction and apathy using neuropsychological measures of executive function, which seem to tap into frontal processes, has been verified. Researchers observed that Alzheimer's disease patients with apathy display significantly impoverished scores on tests of executive function (McPherson, Fairbanks, Tiken, Cummings, & Madruga, 2002). Moreover, an investigation of neurobehavioural frontal dysfunction in psychotic Alzheimer's disease patients has shown a trend for scores on the apathy scale to be significantly different for groups with psychosis and those without.

An anatomical association between Alzheimer's disease psychosis and frontal dysfunction has been clearly demonstrated (Flynn et al., 1991; Jeste et al., 1992; Zubenko et al., 1991). A neuropsychological association between Alzheimer's disease psychosis and frontal dysfunction has been found in studies reporting higher perseveration errors on the

Wisconsin Card Sorting Test (WCST)⁴ in a delusional group when compared to the nondelusional group (Jeste et al., 1992). Thus, apathy correlates with frontal dysfunction on a neuroanatomical level and to executive impairment on a neuropsychological level.

3.2.4.2 Agitation /Disinhibition

Agitation includes measures of gross motor disturbances, pacing, and repetitive motor behaviours (Gilley, 1993). In several studies, aberrant psychomotor behaviours such as wandering and aggression assume a place in the category of agitation. Moreover, unspecified irritable behaviours also fall under the rubric of the agitation category. The inclusion of a myriad of activity disturbances under a single measurable category has contaminated descriptions and estimates of agitation.

3.2.4.2.1 Prevalence of agitation/disinhibition

According to Tractenberg, Weiner, and Thal (2002) extreme agitation occurs in approximately 68% of the community dwelling Alzheimer's disease population, whereas Reisberg et al. (1987) and Teri et al. (1988) report lower occurrences and a modest association with cognitive deterioration. Notably, of all the behavioural symptoms found by Reisberg et al. (1987), agitation of a nonspecific nature is the second most frequent behavioural disturbance reported by caregivers. Confirmation of this result comes from a later study that reports agitation to be the second most common disturbance after apathy (Mega et al., 1996). However, in this latter study the agitation category included aberrant motor behaviour and measures of physical and verbal aggression.

⁴ Neuropsychological assessment tool that taps frontal lobe function particularly prefrontal activity (Lezak, 1995).

3.2.4.2.2. Co-occurrence with patient characteristics

In comparison with extreme agitation, modest increases in activity levels is noticed in 40%to 60% of outpatients, and these changes show no correlation with cognitive deterioration (Merriam et al., 1988). Rubin et al. (1988), in a longitudinal study, show that the progression of agitated behaviours (including purposeless hyperactivity) increases throughout the course of Alzheimer's disease (25% to 67%), whereas self-centred behaviours increase until a moderate dementia level.

Due to the fact that at the time of the research no standardised instrument existed that measured a wide range of noncognitive symptoms, Teri, Borson, Kiyak, and Yamagishi, (1989) compiled a Behavioural Problem Checklist that uses frequency ratings of Alzheimer's disease caregivers to elicit information about challenging behaviours that occur during the disease process. The Checklist reflects the range of behaviour occurrence i.e., occurrence of a symptom twice a week for the past month is considered as a persistent behaviour. After administering the instrument to 56 caregivers of Alzheimer's patients they report that overactivity or pacing occurs in 16% of Alzheimer's disease patients more than twice a week together with emotional and activity (apathy) disturbances that occur in 20% to 43% of the sample, respectively. Mega et al. (1996) concur with the findings on co-morbidity of symptoms but add that different behaviours occur together as a function of disease severity. They found that agitation correlates with different behaviours at different stages of the disease. In the mild stage, agitation correlates with anxiety, disinhibition, and irritability, and in the moderate stage, psychotic disturbances correlate with agitation.

Agitative activity may be problematic for the caregiver but is not necessarily negative for the patient. According to Niesten and Siegal (1996) although agitation may annoy the caregiver, it can also be a self-soothing mechanism for the patient. In addition, motor activity may be a patient's way of providing self-stimulation in order to overcome the paucity of environmental stimuli. These results reflect the changing antecedents of agitation in the disease process, and caution against the use of a single treatment for a behaviour that may have multiple origins or causes relating to neuropathology or psychosocial needs.

Disinhibition often accompanies agitated behaviour in Alzheimer's disease. Chen et al. (1998) found that the disinhibition/agitation score is significantly associated with executive abilities in subjects with Alzheimer's disease. In psychotic Alzheimer's disease groups, this significant association between disinhibition and frontal/executive dysfunction is also observed (Paulsen et al., 2000). Disinhibition in Alzheimer's disease patients manifests as a variety of actions, which include impulsivity, emotional instability, sexual inappropriateness, psychomotor restlessness, and wandering.

3.2.4.2.2 Underlying substrates

Disinhibition syndrome and agitation seem to be the result of limbic activity disruption, which produces episodic lack of control and frontal pathology. As mentioned previously, dysfunction of the prefrontal cortex diminishes the ability to hold down a dominant response in comparison with an appropriate one. On a neuropsychological measure like the Stroop test patients with frontal lesions perform poorly because of the diminished ability to inhibit prepotent responses (Cohen & Servan-Schreiber, 1992).

In Alzheimer's disease patients, executive dysfunction is significantly associated with disinhibition/agitation and 52% of these patients report difficulty in performing the Stroop interference test (Chen et al., 1998). Neuropsychological and other data provide substantial evidence for the matchmaking role of the frontal cortex for stimulus and response pairing. The frontal area accomplishes this by a process of inhibiting prepotent tendencies. Disruption of this system is evident in the responses provided by schizophrenics, Alzheimer's disease patients, and persons with frontal lesions. These groups share insensitivity to context and display dominant response tendencies, which tend to distort the observable behavioural reactions (Cohen & Servan-Schreiber, 1992).

3.2.4.3 Aggression

Aggression is an extreme behavioural referent of agitation and includes physical reactions and verbal outbursts. The occurrence is often underreported because of the confusion surrounding the term (Stokes, 1996). Unlike wandering, which is over-reported because a wide range of psychomotor disturbances are often considered as wandering behaviour, aggressive behaviours tend to reflect observer perception of the threat of physical harm.

A factor analysis on data from institutionalised dementia patients showed that the factor aggression has a high loading for items referring to verbal aggression, physical aggression and resistance behaviour (Näsman et al., 1993). Moreover, this factor is significantly associated with functional impairment. Hope et al. (1997) replicate these findings and show significant associations between physical aggression, aggressive resistance, and verbal aggression in a group of Alzheimer's disease patients. They conclude that these behaviours constitute a behavioural syndrome, which if accepted as an operational definition can be utilised to elicit unambiguous information and prevalence rates concerning aggression in Alzheimer's disease.

3.2.4.3.1 Prevalence of aggression

Mendez et al. (1990) report aggressive actions in 25% of Alzheimer's disease outpatients. Webster and Grossberg (1996) found that physical aggression occurs in approximately 20% of community based Alzheimer's disease patients and in 50% of those in placement care. Neistein and Siegal (1996) report a slightly higher figure (66%) for aggressive tendencies in institutionalised patients. Burns et al. (1990d) endorse this trend of a higher proportion of inpatients manifesting with aggression as compared to outpatients. In a comparative sample, they found that 11% of outpatients and 34% of inpatients report aggressive episodes. Almost half of all patients in both communities and care facilities also exhibit some form of verbal aggression. Ware et al. (1990) found that the majority of subjects (46%) with dementia exhibit a mild form of aggression (resistance or pushing away), 43% a severe episode (hitting, kicking) and 11% verbal outbursts. Likewise, Chemerinski et al. (1998) documents more episodes of physical than verbal aggression. Swearer et al. (1996), however, show a higher prevalence for verbal aggression than physical aggression and found that caregivers indicated that these outbursts were equally disruptive to the caregiving situation.

3.2.4.3.2 Co-occurrence with patient characteristics

In a recent population based study aggression is reported as a frequent disturbance and observed in 30% of the large sample (Lyketsos et al., 2002). According to the authors there are only two other population-based studies evaluating the prevalence of noncognitive disturbances in Alzheimer's disease. In a multi-ethnic sample, aggression is reported in 64% of cases and is associated with moderate and severe dementia (Chen et al., 2000). According to Gilley (1993) retrospective studies seem to corroborate on the

estimates of verbal aggression but reflect a greater disparity in estimates of physical aggression. He contends that this is an artefact of patient characteristics (dementia severity) since studies using the same instrumentation but mixed severity groups of Alzheimer's disease patients yield atypical results.

3.2.4.3.3 Symptom co-morbidity

Physical aggression and psychotic episodes seem to share a common underlying substrate. Deutsch et al. (1991) reports that delusions, misidentifications, and hallucinations co-occur with aggressive acts in 90%, 91% and 88% of subjects, respectively. Many of these aggressive episodes occur during interactions between caregivers and patients. Drug trial studies have shown that atypical antipsychotics have the strongest effect on psychotic and aggressive behaviours, reducing them from as early as the second week of drug intake (Katz, Jeste, Mintzer, Clyde, Napolitano, & Brecher, 1999). This association between psychosis and aggression implies that to understand the nature of the aggressive acts (physical or verbal) one must understand the contexts in which they occur.

Ware et al. (1990) attempted to elicit information about the context of disturbed behaviour in their study of aggression in dementia patients. According to the researchers, this is important for understanding the aetiology of aggression and choice of efficacious treatment in dementia. Their interview-derived data from a community sample shows that certain events or contexts act as antecedents for aggressive episodes. The majority of these contexts involve some form of interaction between caregivers and patients with the two common situations reflecting daily activities of intimate care and delusional episodes.

The former is more amenable to behaviour modification techniques and the latter to drug intervention.

Although behavioural disturbances in dementia are distinct from those observed in nondemented individuals, the changes manifested still follow ordinary rules of stimulus and response effects. Circumstances can serve as antecedents and trigger specific behaviours, and responses can reinforce them. As with any other behaviour, changing the pattern of triggers may influence the rate of occurrence of specific behaviours.

3.2.4.3.4 Underlying substrates

The primary brain areas that appear to regulate aggression are the amygdala, hypothalamus, and hippocampus. These are also primary sites damaged in Alzheimer's disease. These areas have cholinergic circuits that serve to mediate aggressive actions. Post-mortem studies of Alzheimer's disease brains show that patients with aggression have greater loss of 5-HT neurons in the orbital gyrus and lower serotonin levels than those without aggression (Mintzer, 2001; Palmer, Stratmann, Proctor, & Bowen, 1988; Ware et al., 1990). With relation to gross atrophy, Burns et al. (1990d) observe a correlation between aggressive tendencies and degeneration of temporal and frontal lobe. Atrophy of the frontal lobe results in disinhibition of behaviour, and this degeneration of the inhibitory circuit of self-control releases impulsive behaviours associated with aggressive acts (Stokes, 1996).

Several studies have investigated the relationship between premorbid personality and aggression (Kalanowski & Garr; 1999; Swearer et al., 1996; Ware et al., 1990). Using a classification based on profiles of change, Ware et al. (1990) found that 58% of their aggressive cases act in an exaggerated premorbid manner and 39% have a different

premorbid aggressive profile. Thus, premorbidity predicts to some extent the occurrence of aggressive acts in 58% of the cases. In a study confined to understanding the predictors of physical aggression in dementia, the NEO-PI measure of premorbid neuroticism is found to relate to physical aggression, albeit not significantly (Kalanowski & Garr, 1999).

Swearer et al. (1996) found mixed results for the relationship between premorbid personality and aggression. In their longitudinal study, they found that participants who displayed aggression at baseline are more likely judged by caregivers as premorbidly aggressive, whereas participants who develop aggressive tendencies at follow-up are not judged as aggressive premorbidly. They conclude that either retrospective bias influences the results or that aggression as a complex behaviour is influenced by both premorbid personality and disease characteristics.

3.2.4.4 Wandering

Increases in activity levels among Alzheimer's disease patients have been noted in many studies (Gilley, 1993; Merriam et al., 1988). According to Cummings and Victoroff (1990) psychomotor overactivity in Alzheimer's disease refers to behaviours such as restlessness, pacing, wandering, and agitation. Wandering is a term used in literature to elucidate a wide range of motor behaviours observed in dementia patients.

According to Stokes (1996), the term wandering is exposed to the most amounts of ambiguity and speculation than any of the other behavioural definitions. Hope and Fairburn (1990) suggest that various activity behaviours befit a classification of wandering. Their study comprising interviews with dementia sufferers yields a descriptive topology of wandering. Several activities were included such as checking/trailing, pottering, aimless walking, activity towards inappropriate purpose, activity towards appropriate purpose but

inappropriate frequency, excessive activity, night walking, lost outside the home, and attempts to leave home. Ballard, Mohan, Bannister, Handy, and Patel (1991) add the activity of getting lost inside the home to this proposed typology.

According to Gilley (1993) wandering should be equated to features of psychomotor agitation, but several researchers have assessed wandering based on behavioural definitions such as getting lost. Hope and Fairburn (1990) report that the three most frequent activities of Alzheimer's disease patients, as derived from interviews with caregivers, include subjects who wander away from home and have to be brought back, subjects who engage in aimless walking activity, and walking for an inappropriate purpose (e.g., looking for a deceased relative). Stokes (1996) proposes that an operational definition of wandering should include the descriptive typology of Hope and Fairburn, but should also reflect three distinguishing criteria. The criteria pertain to wandering in the context of personal risk, annoyance to others, and maladaptive overactivity of regulatory behaviours (eating, sleeping, etc).

3.2.4.4.1 Prevalence of wandering

Psychomotor behaviour such as wandering has variable impact on both caregiver and patient. This variability is dependent on the environment in which it occurs. Wandering behaviour in a nursing home patient and in a community-based patient causes different levels of disruption and will be evaluated and assessed accordingly in terms of disturbance. Ballard et al. (1991) found a significant discrepancy between the proportion of patients who wandered and the carers who report this as a problem. They also show a discrepancy between the reported rate of wandering obtained via an interview with caregivers (37%) and by using a behaviour schedule/rating scale (21%).

This may partly explain the discrepancy of results obtained in several studies. Almost half of the patients evaluated by Jost and Grossberg (1996) display wandering behaviour, and this occurs early in the disease course (11.6 months after diagnosis). Swearer et al. (1996), on the other hand, report that wandering behaviour is rare in their longitudinal study of Alzheimer's disease patients.

3.2.4.4.2 Co-occurrence with patient characteristics

Burns et al. (1990d) and Lyketsos et al. (2000) also observe low rates of wandering but found significant relationships between wandering and dementia severity. Likewise, Teri et al. (1988) found that wandering is positively associated with levels of cognitive dysfunction and dementia severity as measured by both the Mini Mental Status Exam and the Blessed Rating Scale. Conversely, Ballard et al. (1991) found no significant correlation between the prevalence of wandering and dementia severity.

The equivocal results are attributable to the different aspects of the typology that are included in several studies. Hope and Fairburn (1990) and Ballard et al. (1991) assess specific activity behaviours related to day/night activity inside and outside the home, whereas Burns et al. (1990) assess other aspects of wandering behaviour that may have associations with cognitive decline. Swearer et al. (1996) evaluate two items that give them a composite score for wandering and this could justify the findings that wandering is rare in an Alzheimer's disease sample.

Utilising a large group of institutionalised patients, Näsmann et al. (1993) identify wandering as one of six behavioural syndromes that occurs across the spectrum of Alzheimer's disease severity. In a later study, Hope et al. (1997) also found evidence for the identification of wandering/overactivity as a distinct syndrome. However, they reflect that

the behaviours evaluated and described under the rubric of wandering are too wide. They found robust correlations for items describing purposeless walking, trailing, and increased walking activity but not for items related to straying and getting lost.

These studies affirm that wandering is one of the dementia behaviours that increases the management challenges and influences the amount of physical strain placed on nursing staff and caregivers. Rabins et al. (1982) demonstrate this negative influence of wandering on caregiver stress. They found that 70% of carers describe wandering as a tiresome problem, and the subjective burden (emotional reactions resulting from demands placed on carer) of caregivers is greater when patients display psychomotor disturbances such as excessive walking (Donaldson et al., 1998).

3.2.4.4.3 Phenomenology of wandering

The aetiology of wandering is ascribed to environmental factors, life events, cognitive deficits, brain atrophy, or premorbid personality (Cummings & Victoroff, 1990; Little & Doherty, 1996). In terms of neuropathology, it is associated with decreased cell numbers in the suprachiasmatic nucleus, which is involved in the regulation of the sleep-wake cycles. The destruction of suprachiasmatic cells in Alzheimer's disease is likely to contribute to increased walking at night and overactivity in the late afternoons (Hope & Fairburn, 1990). Data derived from CT scans of Alzheimer's disease patients show an association between wandering and a larger Sylvian fissure, which is the cleft that separates the frontal and parietal lobes from the temporal lobes. This might indicate atrophy to the fronto-parietal and temporal lobes, and structures that lie beneath the fissure (Burns et al., 1990d).

Specific behaviours pertaining to wandering (for example, trailing and checking) are linked to the attachment theory concept of separation anxiety. Hope and Fairburn, (1990) contend that dementing patients may retain a level of insight into their own lack of abilities and attach themselves to caregivers. Miesen (1993) explores a derivative of this concept (parent fixation) and uses the framework of Bowlby's attachment theory.

According to attachment theory, behaviour displayed to maintain proximity to a significant other manifests in situations of unfamiliarity and times of fear experienced when one is alone. It is a well-documented fact that Alzheimer's disease patients frequently invoke the memory of deceased parents and communicate with them as if they were still alive. This is assumed to derive from memory dysfunction, psychotic disturbances, or a communicated need by the patient to feel safe and secure.

Miesen's (1993) study is unique because he derives data on the emotional features and meaning of behaviours from the Alzheimer's disease patients themselves. He concludes that parental fixation is evident in 68% of his sample and occurs frequently among patients with lower cognitive abilities. Furthermore, when attachment figures are unavailable it seems that parent fixation becomes more acute. This is corroborated by findings that nursing home residents seem to have more parent fixations than patients at home because of the loneliness and unfamiliarity of the nursing home environment and people (Lazarus et al., 1996).

3.2.4.5 Neurovegetative features

Sleep disturbances refer to problems such as insomnia, intermittent nightly nocturnal arousal, and night walking. These circadian-rhythm changes are prominent in Alzheimer's disease patients, and relate to cell loss in areas that regulate sleep and cell loss in the

hypothalamus and suprachiasmatic nuclei. The disruptions seem to intrude more in the clinical presentation, as the disease gets progressively worse (Reifler, 1996). Increases in the levels of agitation, cognitive decline, restlessness, and psychomotor disturbances appear to be proportionate to increases in diurnal rhythm disruptions.

Several studies that reported high rates of sleep disturbances found that caregivers allude to the co-occurrence of incidences of agitation, delusions and lower concentration abilities in these Alzheimer's disease patients (Jost & Greenberg, 1996; Merriam et al., 1988; Reisberg et al., 1987). These researchers report sleep disruptions in 56%, 45% and 42% of the samples, respectively. Teri et al. (1989), on the other hand, document lower rates of occurrence and found that 11% of the sample experiences sleep problems more than twice a week. Eighty-one percent of patients in Donaldson's et al. (1998) study experience sleep disturbances and this noncognitive manifestation has a significant association with caregiver psychological morbidity.

In a longitudinal study of 65 patients with Alzheimer's disease, Mortimer, Ebbitt, Jun, and Finch (1992) collected information on mildly/moderately-impaired persons on a quarterly basis over a period of 4 years. Based on the longitudinal and not cross-sectional design of their study, they were able to report on changes in noncognitive symptoms and predict the association between these changes and rate of cognitive decline. They note that participants who enter the study with greater language impairment and sleep disturbances are more likely to show faster cognitive deterioration than those without these problems in the first year of observation. These results could be a derivative of methodological deficiencies rather than patient characteristics.

In the case of language impairment, it is likely that this reflects more underlying neuropathology in the left hemisphere and the test used to assess cognitive functioning (Mini Mental Status Exam) relies heavily on language processing skills. By implication the global measure of cognition will be affected if patients with more acute atrophy in the left hemisphere are tested by means of instruments that rely on the efficient processing in that side of the brain. Furthermore, in terms of sleep disturbances and faster rate of progression it is worth noting that disrupted sleep in the elderly are not always associated with the dementia itself and the disturbance is often secondary to other medical or environmental conditions (Reifler, 1996).

Hoogendoijk et al. (1996) contemplate the notion that sleep disturbances may be attributable to environmental conditions. According to these authors in-patients experience more sleep disturbances than outpatients living at home do. They state that the environmental conditions in a nursing home exacerbate the problem. Patients with Alzheimer's disease undergo degenerative alterations in the retina and optic nerve. This decreases the amount of light that enters the visual system. Often patients in nursing homes spend most of their time indoors under dimly lit conditions and sleep in residences that are usually lit all night. These factors influence the biological clock and desynchronise the sleep-wake pattern.

Cummings and Victoroff (1990) state that internal and external feedback circuits regulate sleep patterns. The neural degeneration affects the internal synaptic communication as well as external daily routines. The altered routine together with the diminished exposure to light disrupts the external feedback loops that influence the impaired neural functioning. Disruptive neurological feedback together with, the concomitant use of medication, comorbid affective states, and stress, breaches the synchronous workings of the biological

clock. Thus, it appears that the reciprocal disturbances in the internal and external feedback loops possibly underlie diurnal rhythm disturbances in Alzheimer's disease.

In addition to sleep disturbances, changes in eating patterns also accompany Alzheimer's disease. Eating disturbances are characterised as either increases or decreases in appetite and dietary changes in food choice. Merriam et al. (1988) observes appetite changes in 130 of 175 patients, whereas Reisberg et al. (1987) report minimal incidence (9%) of appetite disturbances in their patients.

The causes of alterations in dietary behaviour are not well established. Burns et al. (1990d) found that widening of the third ventricle and atrophy of frontal and occipital lobes is observed among patients with hyperorality. They hypothesise that a change in dietary habits may be linked to the hypothalamus, which is in close proximity to the third ventricle. The neural feedback systems may also be disrupted by atrophy of eating centres, dysfunctional interpretations of food cues, or alterations in levels of the neurochemicals galanin and serotonin (Victoroff & Cummings, 1990). Eating and sleep disturbances are robustly correlated and this implicates hypothalamic dysfunction as a causative factor for both symptoms (Victoroff & Cummings, 1990).

3.2.5 Summary of neurobehavioural disturbances

Due to disturbed brain processes, many inappropriate behaviours occur. Outburst of anger at being asked to take a bath or dressing, for example, may be caused by a lack of understanding or a loss of memory associated with this sequence of actions. Taking of clothes in public when the patient is hot is a natural consequence for the dementing person who has lost the nuances of social graces. The anger, anxiety, emotional lability,

and inappropriate behaviours are all masks of despair, a form of primitive communication emerging from an unravelling self.

An inference based on the review of several studies suggests that behavioural anomalies have a stronger association with the stages of dementia when compared to neuropsychiatric disturbances. This observation implies that the basis for behavioural problems is more likely an advanced cerebral degeneration that is structurally and functionally distinct from those underlying neuropsychiatric disturbances.

3.2.6 Conclusion

Alois Alzheimer described the symptoms of his patient from multiple perspectives, and included cognitive and noncognitive correlates. After his initial description, the noncognitive features of the disease were dismissed and the definition of Alzheimer's disease was narrowed down to reflect the dominant cognitive paradigm. With the advancement of neuroscience, the historical developments in neurophilosophy pre-empted a synergy of thought on the mind-brain dialectic and encouraged research into the neural substrates of noncognitive characteristics.

After considerable revision, neuropsychological theories began to espouse models that validated the interwoven reciprocity between cognitive and noncognitive neural systems. The increase in the volume of studies related to noncognitive features attests to their wider recognition as an important concomitant of Alzheimer's disease. There is still debate as to whether it is a core symptom of the disease or a secondary correlate of cognitive impairment. The best-fit model is one that incorporates the biological, psychological, and social referents. This would reflect the complex nature of the component behaviours together with their multiple potential determinants.

Research dealing with the noncognitive features of Alzheimer's disease is warranted on many levels. Such investigations can yield insight into underlying neuropathological process, efficacious interventions, social context of occurrence, psychological factors, and the role of premorbid temperament in the genesis of noncognitive disturbances (Frisoni et al., 1999; O'Connor, 1987). In keeping with these research goals, the role of premorbid temperament in the genesis of neuropsychiatric and neurobehavioural disturbances forms the focus of the current study. In the following chapter, the discussion centres on the various theories of temperament.

CHAPTER 4

THEORETICAL FOUNDATIONS OF TEMPERAMENT

*In the end you are – what you are.
Set on your head a wig with a million curls,
Set your feet on heels half a yard high,
Still, always, you stay what you are.* Von Goethe (2001, p. 95)

From the previous chapter reviews a deduction that gross neurological impairment accompanies Alzheimer's disease, that all patients display erosion of cognitive functions, and most have to endure neurobehavioural and/or neuropsychiatric disturbances, seems accurate. The researchers are in fundamental agreement that neurological and neuropsychological deterioration characterise Alzheimer's disease. However, the contentious issue revolves around the diverse explanations for the individual variances in the symptomatic profile of the disease.

The dominant explanation of a one-to-one correspondence between neuropsychological impairment and specific neuropsychological impairment has proven to be an inadequate retort, based on linear causality. Several investigators have suggested that the symptomatic manifestation of dementia may be the result of a complex interaction of factors such as premorbid personality or temperament, biography, health, pathoplastic effect of personality, social-environmental influences, and distinct neurological impairment (Agnew & Morris, 1998; Berrios, 1989; Cummings, 1992; Frisoni et al., 1998; Kitwood, 1993).

Grigsby and Stevens (2000) believe that the mental or psychological, however, should not be divorced completely from their neural substrates because mental states and psychological activity are identical to and emergent from the specific processes of the brain, which function in a complex environment. Therefore, an aetiological model that

allows premorbid temperament to be part of a nexus of other causal factors and not just a static trait description remains true to the psychological-neural synthesis.

The aim of this study is inter alia to elucidate the role of premorbid temperament, as part of the aetiological nexus, in the genesis of behavioural and psychiatric disturbances. This chapter attempts to clarify the methodological and theoretical aspects of temperament and its aetiological relevance for the emerging neuropsychological profiles in Alzheimer's disease. The discussion is modelled on the contentious elements that characterise temperament research namely: conceptual attributes, composition, and biological premises.

4.1 Analogues of temperament

The referents one uses to define human individuality oscillate between descriptions of temperament, personality, and character. In antiquity, thinkers such as Hippocrates believed that the disposition of a person was dependent on the four humors or fluids within the body and the Greek names for this fluid characterised the four specific temperaments (Simonov & Ershov, 1984/1991). Since those times, temperament shared with other psychological constructs a protean form and character. This descriptive inconsistency still contributes to the methodological issues in temperament research.

Scientific revisions arose to quell the controversial debates, and limit the varied definitions proposed by experts such as Eysenck, Gray, Mehrabian, Thomas, Chess, Strelau, etc. As many researchers have pointed out, attributes of personality, emotion, cognition, and behaviour contaminate the term temperament. The cumulative effect was a proliferation of descriptive traits and diagnostic tools to measure them (Strelau, 1983). For example,

temperament can be understood as pertaining to any combination of more than 80 dimensions or traits identified by various authors, and traits such as negative affect can be measured as an emotional, cognitive, behavioural, or personality related function on as many as 30 psychometric instruments (Netter, 1991; Strelau, 1991; Strelau, 1994). Moreover, temperament has been attributed either a continuous or a discrete connotation, with Eysenck and Eysenck (1985), for example, considering all traits outside intelligence to be (dichotomous) temperament traits and others considering traits as degrees of temperament. The following sections outline the various meanings that have been given to the term temperament and the concomitant influence on how individual differences are perceived.

4.1.1 Temperament and personality: Interchangeable concepts

Many of the biologically oriented theorists use the term temperament and personality as interchangeable concepts. The theoretical divergence lies in the definitions that they attach to dimensions of personality. Eysenck (1966) and Gray (1991) are two theorists that equate personality and temperament but attribute different features to their models of personality. Zuckerman, Ballenger, and Post (1984) on the other hand, contend that personality traits are moulded by biological activity but had not invoked the use of the term temperament in their studies.

Eysenck (1991) proposes that personality and temperament refer to the same dimensions. His proposal has been based on the link between three factors (psychoticism, extraversion, and neuroticism) and neurobiological activity. Exogenous influences are considered as secondary determinants of personality or temperament disposition. The

interaction between genetic predisposition and social interaction appears as a function of psychophysiological features such as neural structure and biochemical function.

According to Gray (1991) the lack of differentiation between the terms personality and temperament is based on the assumptions that temperament is accountable for the individual dispositional variance towards particular emotions and that situations reinforce emotional brain states. Gray (1991) contends that after factoring in cognitive aspects and intelligence the remaining variance forms the core of temperament or personality, whereas Eysenck (1991) discounts concepts such as values, attitudes, and interests from his model. Their interchangeable use of the terms therefore, rests on their restrictive formulations of core personality. Personality traits identified by Gray include anxiety, impulsivity, aggressive-defensive behaviour, and emotionality. Similar to Eysenck's (1970) model these core traits are associated with activity in brain regions comprising the behavioural inhibition, flight-fight, and behavioural approach systems.

Zuckerman (1991) favours the term personality although his explanations of traits such as impulsivity, novelty, and sensation seeking are augmented by biochemical theories. The neurochemicals associated with particular dispositions include dopamine and impulsivity, GABA and serotonin and anxiety. The chemical link with personality stems from the understanding that personality traits arise from elementary reflexes, and are governed by various behavioural activities regulated by biological mechanisms. The neuronal composition and its biochemical activity appear to be genetically determined.

Compressing the terms personality and temperament into one description, Watson (2000) considers temperament or personality to be an expansive general disposition that includes

many emotional traits. For example, traits such as anxiety, depression, and hostility are considered substrates of the broader temperament dimension of neuroticism.

4.1.2 Temperament: An affective trait/state

Allport (cited in Eysenck, 1966, p. 24) proposes one of the earliest definitions of temperament as an emotional trait and suggested that

temperament refers to the characteristic phenomenon of an individual's emotional nature, including his susceptibility to environmental stimuli, his customary strength, and speed of response, the quality of his prevailing mood, and all peculiarities of fluctuation and intensity in mood.

A derivative of this is Gray's (1991) idea that personality traits reflect the emotional underpinnings of behaviour. Mehrabian (1991) elaborates on this with the proposal that emotion states serve as a mediator between environment, disposition, and behaviour. Temperament can be defined as either an emotional trait or state, with the latter referring to a transitory condition and the former to a static condition. The emotion state or trait delineates a person's emotional responsiveness and provides a balance between variability of behaviours across events and relative stability of responses. Personality comprises the three basic temperament factors or emotion states of pleasure, arousal, and dominance.

Eysenck's (1966) view of temperament as an affective trait is inherent in his notion that personality arises from the interaction of four components namely the cognitive (intelligence), conative (character), somatic (constitution), and temperament (affective)

components. The idea of temperament as an emotive component has been more recently challenged by theories espousing the behavioural connotation of temperament.

4.1.3 Temperament: A behavioural characteristic

A conceptual model of the behavioural bases of temperament, derived from developmental theories, attempts to explain the biological mechanisms of difference from the perspective of *how* an individual behaves. Researchers adopting this stance tend to focus on the reciprocal interaction between individuals and their context (Talwar, Nitz, Lerner, & Lerner, 1991). An example of this is the research by Chess and Thomas (1991) on the goodness of fit model. They state that psychological evolution is not a function of temperament itself, but rather driven by the interaction between temperament, other abilities, and environmental features. The *how* or content free notion of behaviour is encapsulated in theories of temperament that elucidate characteristics such as reactivity, activity, strength of nervous system, and mobility.

If temperament is considered as a formal characteristic of behaviour then three corollaries apply (Strelau & Zawadzki, 1993):

- Individual differences are stable and these manifest as variances in intensities (energetic traits) and time (temporal traits).
- If behaviour is comprised of temporal and energetic characteristics then temperament can be expressed in all kinds of reactions and behaviours.
- Temperament is characterised as a product of biological evolution. Therefore, individual differences are co-determined by genotypic and biophysiological mechanisms.

The energetic and temporal characteristics are interrelated, serve different functions, are driven by different microlevel and macrolevel processes and components, and represent the primary traits on the level of specificity and not on the level of superfactors as postulated by the Five-factor model (Strelau & Zawadzki, 1995). Based on the last contention, Strelau (1987b) also opposes the synonymous use of the terms temperament and personality on the assumption that its equivalence with personality cannot be reconciled with the idea of formal characteristics and the Regulative Theory of Temperament, which is a biologically oriented approach. Table 4-1 highlights a summary of the differences proposed by Strelau (1987b), which supports his view of temperament as independent of the structure of personality, and characterised by its own specificity.

Table 4-1 Differences between temperament and personality (Strelau, 1987b)

Temperament	Personality
Biologically based	Product of exogenous influences
Identified from infancy	Emerges at later stages of development
Individual differences observed in animals as well	Prerogative of humans
Addresses the how and why aspects (formal characteristics)	Addresses the what or content aspect of behaviour
Is a causal concept	Is a teleological concept and is an integrative function of behaviour

4.1.4 Temperament: A subclass of personality

Temperament is also described as a “subclass of personality traits, defined by appearance during the first year of life, persistence later in life, and the contribution of heredity” (Buss, 1991, p. 43). The temperament traits referred to as a subclass of personality include emotionality, activity, and sociability. In agreement, Hofstee (1991) states that temperament is a central subclass rather than a peripheral subclass of personality. In other words, he argues that it is the core of personality.

Simonov and Ershov (1984/1991) argue that temperament does not provide insight into the social characteristics of a person. This aspect, they believe, is conveyed by an individual’s personality, which incorporates the traits of temperament. They afford the term personality the highest position in a hierarchy of terms relating to individual difference. Many metaphors have been applied to explore the relationship between personality and temperament. One such metaphor equates temperament with a hard ice ball and personality with the softer snowball. The latter consolidates around the former implying that temperament is the developmental core around which personality develops (Graziano, Jensen-Campbell, & Sullivan-Logan, 1998).

Finch and Graziano (2001), who suggest that temperament mediates the relationship between personality and mental disturbances, endorse the idea of temperament as a biological foundation of personality. They proposed that this mediation may occur because of genetic influences on maturation hence, as a diathesis element temperament regulates individual sensitivities to external stressors and socialisation.

Related to this idea of a temperament core, is Cloninger's (1987) hypothesis that the temperament traits of novelty seeking, harm avoidance, and reward dependence are associated with independent neurobiological and psychological correlates of behaviour. His temperament model, through this association, rests on the assumption that the identified traits form the genotypic component from which phenotypic components of the Big-Five (neuroticism, extraversion, conscientiousness, agreeableness, and openness) are constructed.

4.1.5 Summary

In spite of the divergent terms and descriptions proposed by several authors, most agree that temperament is relatively consistent and stable, is partially influenced by genotypic mechanisms and that dispositions of temperament are present at birth. Watson (2000) found in favour of this contention when he tested traits across a long-term interval of 7.5 years. Although subjects experienced major life transitions, and measures of disposition were taken across dissimilar situations, he showed that traits such as negative and positive affect displayed satisfactory stability longitudinally. This result augurs well for the proponents of biological based theories of temperament.

4.2 Composition of temperament

The structure of personality has evolved at the mercy of the engineers who attempted to build it. From the taxonomies of the ancient Greeks to the taxonomies proposed in the late 19th and 20th centuries, the models of temperament evolved historically in composition and character. Amongst others, Plato spoke of anxiety and impulsivity; Galen and Hippocrates believed in the sanguine, phlegmatic, melancholic, and choleric; Norman and Goldberg

created the Big-Five; Eysenck defined the Big-Three, Strelau expanded on the dimensions of the Pavlovian nervous system, and Gray introduced neoPavlovian concepts to temperament research (Simonov & Ershov 1984/1991; Strelau, 1991).

The component building blocks of these models have included a maximum of 16, seven, five, and three factors (Cattell, 1971; Costa & McCrae, 1985; Eysenck, 1991). In addition, there are some theorists building on existing models and using factors that are common (Buss & Plomin, 1984) and others who propose alternative factors (Mehrabian, 1991; Zuckerman & Como, 1983). Theories of trait or type dominate the literature on temperament, with the distinguishing feature between them being a normal distribution for characteristics of trait and a bimodal distribution for characters of type (Eysenck, 1966). Although not discussed in this chapter, it is worth noting that temperament researchers who study children tend to distinguish between temperament and personality, and their models reflect more specific traits as opposed to the superfactors that represent broader and more general dispositions (Chess & Thomas, 1991; Talwar et al., 1991).

The relation of these superfactors or types to temperament depends on how the theorist perceives the relationship between temperament and personality. The preceding discussion implies that those who perceive personality and temperament to be synonymous (Eysenck, Gray, and Mehrabian) would merely describe temperament as reflecting the same dimensions of personality.

Theorists in the west and in Eastern Europe have proposed numerous approaches and models of temperament. Following the fundamental principles of arousal theory, which has its roots in the Pavlovian approach, Eysenck, Gray, and Strelau have proposed the PEN (psychoticism, extroversion, neuroticism), the neuropsychological, and the Regulative

Theory of Temperament approaches, respectively. These are characteristic reflections of neurobiologically based theories, arising from Western and Eastern European influences, which endorse a relationship between a descriptive taxonomy and explanatory theory (Stelmack, 1997).

Neurobiologically based theories draw on the fundamental assumptions endorsed by the Pavlovian notion of nervous system types and arousal mechanisms.

4.2.1 The Pavlovian influence

A revolutionary advancement in the study of the biological bases of individual differences was initiated through the work of Pavlov (Eysenck, 1987; Robertson, 1987; Simonov, 1987; Simonov & Ershov, 1984/1991; Zuckerman, 1987a). Beginning with applications of nervous types to the conditioned reflexes of dogs, Pavlov extended his theory to human personality. After observing conditioned reflexes, he concluded that types of nervous system activity are comparable to the temperament types described by Galen and Hippocrates, with specific aspects of emotionality characterising each type. Strelau, Angleitner, Bantelmann, and Ruch (1990) argue that Pavlov provided the most satisfactory biophysiological explanation of the Galen-Hippocratic types.

Pavlov's explanation of abnormal states in humans rests on the assumption that essential properties of the central nervous system can produce variations in behavioural and psychological outputs. Hence, the observed behaviour results from higher brain activity and the individual differences seen in this behavioural output are traceable to differences in a person's brain functioning. On a microscopic level, the brain activities allude to the intensity, homeostasis, and mobility of nerve cell stimulation and inhibition.

4.2.1.1 Nervous system types

The human brain, according to this theory, differs in specific fundamental properties that relate to strength or the capacity of the nervous system to endure intense stimulation. To account for the variability of responses to stimuli, Pavlov had to incorporate two opposing brain processes into his theory namely excitation and inhibition. The effectiveness of these processes depends on the endogenous differences in strength and this differential essentially maintains a balance between strength of excitation and strength of inhibition. In some instances, the excitatory and inhibitory processes are equal and in others, the excitatory processes are strong and inhibitory processes are weak.

These differences are related systematically to differences in behaviour that are classified according to type, for example, a sanguine temperament associated with a strong nervous system and a melancholic type related to a weak nervous system characterised by inhibition. A strong nervous system is also characterised by other properties such as mobility. This property determines the speed at which an individual can adopt specific appropriate responses to environmental stimuli. Thus, mobility underscores the adaptive capabilities of a person. Pavlov's classification confers both on the sanguine and phlegmatic type strong excitatory processes that are balanced by strong inhibitory processes. It seems that the differentiation lies in the third property, namely the mobility of the nervous system (Strelau, 1983).

Using the parameters of strength, equilibrium, and mobility, Pavlov extended his theory to include a higher order of central nervous system functioning. The intervening link between micro activity and overt behaviour lies in the reciprocal interaction of macro structures, which represents functionally distinct regions of the brain. For example, he associates the

functional specialisation of the neocortical and the subcortical areas with the intellectual and artistic type, respectively.

4.2.1.2 Nervous systems properties, arousal and temperament

The Russian researchers (Nebylitsyn and Teplov) adapted Pavlov's theories and suggested that characterisations of the nervous system based on the Galen –Hippocrates types, revert to characterisations based on properties of the nervous system (Simonov, 1987). Eysenck's model shares theoretical foundations with that of the Pavlovian/neo-Pavlovian approach to temperament. The strength of nervous system functioning has similarities with the concept of arousal. For example, a strong nervous system requires more intense arousal than a weak nervous system because the latter is quickly aroused. The interaction of the ascending reticular formation with frontal neocortical areas determines the strength properties of the central nervous system, and this relates to extraversion and introversion. Gray (1981) modified Eysenck's ideas, added the hippocampus and septal area to the neuroanatomical scheme, and related a strong nervous system with extroversion and a weak nervous system with introversion.

In summary, Pavlov identified three fundamental properties of the central nervous system that determined individual differences in temperament. The ability to withstand intense and persistent stimulation without exhibiting protective inhibition, the ability to evoke and preserve a state of conditioned inhibition, and the response capabilities of the central nervous system to continuous alterations in the environment (Simonov & Ershov, 1984/1991; Strelau et al, 1990; Strelau & Zawadzki, 1993). The links between Pavlovian and neo-Pavlovian concepts are evident in the similarities between strength of nervous system, arousability, and temperament dimensions such as extraversion and introversion.

4.2.2 Temperament and arousal

The biological mechanism of arousal is considered one of the essential factors mediating temperament. The Pavlovian idea of arousal is associated with the excitatory mechanisms of the central nervous system that involves excitatory process, stimulus intensity, and transmarginal inhibition (Eysenck, 1970). The first premise underlying Pavlovian arousal entertains the idea that the intensity of stimuli determines the intensity of excitation, and the second premise holds that at a set point excitation translates into transmarginal inhibition. In other words, the intensity of actions is equitable with the level of arousal or excitation, and performance or reaction would decrease at levels of arousal that transcend the critical point.

In Strelau's (1987b) theory, the idea of optimal levels is used to determine how different temperaments weigh intrinsic and extrinsic stimulation in order to regulate the stimulus and moderate the response. Eysenck (1966, 1970) adopts the concept of optimal level of performance to explain the relationship between reactions and temperament characteristics. For example, extroverts have a low level of arousal hence, a high optimal setpoint. Another aspect governing the laws of arousal is the non-linear inverted U relation between performance and arousal (Yerkes-Dobson law), which implies that optimum levels are a function of the complexity and difficulty of tasks and situations. Easy tasks have a high level and challenging tasks a low level of arousal. Any stimulus that evokes levels beneath and beyond the optimum will impair performance.

Geen (1984) found that introverts choose a lower noise level than extroverts do, and both groups show no difference in arousal and performance when the noise levels were set at

the preferred point. This result suggests that optimal performances occur when stimulation is at an appropriate critical point, and supports the Yerkes-Dobson law. Amelang and Ullwer (1991) explain that although extroverts occupy positions near the inhibition pole and introverts occupy positions near the excitatory end, both participants perform equally at optimum levels because of this protective mechanism that counteracts further arousal.

Eysenck (1966) differentiates between cortical arousal and autonomic arousal (activation), with the former tied to extraversion-introversion and the latter to neuroticism. Cortical arousal is tied to the cortico-reticular loop and autonomic arousal represents the functioning of the autonomic nervous system and hypothalamic activity (Eysenck, 1966). The limbic system (visceral brain) together with the hypothalamus forms the central circuit of emotion (Kalat, 2001). Gray (1991) expands on the neuroanatomical correlates by proposing distinct systems that regulate arousal mechanisms and stimulus sensitivities such as reward and punishment. The states (emotional construct) and processes of an individual determine the level of cortical arousal. Cortical arousal and activation, therefore relate to each other in complex ways.

To distinguish his idea from that of Eysenck and others, Gray (1991) expands on the meanings of arousal by using terms such as determinants, indices, and determinates. His theory focuses on determinates (signal sensitivity) and specific types of arousal, whereas Eysenck focuses on the determinant (conditionability) and general arousal. The implication of this distinction is that Gray's idea of arousal is associated more with neuroticism than with extraversion and the extraversion-introversion continuum represents a balance between sensitivity and arousability. Strelau, on the other hand is regarded as a general arousal theorist because of his contention that many physiological mechanisms

engaging with energy storage and release processes underlie the trait of reactivity (Zuckerman, 1987b). The dominance of any one system is dependent on the task and situation and differences exist in the biophysiological arousal processes responsible for reactivity. Arousal as a physiological and psychological construct, therefore integrates many of the approaches discussed in this chapter.

4.2.3 The PEN model

The PEN model serves as a biologically based explanation of interindividual differences in personality and temperament. This structural model of the phenotypic traits was derived from the seminal work of Hans Eysenck (1966, 1987). The three factors identified by Eysenck include psychoticism, neuroticism, and extraversion, and these are believed to have strong biological roots in which arousal, visceral brain activation, and hormones actuate the three dimensions, respectively.

The two components of the model are the state–trait distinction and the taxonomic theory. The former allows for a distinction between a relatively permanent disposition (trait) and a transitory intrinsic condition (state). At the core of this structural framework is a hierarchical taxonomy of temperament containing four levels of behavioural organisation (Eysenck, 1997). At the lowest level are simple behaviours that occur at a single moment. At the next level are habits or recurring behaviours, and the third level contains traits or factors, which are developed from interrelated sets of habits. The highest level contains the orthogonal superfactors (P, E, N), which are comprised of constellations of traits.

Eysenck (1966) suggests that level three and four denote types and traits of temperament, respectively. Thus, the hierarchy represents a type (e.g., extraversion) and a trait (e.g.,

social activity). The emphasis is on the dimensional rather than categorical aspects of temperament. For example, the model allows individuals to have some degree of P, E, or N on a co-linear continuum rather than an all or nothing score on the factors. The empirical validation and universal appeal of the tripartite model has been demonstrated across many countries. Evidence for this comes from cross-cultural studies in which data was analysed from 25 countries spanning seven continents (Barret & Eysenck, 1984). The analysis revealed significantly identical factors with a factor comparison that averaged .98. Eysenck's (1991) key conclusion from this study was that biological mechanisms such as arousal and activation serve as the main determinants of temperament.

A similarity exists between Eysenck's ideas of activation and arousal, system activities that vary in strength and synergistic rhythms, and the Pavlovian idea of the strength of nervous system (Fahrenberg, 1991; Newberry et al., 1997). By combining the extraversion and neuroticism dimension one can, for example, equate the sanguine with the stable extrovert, the phlegmatic with the stable introvert, the choleric with the unstable extrovert, and the melancholic with the unstable introvert. Furthermore, extroverts have low arousal patterns and slow/weak generation of excitatory potentials or in Pavlovian terms a strong nervous system, whereas introverts have high arousal patterns and quick/strong reactive inhibitions or weak nervous systems (Eysenck, 1970; Robertson, 1987). The latter represents the Pavlovian sanguine type and the former the phlegmatic type.

Therefore, Eysenck's PEN structure contains three dimensions and the individual differences in these dimensions are attributable to the notion of arousal and activation with extraversion associated with arousal and neuroticism linked to activation.

4.2.3.1 The PEN dimensions and biological substrates

In comparison with other proposed dimensions, neuroticism and extraversion have limited invariance in factor analyses and high validity estimates in predicting peer ratings (Amelang & Ullwer, 1991). In addition, they derive support from specific theories that enable them to transcend the purely descriptive levels assigned to other dimensions. The achievement of this lofty status comes from empirical evidence of a strong neuroanatomical bases for the variance observed amongst individuals displaying these dispositions. The following sections will elaborate on the anatomical and physiological mechanisms underlying the extraversion and neuroticism dimensions.

4.2.3.2 Extraversion and arousal

The biological parallel for the extraversion dimension is the activity level of the cortico-reticular loop. It is important to note the afferent and efferent connections to the cortico-reticular loop because these pathways are susceptible to the degenerating effects of aging and Alzheimer's disease. The cortico-reticular loop is part of the ascending reticular activating system, it is responsible for functions such as attention and arousal, and is regulated by the brainstem and parts of the thalamus (Woodruff-Pak, 1997). The subcortical structures are responsible for oscillations in rhythmic arousal patterns and the cortical frontal systems are responsible for the inhibitory control of the reticular system. Consequently, the neocortex imposes a restraint on the subcortical areas so that cortical excitation (high efficacy of cortex) would manifest as decrease in extraversion and an increase in introversion.

Inhibition of cortical activity, on the contrary, would release lower centres from control and result in an increase in extraversion and a decrease in Introversion. Neural impulses, according to Eysenck (1970), travel to projection areas in the cortex and to the reticular formation. The established reciprocity between the reticular formation and cortex occurs when arousal messages are sent from the reticular formation to the cortex and the cortex instructs the reticular formation to continue with the excitatory impulses or to switch to inhibition. The feedback loop is the nerve centre for arousal and according to the arousal theory its functioning explains the difference between extroverts and introverts. Eysenck (1970) equates the activity of the cortico-reticular loop to the construct of cortical arousal.

Introverts, according to Eysenck (1970) have a higher level of arousal than extroverts do because extraversion is a derivative of the slow functioning of the ascending reticular activating system. His theory rests on the presumption of hereditary components that determine the association between excitatory and inhibitory processes in the nervous system. Thus, position on the excitation-inhibition continuum would determine whether an individual is an extrovert or an introvert.

The optimal levels of arousal according to this theory differ for introverts and extroverts because of the difference in general arousal levels. Introverts can tolerate less intense arousal than extroverts can because the latter begin with a higher threshold. The introvert's neocortex exerts more inhibition on the subcortex, and the introvert displays more inhibited behaviour than an extrovert because of this biological mechanism. Support for this hypothesis comes from recent studies that showed arousal to be associated more with the impulsivity rather than the sociability component of extraversion (Revelle, 1997).

There has been some disagreement on the association between arousal and extraversion, and part of the problem lies in the inconsistent operationalisation of theoretical constructs such as arousal (Fahrenberg, 1991). Several investigators measured EEG recordings of extroverts and introverts and found that extraversion was not associated with arousal but rather that persons with a high psychoticism score have low cortical arousal (O'Gorman & Lloyd, 1987). In a study of respondents with high and low psychoticism scores, Robinson and Zahn (1985) found that high psychoticism scorers manifested with physiological hypo-responsiveness, which indicated a low arousal level.

Another criticism of the extraversion-arousal relationship deals with the limited scope of the theory, which deals exclusively with cortical arousal. Researchers found that the motor neuronal reflex decreases in persons with high scores on extraversion and the Disinhibition scale. This implies that arousal theory can include subcortical involvement and the result that lower subcortical excitability is associated with temperament may suggest a link with biochemical markers particularly dopamine (Pivik, Stelmark, & Bylsma, 1988). Introverts and extroverts differ on performance tasks when subjected to a drug that mediates movement and reaction time through inhibitory effects on dopamine synthesis, with the drug increasing movement and reaction time for introverts but not extroverts. These results attest to the contribution of dopaminergic activity and subcortical arousal as an important determinant of individual differences in the extraversion domain (Stelmack, 1997).

4.2.3.3 Neuroticism and activation

The regions associated with neuroticism include the limbic area and the autonomic nervous system, which is responsible for the expression of emotionality via arousal of the

ascending reticular activating system. More specifically, activities of the visceral brain (sympathetic nervous system), which includes the hippocampus, amygdala, striatum, septum, and hypothalamus, mediate neuroticism. These structures regulate important functions and their idiosyncratic levels of activation and action thresholds determine output of emotional and biological states. Linked to emotionality/neuroticism is an information pathway that forms when the visceral brain sends messages to the reticular formation and arouses the cortex via the ascending reticular activating system. This mechanism is referred to as activation and individuals with high scores on neuroticism have greater activation levels and lower excitation thresholds in the visceral brain (Eysenck, 1991). In other words, they are more susceptible to psychological distress.

The biological explanation gains favour when one considers the interaction between the two systems implicated in extraversion and neuroticism. Eysenck (1966, 1970) demonstrated that subjects who had high neuroticism scores showed an inverse correlation between extraversion and neuroticism. He assumed that the ascending reticular activating system arousal (cortical) does not affect limbic activation (autonomic), but the latter causes an increase in reticular and cortical arousal. This implies that cortical arousal occurs without any autonomic-emotional arousal whereas autonomic nervous system activity involves the hypothalamus and amygdala and mediates cortical arousal processes. Although arousal depends on impulses travelling through two loops, there is a degree of independence between the two loops, with the activation loop producing arousal, but the arousal loop bypassing the activation loop.

4.2.3.4 Neuroticism and anatomical asymmetry

The biological theory of neuroticism as postulated by Eysenck is not conclusive and other researchers have attempted to expand on the search for biological roots. One such attempt by Tomarken and Keener (1998) indicates that differences in frontal cortex activity amongst persons who displayed negative and positive affective traits, which represented aspects of neuroticism and extraversion, could be linked to brain asymmetry. They found that individuals with negative traits displayed more right frontal activity, and left prefrontal rest activity was evident in persons with positive traits. They conclude that prefrontal activity appears to be associated with disposition.

This anatomical asymmetry underlies the actions of neurotransmitters, and this link between asymmetry and neurotransmitters provides support for Eysenck's (1970) contention that disposition is the result of the interplay between heritable features. Temperament, for example, has been linked to monoamine systems (Zuckerman, 1991) and these nuclei have ascending projections to the frontal areas (Kalat, 2001). Research on schizophrenic patients has shown that dopamine is linked to positive affect and this is corroborated by anatomical studies that show a distinct asymmetry in the frontal cortex with more dopamine nuclei in the left prefrontal area (Cohen & Servan-Schreiber, 1992; Lezak, 1995).

In sum, the Pavlovian concept of excitation-inhibition has been used in a general sense by Eysenck to distinguish arousal and activation patterns of the temperament types he proposed. The structure of his model follows a top-down approach where he defined the basic traits and thereafter investigated their occurrence in behaviour, and associated differences in physiological mechanisms to different personality types.

4.2.4 A neuropsychological approach

Gray (1981) concurs with the idea of a hierarchical taxonomy of temperament, but unlike Eysenck's top-down approach, his research represents the bottom-up approach. He postulates on the biological substrates of behaviour that he derived from lesioning studies and brain stimulation investigations, and extends the results to human behaviour, thus following a bottom-up approach in the construction of his model.

Gray disagrees with two fundamental notions of Eysenck: the notion that extraversion and neuroticism are the only potential candidates defining human temperament, and the idea that optimal level of arousal was the only construct explaining individual differences. He adapts the latter construct to form a bridge between his neo-Pavlovian theory and Eysenckian concepts.

In Gray's (1981, 1991) reformulation of his reinforcement-sensitivity theory, impulsivity and anxiety adopt positions on the fundamental axes of personality. Extroversion and neuroticism, according to this theory, are merely distal consequences of the interaction between anxiety and impulsivity. This reformulation proposes that neuroticism and extraversion are underscored by the reactivity differences in two distinct anatomical regions (Gray & McNaughton, 2000). Non-reward and punishment sensitive reactivity in one region determines trait anxiety, and reward and non-punishment sensitive reactivity in the other region determines impulsivity.

The key element in this model is emotion and its definition as a transitory position evoked by reinforcing stimuli or situations that mediate functional behaviour (Mehrabian, 1991). From this starting point, Gray postulates that three emotional states exist that collaborate

with specific reinforcers and respond with specific behaviours. Furthermore, the emotional states have corresponding neuroanatomical structures that underlie specific information processing mechanisms. Gray's theory is based on the postulate that all psychological functions depend on brain activity, and if there is a psychology of temperament then there has to be a neuropsychology of temperament, which attests to the relationship between brain and behaviour.

4.2.4.1 The divergence between Gray and Eysenck

The first divergence in the Gray and Eysenck models involves the trait of impulsivity. Gray assumes it is a defining trait, whereas Eysenck and Eysenck (1985) reformulated their theory and moved impulsivity from the extraversion domain to the psychoticism dimension, with sociability replacing it under its former dimension. However, several studies show that the inclusion of impulsivity rather than sociability as an extraversion trait made more anatomical sense because impulsivity was associated with ascending reticular activating system mediated diurnal arousal patterns, and as an energetic aspect of extraversion it is related to the excitation-inhibition balance (Amelang & Ullwer, 1991).

In a review of several studies, which included psychopharmacological experiments and motor and visual reactivity tasks, Amelang and Ullwer (1991) reiterate that sociability has an insignificant association with the arousal theory of extraversion, and this theory of extraversion is based on the trait of impulsivity as the main component of extraversion. According to available data, impulsivity is the trait responsible for the observed differences amongst introverts and extroverts in experimental and psychophysiological activities.

The second divergence is Gray's revision of the arousability construct. He defined arousal as a function of separate biological factors determining individual differences in response to reward and punishment, as opposed to Eysenck's general notion of arousal, which explains the relationship between performance and position on a particular dimension. The sites and expressions of these biological systems are separate and different. Activity in the behavioural inhibition system (hippocampal formation, Papez circuit, and septal region) is associated with anxiety traits and in turn to signals of punishment and non-reward. The flight/fight system (amygdala and central gray matter) is activated by unconditioned stimuli such as punishment, and the output behaviour tends to be defensive aggression or escape behaviour. Lastly, the behavioural approach system (basal ganglia, ascending dopaminergic fibers, thalamic nuclei, and neocortical areas) is responsive to reward or cessation of punishment and has been tentatively linked to conditions such as impulsivity, happiness, elation, and hope.

4.2.4.2 Gray's challenge to the general arousal hypothesis

The association between emotional systems and temperament lies in the role of temperament as a mediator of operations and enforcer of boundary attributes for the three emotional systems. According to Gray (1981) an individual who contains a more robust behavioural inhibition system of anxiety than a behavioural activation system of impulsivity is most likely be introverted, and one who contains a more powerful behavioural activation system of impulsivity as opposed to a behavioural inhibition system of anxiety may become extroverted. Therefore, neuroticism and extraversion cannot be superfactors because they are derived from the interplay between the emotional systems rooted in brain structures, and not merely from differences in arousal and activation thresholds.

Gray's theory, moreover, introduces the idea of biologically based sensitivities to positive and negative signals and the extroversion-introversion dimension represents the balance between the sensitivities and arousability (Zuckerman, 1987a).

In an attempt to understand how the differential functioning of these systems correspond to personality traits described by Eysenck, learning and performance were assessed in introverts and extroverts using positive and negative reinforcers. Gray (1991) predicts results that oppose Eysenck's formulations. He established that introverts were more likely to learn when the reinforcement was negative, whereas Eysenck's formulations would favour the reverse. The latter is understandable, since negative reinforcement is more arousing and should according to Eysenck's arousal theory facilitate the performance of extroverts.

Although Gray's findings showed a contrast between the two postulations of temperament, the emotional models are speculatively useful for confirmation of the arousal hypothesis underlying Eysenck's model. The level of arousal of an individual is attributable to the comparative balance between the behavioural inhibition system and behavioural activation system and the negative reinforcers are more arousing than positive reinforcers. It follows that a negative reinforcer would augment the arousal level of a person with a higher sensitivity to it (introvert) than to a person who is more sensitive to positive reinforcement (extrovert). Thus, introverts are at a higher level of arousal than extroverts because of the different reactivity thresholds of their behavioural inhibition system and behavioural activation system.

A further challenge to the general arousability hypothesis came from the results of a study using caffeine as a stimulant. Revelle, Humphreys, Simons, and Gilliland (1980) establish

that small doses of caffeine affected the performance of introverts and aided the feat of extroverts. However, this result was influenced by diurnal arousal patterns and impulsivity. In the morning, individuals with low impulsivity showed a negative reaction and high impulsives a positive reaction to caffeine.

This result implies that arousal levels between low and high impulsives fluctuate and the groups differ in accordance with the diurnal cycles instead of over-and under-arousal, respectively. Introverts were more aroused in the morning and extroverts in the afternoon. Anatomically this makes sense because the ascending reticular activating system, which regulates patterns of arousal and attention, is also involved in sleep-wake cycles (Kiernan, 1998). Findings of this nature highlight the situational influences on arousal, and challenge the general principles of the arousal theory by questioning the assumption that extroverts are always less aroused than introverts.

Gray challenges the important principles of Eysenck's theory, however, Eysenck's theory forms the basis of the neuropsychological theory of temperament. Moreover, additional research is needed to verify the structures that comprise the emotional systems (behavioural and fight/flight systems), and their contribution to individual differences in temperament.

4.2.5 A unification of Gray and Eysenck: Cartesian theory

A three-axis orthogonal theory forms the structure of Eysenck's PEN model. Hammond (1994) argues that the principles of an axiomatic theory and its application of a Cartesian division on human form could help establish the neurobiological roots of P, E, and N. The presupposition of a three-axial division allows for the central nervous system and spinal

cord, the central fissure, and the medial fissure to represent basic Cartesian geometry. This Cartesian structure evolves through the handiwork of nature during mitotic and embryological processes. Moreover, the tri-axial anatomical design shows marked differentiations on each axis namely the neuroaxial formation (stem-limbic area), the Bell-Magendie crossover, and Sperry lateralisation (Hammond, 1994).

According to Iverson, Kupfermann, and Kandel (2000) the concept of the limbic system (first axis) underwent a considerable expansion because of the work of Maclean, who revised the Papez system and included structures such as hypothalamus, septal area, nucleus accumbens, neocortical regions and most importantly the amygdala, which is a key player in the neural circuitry of emotion. The Bell-Magendie law states that entering dorsal roots carry sensory information and departing ventral roots carry motor information to muscles and glands (Kalat, 2001). Thus, the central axis (central Rolandic fissure) cleaves the brain dorso-ventrally because it has the Bell-Magendie differentiation on either side of it.

The last axis imposes a relatively bilateral symmetry on the brain. An important discovery that all mental functions are divisible into subfunctions composed of various independent information processing components advanced the idea of functional lateralisation, the underlying idea being that mental processes have a modular nature because they require the co-ordination of several distinct brain areas (Kandel, 2000). Sperry (cited in Kalat, 2001) is one of the first researchers to provide evidence for the localisation of function by demonstrating the specificity of axonal connections during regeneration and he is also commended for identifying the neuropsychological function of the medial axis. Adding to his work on split-brain patients, Gazzinaga (1987) found that in commissurotomised

patients each hemisphere processes information and responds independently from the other, and each hemisphere is dominant for a specific higher cognitive function.

Based on the Cartesian differentiation, Hammond (1994) suggests that the neuroticism, extraversion, and psychoticism continuums represent the Sperrian lateralisation, the Bell-Magendie function, and the neuroaxis, respectively. He contends further that this would also support Eysenck's idea that extraversion, neuroticism, and psychoticism reflect processes of cortical arousal, limbic activation, and neuroaxial modulation via the ascending reticular activating systems, respectively. Gray's model of emotional subsystems is reflected as a neurologically connecting design that directly associates the diagonally positioned lobes of the brain and creates, in addition to Eysenck's personality axes, a set of diagonal axes of personality (Hammond, 1994).

Gray's behavioural inhibition system is responsible for states of anxiety and impulsivity. The main function of the septohippocampal system is to act as a comparator and enforce behavioural inhibition. Exterceptive sensory input is compared to predicted or expected events generated by interoceptive sensory input travelling through the Papez circuit. If the comparator detects a discrepancy between the two it creates a reactive state of anxiety (Gray & McNaughton, 2000). Hammond (1994) argues that the septo-hippocampal system has a decussation and thus follows the Bell-Magendie division of a dorsal-ventral symmetry and a bilateral symmetry. The latter suggests that the left hippocampi control the anxiety factor and the right hippocampi control the impulsivity factor.

A unification of Eysenck's and Gray's theories can only be successful if Cartesian principles are applied to the conceptions of causality. The extraversion and neuroticism factors appear to have positions in the four lobes of the brain as evidenced by the bilateral

division of the medial fissure and the central fissure's dorsoventral division. Gray's comparator collates information or expectations from the four lobes and they provide highly processed information into the Papez circuit. The unification is complete if one perceives Gray's "diagonal system as a mediator of personality conflict ...and as a functional corollary to the underlying Eysenckian structure of personality" (Hammond, 1994, p. 4). Therefore, the Cartesian theory implies that there are three neuropsychologically founded axes in the structural design of personality, and two concurrent neurologically founded axes of personality conflict. This design yields a five-factor model based on anatomical differentiation.

The neuropsychological approach to temperament has yielded insightful associations between temperament dimensions and specific neuroanatomical systems. On the one hand, it provides a framework from which clinical symptoms of neurological impairment can be approximated. A necessary caution, however, is that the functioning and components of the behavioural activation and behavioural inhibition systems and their link to specific temperament traits have been subjected to limited scrutiny because of the specificity of the neuronal systems involved. Strelau (1991) accepts Gray's premise of temperament as a function of its neuromodular interactions, but suggests that the neuroanatomical bases are not specific and the regulation of temperament involves the functioning of many complicated systems.

4.2.6 The Regulative Theory of Temperament

Most of the authors that follow the Pavlovian or neo-Pavlovian tradition spurn the constitutional approach to temperament and its accompanying trend of using temperament and personality synonymously (Strelau, 1991, 1987c). The division between the Eastern

European, American, and British researchers is reflected in the work on temperament from each region. There exists a differential focus on biophysiological mechanisms, social influences, experimental studies, clinical studies, paper-pencil techniques, and target populations (children and adults), with researchers in East Europe focusing on biological causation, experiments, and adult populations.

Strelau (1983) developed the Regulative Theory of Temperament and based it on the principles derived from both eastern and western influences. According to Strelau and Zawadzki (1995) many theories and descriptions of temperament serve as a source for the structure of the Regulative Theory of Temperament. The Pavlovian typology, the characterisations of the 1800's when temperament was described as strength and changeability of disposition, and the characterisation of the 1900's when temperament was seen as a dynamic feature of activity, provided rich sources of data for the development of this theory. The underlying motivation for its development comes from the realisation that traditional views of arousal or activation levels are of little value in understanding systematic interindividual differences in behaviour (Klonowicz, 1987). Moreover, the Regulative Theory of Temperament imbues the idea that stable differences in arousal exist between people and this is evident in the variable stimulation-processing coefficients that drive individual styles of behaviour.

The Regulative Theory of Temperament begins with a conceptualisation of temperament not as the content of behaviour but rather as a reflection of formal aspects of behaviour. In other words, temperament has no content and is not directly responsible for the content of behaviour. Dual levels comprising the energetic and temporal aspects mediate its effects on the form of behavioural output.

4.2.6.1 Energy level

An energy system allows humans to exchange energy with the environment, learn from these exchanges, and ultimately interact with efficiency to conserve energy. This process works in a systemic way and involves exchange, transmission, feedback, and control mechanisms.

In order to relate this to the idea of individual differences in temperament, the energy system has to be perceived as a four-component structure comprising acquisition, expression, storage, and monitoring elements (Gale, 1987). Energy acquisition follows a slow or quick and frequent or rare path. Imbued energy derives from either a few or many sources. The acquisition differentials mediated by the functioning of the acquisition system are observable in behaviour. For example, extroverts would likely have a busy acquisition system (intense, frequent, and varied energy exchanges). The expression system in extroverts is characterised by high motor displays that require intense energy conversion and output. Efficient and inefficient storage systems are able to either store and distribute energy to appropriate behaviours or waste energy output, respectively. An individual high in neuroticism would seem to have an inefficient storage system.

Each of the systems operate with a monitoring system that works towards efficiency, however, depending on the temperament of an individual the control system would focus on different things and maintain differential thresholds. In other words, extroverts and introverts have an efficient expression and acquisition system but the latter functions at a low threshold and the former at a high threshold. However, the control system of the extrovert is biased towards expression (high output), and the control system of the

introvert towards acquisition (low input). Therefore, the interaction of these four energy level systems accounts for the differences observed in behaviour.

Three anatomical systems determine the energetic features of temperament (Simonov, 1987; Strelau. 1987b). These include the neuroendocrine system, the ascending reticular formation (neocortex-hypothalamus-hippocampus-amygda system), and the frontal cortex.

The energetic level has two dimensions that are responsible for individual differences namely reactivity and activity. The former resembles the Pavlovian concept of strength of excitation, is measured by intensity or magnitude of reactions to stimuli, and is a direct aspect of temperament. Sensory sensitivity and endurance combine to form a reactivity construct that is psychological and behavioural in nature, and involves primarily nonemotional reaction phenomena with emotional responses secondary to this (Zuckerman, 1987). The three ways in which reactivity influences a person's activities are as follows (Schulz, 1986):

- In stressful conditions reactivity influences performance.
- A person's style of behaviour is moderated by reactivity.
- Reactivity modulates individual performances for various situations according to their stimulus properties.

Klonowicz (1986), using the arguments of Teplov and Strelau, states that the stable individual differences observed in the organisation of goal-directed activity have their origin in a person's individual style of behaviour (reactivity). The two extremes are high reactivity (high sensitivity, low endurance) and low reactivity (low sensitivity, high endurance), which are governed by the physiological mechanism underlying stimulation processing. For

example, a high stimulation-processing coefficient correlates with high reactivity and a low stimulation-processing coefficient with low reactivity. Furthermore, it seems that reactivity controls the levels of arousal by acting as a filter for environmental stimuli that have arousal potentials (Eliasz, 1987). Hence, as a temperament dimension it influences the acquisition, storage, expression, and control of energy levels.

Activity, on the other hand, pertains to goal directed behaviour that is characterised by a specific stimulus value, specifically the amount and range of the behaviour undertaken. According to Strelau and Zawadzki (1995), most temperament theories consider activity to be a motor feature. However, activity can be related to many features manifested in social situations and has associations with motor behaviour as well as with extraversion and sensation seeking. The stimulation for activity can arise from a number of sources both extrinsic and intrinsic. External sources would include events, tasks, or environment, and internal sources include behaviour, emotions, and idiosyncratic reactions.

An individual's optimal level of arousal and level of reactivity co-determines the regulation of activity. Furthermore, there is an inverse relationship between reactivity and activity. For example, individuals with high reactivity and a low optimal arousal set point (introverts) are less likely to be active than individuals with low reactivity and a high optimum arousal set point (extroverts). Therefore, persons with high reactivity have complex biophysiological processes that augment stimulation, whereas low-reactives have processes that repress stimulation. Due to this difference in activity levels that arise from the expression system, persons with high reactivity have control systems that monitor input sources and low reactives have control systems that monitor output because of their tendency for increased activity and energy expansion (Gale, 1987; Strelau, 1994). The

following table outlines the three main differences between reactivity and activity (Schönplug & Mündlein, 1986):

Table 4-2 Differences between reactivity and activity (Schönplug & Mündlein, 1986):

Reactivity	Activity
Situation dependent (input)	Goal-directed (output)
Stereotyped	Flexible (adaptive)
Reaction = situation (bound to the present)	Activity = adaptation (future directed)

4.2.6.2 Temporal level

Five temperament traits, according to the Regulative Theory of Temperament, represent the temporal level of behaviour. These include mobility, persistence, recurrence, regularity, speed of reaction, and tempo of reaction. In comparison to the research on energetic aspects, the temporal dimensions are underscored by limited scrutiny. The temporal aspects represent the mobility of the nervous system, as characterised in Pavlov's typology. The five characteristics are defined as:

- *Mobility*: refers to an individual's flexibility in changing behaviour according to changes in the environment. A positive correlation exists between mobility and strength of excitation.
- *Speed*: involves the idiosyncratic reactions to stimuli. The impulsivity dimension contains this characteristic.
- *Tempo*: refers to the frequency of stereotyped reactions within a time frame

- *Recurrence*: characterised by repetitive reactions after termination of stimuli.
- *Perseverance*: refers to the maintenance of reactions after stimulus termination.

Strelau and Zawadzki (1995) outline three reasons for the separation inherent in their structure of temperament. Firstly, intensity of behaviour and speed of reaction underlie separate functions. Secondly, the biophysiological substrates of temporal and energetic components are distinct. Thirdly, temperament is characterised on a level of primary traits and the dual structure of Regulative Theory of Temperament allows for the specificity of these characteristics to be highlighted.

4.2.6.3 Summary

The Regulative Theory of Temperament as proposed by Strelau (1983, 1987c) identified dimensions relating to the style of behaviour thus, providing a definitional component of temperament. In its opposition to personality, temperament in this approach pertains solely to aspects that modify and regulate behaviour as well as to the way behaviour expresses itself. Temperament manages these processes by regulating reaction levels proportionate to exogenous stimulative and endogenous activity values.

The PEN model, Gray's neuropsychological approach, and Strelau's theory all postulate on the neurobiological basis of temperament. The inherent differences among them often stem from the varied conceptualisations of arousal and its relationship with disposition. Arousal has been conceived as a drive, stimulation source, stimulation concomitant, trait quality, or as an individual difference trait (Gale, 1987). However, whether these theories consider arousal as a state or trait measure, they endorse the idea that process is more important than outcome. Two individuals, with distinct scores on the neuroticism scale

may behave in similar ways but achieve that outcome through different routes. The neurodynamic approach to temperament endorses the emphasis on process and considers temperament or disposition as a function of probabilistic neural processes.

4.2.7 A neurodynamic view of temperament

Before embarking on a discussion of this nature, clarification of a contentious point is necessary. This deals with the vociferous protests of traditional psychological thinkers who believe that neuroscience is attempting to map the language and processes of the brain onto the territory of psychology or the mind, and from this believe they garner the accusation of improbable reductionism. An accusation of reductionism only holds true if one believes that there is a perfect fit between molecular and neural activity and brain states. However, knowledge of both psychology and neuroscience reveals that there are no perfect fits, only probabilistic associations between molecular/neural processes and psychological activity. These probabilistic equations allow for novel ways of understanding and evaluating psychological phenomena in the context of neural science, without the agenda of conquest and extinction of one discipline for another. .

The science of neurodynamics is the study of neural processes with the understanding that processes characterise structure and emergent psychological activity. A neurodynamic view of temperament differs from the conventional stance that temperament is a reflection of dimensions or trait characteristics, and postulates that temperament is a process that affects the probabilities of neural functioning, and through this influence it is responsible for emergent psychological experience. It is thus a functional theory as opposed to a trait theory of temperament.

The roots of this functional theory can be traced to the discourses on cybernetics that were proposed by Bateson and Maturana and Varela (Capra, 1997). The computer/information processing model of cognition, which was dominated by notions of sequential processing and localisation, was replaced by the view that cognition is driven by structure, pattern, and process. The latter approach replaces notions of representation with connectivity, narrow conventions with global coherence, and information processing with emergent properties (Capra, 1997). This connectionist approach opens up new ways of perceiving temperament that opposes archaic notions of temperament composition.

4.2.7.1 Temperament as an emergent property

The following postulates underlie the neurodynamic view of temperament (Grigsby & Stevens, 2000):

- Temperament affects the activation probabilities of different neural systems.
- Temperament like *state* has no structure or content because it is an *emergent property* of a self-organising system.
- The self-organising system has the architecture of modular distributed hierarchy.
- Structure is equated with functions, which determine its potentialities and constraints.
- The stability of temperament arises from the neuropsychological constituents of temperament, which are relatively stable.
- In addition to genetics, other biological and environmental factors determine temperament.
- Dimensions of temperament are not just psychological constructs but reflect the activity of distributed neural systems.

Central to the understanding of this theory is the conception that temperament like state (a neurodynamic concept) is an emergent property. State is a

complex, multidimensional control parameter influencing behaviour by affecting the probabilities associated with activation of specific neural networks, and influenced in turn on the biological level by the individual's psychological and behavioural activity (Grigsby & Stevens, 2000, p. 164).

Temperament, by sharing the status of emerging phenomena with state, would also share in this definition. Inherent in the definition is a reciprocity element that would allow the perception of temperament as genetically determined and influenced by other neural mechanisms and exogenous factors. Temperament as a neurodynamic concept shares attributes with conceptions of Zuckerman and Thomas and Chess thus transcending both the phenotypic-genotypic and the explanatory-descriptive divide. The following properties of state, as defined by Grigsby and Stevens, (2000), are applicable to the neurodynamic interpretation of temperament.

1. State is derived from nonlinear interactions between many subprocesses and it is an instantaneous and evolving process.
2. States determine the probabilities of activation of neural systems and on a psychological level determine the possibilities of certain dispositions in thought, affect, and behaviour.
3. States undergo oscillations and bifurcations.

These descriptions pertain to the nature of temperament. The probabilistic functioning of neurons reflects the consistency of a person's temperament. Descriptions (2) and (3)

suggest that the shifting constitution of temperament on a microlevel may explain why certain temperament types show a larger amount of variability across time or situations.

The idea of functional systems and hierarchical processing, as espoused by the neurodynamic approach, has been explored in neuropsychological literature. A brief review of the principles and protagonists of theories of hierarchical functional systems, will be attempted in the following section

4.2.7.2 Underlying brain architecture

The idea of a hierarchical modular architecture is borrowed from the writings of Bastian (1902), theories of Luria (1966), and the works of neuroscientists, for example, Wernicke and Broca (cited in Kandell, 2000; Lezak, 1995; Martin, 1998). Luria (1966) states that a dynamic theory of localisation could not accommodate a narrow definition of localisation of function. He collated function with the idea of “functional systems” and “working mosaics”, which is based on a “dynamic, complex constellation of connected systems at different levels of the central nervous system” (p. 23, p. 24). This view of function is systematic rather than concrete, implies that hierarchical relationships exist between different levels of the brain, and multilevel functioning is involved in mental processing of executive abilities. Therefore, neither function was envisaged as reflecting the activity of an organ or group of cells, nor localisation confined to particular parts of the brain or groups of cells. Instead, structure is synonymous with functional pluripotential implying successive and simultaneous stages rather than isolated static centres.

Wernicke discovered that only elementary processes were localised in specific parts of the brain and complex functions arose from the interactions between many functional areas.

Thus, mental functions were an aggregate of their sub functions with component processing representations in different areas. What followed from this discovery was the idea that processing had to be distributed and of a parallel and sequential nature. More recently the discoveries of Wernicke and Broca on language functions in the brain was confirmed through experiments on a conscious living individual (Calvin & Ojemann, 1994).

Neuropsychological studies have also shed some light on the general anatomical localisation of affective traits and personality. Kandel (2000) uses the example of temporal lobe epilepsy. The interictal phenomena accompanying this type of epilepsy shows distinctive personality traits in comparison to epilepsy patients with foci outside the temporal lobes. One of the key problems generated by a modular conception of functioning is the binding problem, which is as yet one of the unsolved mysteries of brain-behaviour relationships. This quagmire stems from the paradox inherent in the workings of a distributed functioning system and its ability to give rise to a cohesive sense of experience (Wurtz & Kandel, 2000).

From the theories of modularity and hierarchical processing, Grigsby and Stevens (2000) formulate the idea that personality or temperament is a modular, distributed, hierarchically organised system. As the first premise they adopt Luria's notion that functional systems comprise both structural and functional components and thus structure and function are synonymous. The second premise underscoring their theory involved equating the functioning systems of neuropsychological domains to neural functioning of temperament. If perceptual, motor, sensory, and cognitive functions can follow a modular organisation then according to them temperament is no different because it is also a psychological phenomenon that is an emergent property of functional systems.

4.2.7.3 Contributions of a novel view on temperament

Two important implications arise from a neurodynamic view of temperament. The first relates to the underlying hierarchical and modular functioning of neural systems. Because these systems act in either opposing or facilitatory ways with each other, features of temperament, which are an emerging property of this interaction, are not likely to be orthogonal in their relation to one another. The second relates to the notion of self-organising or self-regulating systems. Temperament arises from the interactions of such systems hence, optimal levels of arousal cannot account for the self-regulatory mechanisms of temperament inherent in this framework (Rothbart, Derryberry, & Posner, 1994). In comparison with the theories discussed above, the neurodynamic view of temperament discards the idea of orthogonal traits and arousal as the key dynamic determining temperament positioning.

The similarities between this theory and the Regulative Theory of Temperament lies in the conceptualisation of temperament as content free dispositions. It shares with the Pavlovian typology, a strong affinity for neurophysiological descriptions of concepts, and differs from the behavioural emphasis inherent in Strelau's Regulative Theory of Temperament. Unlike most other accounts of temperament, which are either trait or type theories, the neurodynamic view claims to be a functional theory of temperament and expands on the arousability hypothesis by considering the self-regulatory nature of neural systems.

4.2.8 An aside on the Big-Five

Unlike the PEN model, which includes both descriptive and causal elements in its theory, other trait theories such as the five-factor model is based on the lexical approach and adopts a descriptive framework (McCrae & Costa, 1987; Eysenck, 1997; Watson, 2000). This approach envisages natural language to have the engrams of essential traits because traits are the cornerstones of human relations. Therefore, analyses of language would provide the precursors of a structure of personality (McCrae & Costa, 1997).

4.2.8.1 A brief history of the Big-Five

According to its critics the crucial fragility of this framework as a scientific explanation lies in its disregard for causal relations and its inductive as opposed to hypothetico-deductive approach to identifying temperament or personality dimensions (Eysenck, 1997). Although the five-factor model is hierarchical, it does not differentiate between levels as rigorously as the three-factor model. Moreover, the structural framework of the five-factor approach is more inclusive than other trait theories, includes cognitive referents, and regards intellectual process and emotional processes as components of temperament. For example, at the top level of the pyramid is the factor intellect or openness thus overlapping with other factors that have strong emotional bias.

Block (1995), an ardent opponent of the Big-Five, describes the revisionist history of the development of this approach, with the intention of invalidating its claim as a comprehensive typology of personality. The chronology of its revisionist history is as follows:

- An initial attempt was made to sort through a 400 000 list of terms in order to compile a comprehensive trait description of human difference,
- Allport thereafter compiled a primary list with 4504 terms,
- Cattell backed by a lexical hypothesis and factor analysis reduced this to 35,
- Tupes, Christal and Norman eventually settled on the initial five factors and,
- Goldberg and Costa and McCrae adapted the Big-Five into its current structure.

This chronological set of events, according to Block, highlights the major shortcomings inherent in the Five-Factor model. These include the limitations of using single word descriptors to identify core aspects of personality, the factor analytic approach and its predictions, and the instability of the factors in heterogeneous populations. The five factors of neuroticism, extraversion, conscientiousness, agreeableness, and openness occur across many cultures and are present even when self-report data was analysed.

4.2.8.2 A descriptive framework of personality

According to McCrae and Costa (1987, 1997) the Big-Five constitute a descriptive paradigm for the study of personality, for it is the best representative of the trait structure of personality. Block (1995), however, argues that these five factors do not constitute a model because of a lack of theoretical and empirical support. Hence, he substituted the use of the term model with that of approach to account for the moderate robustness of the five factors.

Essentially the difference between the descriptive and causal theories relates to the emphasis on phenotype and genotype. In other words, the former attempts to associate

mental and physical dimensions to answer the question *why* and the latter confines explanations to the *what* of personality or temperament.

Watson (2000) notes that essentially the biological explanations attached to the PEN model can be applied to four of the dimensions of the Big-Five. The dimensions of neuroticism and extraversion are shared between the two and the combination of conscientiousness and agreeableness can be represented as psychoticism. Another version of the Big-Five model stems from the unification of Eysenck's and Gray's models. Hammond (1994) suggests that the three orthogonal (Eysenck) and the two diagonal (Gray) factors would be a replica of the five-factors if the Cartesian theory of anatomy is used as a basis of biological causation.

There are many researchers, who adhere to the descriptive approach to temperament, and their theories are not borne from neurophysiologic or neuroanatomic data nor do they rely on this foundation to validate their approach to temperament. Hofstee (1991), as one such adherent, states that the role of personality theorists should be dominated by a descriptive rather than an explanatory discourse. The main argument of Hofstee (1991), driven by his contention that measures of personality and temperament disposition are subjective and judgmental in nature, underscores his hypothesis against biological reductionism. Interestingly, he also discounts the social determinants of personality on this premise. The main thrust of his argument is the determination of bias in temperament measures. Apart from disparity in self and peer ratings there are also different personal views on the social roles. He furnishes the example that parents judge the temperament of their children differently.

Most of the research linking neuro-based functions with dimensions of temperament depends on self-rating measures obtained from inventories and questionnaires. In his view, the only manner to enhance methodological rigour is to use observer ratings because these are replicable, whereas self-ratings are more susceptible to bias without the necessary means of validation. McCrae and Costa (1987) on the other hand, believe that the Big-Five factors provide an adequate framework for understanding individual differences independent of the source of information and the measurement tool. They based their conclusions on results, which showed significant cross-observer agreement on the five factors, using the NEO-PI.

4.2.9 Summary

From the literature it can be ascertained that the composition of temperament varies according to the theoretical model that subserves its construction. Apart from the Big-Five, the composition of Eysenck, Gray, and Strelau derive from the Pavlovian/neo-Pavlovian constructs of arousal and strength of the nervous system. Moreover, the regulative aspect of temperament, in other words its influence on the probabilities of behavioural outcomes derives not from an inherited gene, but rather from the heritable chemical components that regulate synthesis and modulate transmission of neurochemicals.

4.3 Biological bases of temperament

The advocates (Buss, Eysenck, Gray, Zuckerman, etc.) of the biologically based theories rely on the evidence that psychophysiological research has uncovered and supported. These researchers agree that innate biological difference or genotype contributes to temperament variance amongst individuals. Primary support for this comes from twin studies that show heredity to be accountable for almost half of individual variance. In their

review of twin studies using the Big-Five factors, Gilliam et al. (2000) found that neuroticism, extraversion, and openness had the highest degree of variance accounted for by genetic influences followed by conscientiousness and agreeableness. Arousal-oriented temperament researchers do not attribute genetic causation directly, but rather infer that the manifestation of phenotypic differences occurs because of the intervening link that drives central nervous system activity. The combination of inherited neurological structure, neurotransmitters, hormonal, and other determinants combine to mediate central nervous system activity (Eysenck, 1991).

Research on biochemical correlates aims to link specific constructs with its biological mechanisms. In some studies a pharmacological agent is applied, changes in the input and output of nervous system reactivity are quantified, and the oscillations in reactivity measured as reflections of different temperaments. An example of this research would be Eysenck's (1970) attempt to make participants more introverted or extroverted in their cortical arousal by administering sedatives or stimulants. Associating a particular trait with its biochemical markers is another method used to establish physiological roots for psychological referents, for example, Zuckerman and Como (1983) measured MAO levels and found that high sensation seekers had lower concentrations of MAO than low sensation-seekers. These studies attempt to unravel how persons with different temperaments adapt to situations, and identify the biochemical correlates of the underlying differences in behavioural and cognitive mechanisms of adaptation.

Individual differences in traits such as impulsiveness, sensation seeking, and novelty behaviour has also been linked to psychobiological mechanisms particularly to the action of neurochemicals. The following discussion will focus on dopaminergic and serotonergic influences on individual differences in temperament.

4.3.1 Neurotransmitters and dimensions of temperament

Many biochemicals play an influential role in determining temperament differences. Researchers have identified catecholamines, acetylcholine, serotonin, cortisol, and opioids as contributing to aspects of temperament such as approach/withdrawal, distractibility, sociability, impulsivity, sensation seeking, strength of excitation and inhibition, etc. (Buss & Plomin, 1984; Cloninger, 1986; Strelau, 1983; Zuckerman, 1987b).

4.3.1.1 Dopamine

Sensation seeking, novelty seeking, extraversion, activity, and rigidity have been linked to dopamine and the dopaminergic system (Cloninger, 1987; Ebstein, et al., 1996; Watson, 2000; Zuckerman, 1983). Dopamine is also indirectly associated with the traits of flexibility and adaptability (Netter, 1991). Parkinson's patients, for example, have depleted dopamine in the basal ganglia and this manifests as a limited ability for altering their cognitive strategy according to alternate stimuli. Moreover, these patients also display negative affect, low activity, and limited interest and interaction with the environment. The symptomatology is consistent with the function of the ascending dopamine systems (mesocortical and mesolimbic), which innervate the frontal and temporal cortex and the limbic structures of the basal forebrain. Approach-related actions and pleasure seeking behaviours are two psychological activities mediated by these systems (Kandel, 2000).

Depue, Luciana, Arbisi, Collins, and Leon (1994) elucidate the role of the dopamine system and its association with positive affect. They administered dopamine agonists to normal adults and measured the intensity of the system's response. Consistent with their predictions, Depue et al. (1994) found a significant correlation between dopamine activity

and interindividual differences in positive affective traits. They hypothesise that much of the variance in positive affect amongst individuals could be related to the concentration of dopamine cells in specific areas of the brain and certain individuals may inherit greater concentrations of “joy juice” than others (Meehl, cited in Watson, 2000, p. 226). Researchers, who identify a single gene as the causative agent for the manifestation of specific traits confirm this link between genotype and phenotype (Benjamin, Patterson, Greenberg, Murphy, & Hamer, 1996; Ebstein et al., 1996).

Novelty seeking behaviour entails actions characterised by exhilaration in response to new stimuli. According to Gilliam et al. (2000), about 40% of novelty seeking behaviours are heritable and are linked to dopamine receptors. A significant percentage (10%) of the genetic component is traceable to a mutation on the gene that encodes the D4 receptor (Benjamin et al., 1996). Dopamine has five different receptors identified in various areas of the brain. The D4 receptors are located in the hypothalamus and limbic areas and play a role in emotional functions. The mutation on this gene alters the signalling properties of the receptor in response to dopamine and this sensitivity threshold is believed to be the genetic correlate of novelty seeking behaviour.

Ebstein et al. (1996) also establish a significant association between novelty seeking and a mutation on the D4 dopamine receptor gene. However, they also found that traits such as harm avoidance and reward dependence failed to show a significant link with this mutation, thus strengthening the observed correlation between a genetic polymorphism on D4 and a temperament trait. However, in a recent twin study, the genetic base of novelty seeking is only partially supported, and the trait of harm avoidance also showed additive genetic links (Ando et al., 2002). In addition to novelty seeking trait, Benjamin et al. (1996) in their study found correlations between the mutations on D4 and traits of extraversion

such as warmth, excitement seeking, and positive affect, as well as the deliberation facet of the conscientiousness scale.

The dopamine system in the nucleus accumbens is thought to underlie some of these predispositions. This system make up the mesolimbic area, which has a role in reinforcement and reward-dependent learning (Kupfermann, Kandel, & Iversen, 2000). Thus, temperament appears to be reflected in the reward-motivational activities of individuals and certain persons have low dopaminergic tonic activity and are more susceptible to drugs and pleasure seeking activities that impact on dopamine systems (Zuckerman, 1991). However, empirical evidence suggests that noradrenaline and the enzyme dopamine- β -hydroxylase (converts dopamine to noradrenaline) are negatively correlated with pleasure seeking behaviour, and dopamine is associated with this behaviour because the low conversion into noradrenaline suggests more dopamine in the central nervous system (Schwartz, 2000; Zuckerman, 1991).

According to Strelau and Zawadzki (1995), temporal traits are explained by recourse to tempo of reaction, termination, course of the neural process, and interaction between these neural activities. Due to the actions of dopamine in different parts of the brain, Netter (1991) suggests that it might be involved in temporal processes. The arousal-orienting mechanisms appear to be involved with the energetic aspects of behaviour. Moreover, together with dopamine acetylcholine is believed to mediate cognitive styles (reflexivity, selectivity of attention, distractibility) that are reflections of temperament (Netter, 1991).

Strelau and Zawadzki (1995) hypothesise that in general the production and release of neurotransmitters, the sensitivity of their postsynaptic receptors, and the reactivity of nerve

cells to divergent stimuli may explain the energetic traits. More specifically, the traits of sensory sensitivity, endurance, and activity appear to be related to processes of the cortical-reticular system, and emotional reactivity appears to be mediated by the actions of the limbic system and the ANS. Thus, Strelau, Eysenck, and Zuckerman are in agreement regarding the biological underpinnings and the dopamine correlates of action-oriented traits and emotion-oriented traits.

4.3.1.2 Serotonin

Serotonin activity is identified as one of the biological markers determining the threshold for violence and it has been linked to temperament traits such as impulsivity and aggression that are contained in the psychoticism dimension, and to harm avoidance (Cloninger, 1986; Eysenck, 1970). Individuals with low levels of serotonin tend to display more disinhibition, which is a facet of psychoticism, and anxiety and depression, which are facets of neuroticism (Zuckerman, 1991). Eysenck (1992) found that low MAO (enzyme that degrades serotonin) concentrations increase a person's vulnerability to aggressive and impulsive behaviour, and Zuckerman (1987b) found that high scores on the Sensation Seeking scale were inversely correlated with MAO levels.

The results of Eysenck (1992) and Zuckerman (1987b, 1991) provide a glimpse of the atypical role of serotonin on behaviour. Gilliam et al. (2000) relate the story of a Dutch family to demonstrate the complex relationship between serotonin and impulsive behaviour. Fourteen members of the family had a history of impulsive and aggressive behaviour. Each of these individuals had the polymorphism on the gene that encodes for the enzyme MAO A. This genetic defect leads to increased serotonin levels, yet the individuals showed heightened impulsive tendencies. This suggests that both increased

and decreased levels can contribute to specific traits, and due to MAO's involvement with other monoamines the interplay between neurotransmitter balances might also contribute to the behaviour. The action of serotonin on various receptors is of particular importance because it provides clues for understanding how the phenotypic and genotypic factors interact.

4.3.1.3 Summary

The validity of results associating biochemicals to specific traits must be evaluated against the following salient point: determining causal and linear relationships between a specific stimulus and a specific biochemical and between the latter and a behavioural output is not possible. Therefore, the link between a neurotransmitter and dimension of temperament is most likely probable and not definite. This scenario is complicated by the fact that a neurotransmitter could be mediating various behaviours depending on the location of release in the brain. Moreover, a measurement of neurotransmitter levels is conducted indirectly via plasma and urine concentrations and these represent only 5% of the brain levels (Netter, 1991).

Utilising the premise that temperament impacts on behavioural probabilities, many studies are conducted on people who have psychopathologic profiles. An extension of this, are studies that aim to provide a link between certain pathological behaviours and temperament in the presence of traditionally classified brain diseases. In Alzheimer's disease, the noncognitive symptoms are characterised by relative heterogeneity across sufferers and one of the vulnerability factors for occurrence of certain symptoms is hypothesised to be temperament.

4.4 Symptom profiles and premorbid temperament - A case for neurological patient groups.

People with certain psychiatric disorders are often presumed to share vulnerability for pathological behaviours, and one of the attributable factors for increased vulnerability is considered to be personality or temperament traits (Andrews, 1996; Boyce, Parker, Barnett, Cooney, & Smith, 1991). There is a wide spectrum of neuropsychiatric and neurobehavioural features that accompany Alzheimer's disease. Explaining all these symptoms by recourse to causative neurological impairment cannot account for the variance observed in the neuropsychological profiles of patients. Hence, drawing from general research on relationships between personality and psychopathology, premorbid temperament assumed the role of a risk agent responsible for the gamut of noncognitive symptoms in Alzheimer's disease.

4.4.1 Predisposition for specific symptoms

Several studies address the issue of temperament as a predisposition factor for noncognitive pathology in Alzheimer's disease, but evidence that unequivocally demonstrates this correlation is modest.

Utilising regression analysis on data obtained from Alzheimer's disease caregivers, Chatterjee et al. (1992) found that premorbid neuroticism precede the occurrence of depressive symptoms in Alzheimer's disease patients, and patient's with delusions are more likely to be perceived as hostile, less agreeable, and emotional (negative) premorbidly. Meins et al. (1998) also demonstrate an association between depression and premorbid temperament characteristics. Alzheimer's patients, who displayed a low threshold for frustration tolerance premorbidly, appear to manifest with more depressive

symptoms than those patients who have a greater propensity for toleration. Moreover, they showed a positive association between premorbid extraversion and depression.

In both these studies a single informant was used to obtain information about the patients' premorbid temperament and current symptoms. Expanding on the single informant design, Strauss et al. (1997) found that when using two caregiver sources, the relationship between depression and premorbid neuroticism was insignificant. In other words, when the same informant assessed the personality and current symptoms there was a relationship between neuroticism and depression. The only relationship that was significant irrespective of informant source was between anxiety and premorbid neuroticism. They conclude that retrospective bias may cloud caregiver judgement on some current and premorbid behaviours.

Kolanowski, Strand, and Whall, (1997) obtained information about premorbid temperament from a primary caregiver and information about current behaviour from nursing staff most familiar with the patient in order to control for retrospective bias. Current symptoms of aggressive behaviour are positively related to neuroticism and extraversion and inversely related to agreeableness as measured on the NEO-PI. Conversely, Swearer et al., (1996) found no association between aggressive symptoms and premorbid temperament amongst their sample of demented patients.

A possible explanation for the diverse results could be the use of different temperament inventories. In the latter study, the investigators used the Adult Personality Rating Assessment Schedule, which was constructed for use with mentally impaired elderly patient and may not be a reliable measure of premorbid temperament among demented patients. Other reports of associations between premorbid temperament and noncognitive

symptoms in dementia include relationships between premorbid hostility and introversion with delusions, and premorbid openness with hallucinations (Rao & Lyketsos, 1998). Low, Brodaty, and Draper (2002) reported contradictory findings, with associations between higher neuroticism and delusions, higher agreeableness with hallucinations, aggression, and affective symptoms, and higher openness with affective disturbances.

Several other studies have found that specific premorbid behaviours may influence the manifestation of that trait or behaviour during the dementing process. Hamel, Pushkar-Gold, and Andres (1990) and Ryden (1988) observed an association between premorbid aggression and its occurrence in dementia. Analogous research, however, found no significant association between premorbid aggressive traits and aggressive symptoms in dementia (Burns, Folstein, Brandt, & Folstein, 1990; Swearer et al., 1996).

The challenges faced in assessing premorbid temperament include retrospective bias that may contaminate recollections and the difficulty in determining when the disease began in order to distinguish between premorbid disposition and disease disposition. Some of the studies reviewed above have addressed the former challenge by including secondary informants or using a clinician or nurse to rate current behaviours. The main limitation of these studies, however, is the small sample sizes used and the cross-sectional correlational designs that do not address causal relationships.

Meins and Dammast (2000) and Strauss et al. (1997) contend that a relationship does exist between premorbid temperament and specific noncognitive symptoms in Alzheimer's disease, and that this is not a derivative of retrospective bias but rather a premorbid diathesis for neuropsychiatric and neurobehavioural symptoms. The mechanisms underlying this relationship will be elaborated on in the following section.

4.4.2 Pathoplasticity, predisposition, and self-fragmentation

Berrios (1989) considers the pathoplastic nature of personality as a possible reason for the changes observed during a dementing process. For example, he reflects on two change-mechanisms: a mechanism of release caused by the disease and a mechanism of magnification of personality traits. Berrios (1989) believes that in both instances one is likely to observe an exaggeration of the premorbid temperament profile that renders a caricature of a prior self. An exaggeration of premorbid personality was the conclusion that O'Connor (1987) reached to explain the presence of behavioural disturbances in 43% of his sample, and the interpretation of this finding rests on the theory of frontal lobe disinhibition in dementia. However, the idea of a dementing illness causing an exaggeration of personality by whatever means, partially explains the quantitative (energetic, happy) and not the qualitative behavioural displays (delusions and hallucinations) accompanying the disease.

Widiger and Trull (1992) state that there are various forms of the relationship between premorbid temperament and noncognitive symptoms, but separating them is not possible. Thus, the relationship between predisposition and occurrence stems from either a pathoplastic effect or comorbidity of pathoplasty and disease process (predisposition). Several studies have found, however, that persons with dementia retain some of their unique traits despite the disease (Kolanowski et al., 1997; Welleford, Harkins, & Taylor, 1995).

Supporting the argument against the pathoplastic effect of personality on noncognitive symptoms, Welleford et al. (1995) found that the changes observed after the disease onset, are characterised by a stereotypic change, where patients show similar increases

and decreases in certain characteristics while retaining individual variability. For example, several researchers utilising the NEO-PI on dementia patients found a general profile of change, with increases in neuroticism and decreases in extraversion, openness, and conscientiousness from premorbid levels to current levels (Glosser, Clark, Freundlich, Kilner-Krenzel, Flaherty, & Stern, 1995; Kolanowski et al., 1997; Welleford et al., 1995).

The stereotypic changes seemed to occur irrespective of a patient's premorbid temperament, and previous personality traits were not exaggerated during the disease. These results suggest that predisposition is the strong contender as an influential agent for noncognitive behaviours. This contention is enhanced by results showing that neurological patient groups (Alzheimer's and Parkinson's disease) usually exhibit similar changes in personality after onset of disease. Glosser et al. (1995) state that the changes in personality may reflect an individual's attempt at adapting to the accompanying symptomatology. It is the predisposition that determines whether this adaptation or pathoplasticity manifests as pathological behaviour.

A word of caution against the interpretability of the studies pertains to the use of the same personality inventory, small sample sizes ($n= 29-40$), moderately affected patients, and a single informant design that does not address the influence of retrospective bias. A moderately affected group may show specific patterns of change based on the duration of disease course. In other words, these patients are still adapting to the loss of abilities and functions and their adaptive response may be different from a group who are mildly affected or severely affected by the disease. Longitudinal studies are needed to ascertain the 'stability' of stereotypic changes and their relationship to premorbid temperament.

A related view on the association between premorbid temperament and noncognitive disturbances, declares that the self is a “phenomenological agency that co-ordinates the demands of the immediate situation with the constraints imposed on the individual by dispositions and residues of life experiences (Graziano, Jensen-Campbell, & Finch, 1997, p. 393). In other words, the phenomenological self acts as a mediator that converts disposition to situational adaptation.

In Alzheimer’s disease, the essence of the self erodes and the dissolution can create, according to this view, a perturbation in the mediatory processes between self and situation. Lazarus et al., (1996) agree that certain noncognitive symptoms may arise because of the disturbed interaction between personality, self, and situation. However, they contend that a hallucinatory symptom could be an adaptive compensatory mechanism of the dementing patient. Hallucinations relating to deceased parents or kin may relieve the feelings of self-fragmentation, with premorbid dispositions likely to influence the occurrence of noncognitive symptoms in these situations.

4.4.3 Summary

Temperament as the constitutional aspect of personality is a known factor in the genesis of neurobehavioural and neuropsychiatric disorders, particularly anxiety and depression (Andrews, 1996). The comorbidity of a vulnerability factor and a disease process appear to interact and enhance individual liability for the occurrence of noncognitive signs and symptoms. The research to date is supportive of the predisposition hypothesis but is not conclusive. Methodologically, studies of cognitively impaired individuals are dependent on informant reports, utilise different tools, and varied definitions of premorbid time frames.

Such conflicting designs and descriptions underlie the limited research endeavours in this area.

4.5 Conclusion

The relationship between neurotransmitters and temperament disposition appears to be mediated through the variable effects of genetics on production, release, and reuptake in the central nervous system. The brain structures and their activation thresholds are also involved in the biological substrates of temperament and mediate the general heritable predisposition rather than the specific symptoms.

There is little doubt that temperament is a reflection of underlying brain functions such as the workings of distinct neural subsystems and their biochemical and regulatory levels and patterning. The discord concerns issues about the nature and specificity of the representation. Similarly, a growing body of research attests to the significance of a relationship between predisposition and noncognitive symptoms of Alzheimer's disease, but the discord pertains to the nature and specificity of this relationship.

CHAPTER 5

EMPIRICAL INVESTIGATION

Based on the reviews in the preceding chapters the following deductions can be made:

Firstly, that noncognitive symptoms are common in Alzheimer's disease patients and lead to psychological morbidity among caregivers, and secondly one of the factors, which may contribute to the manifestation of specific noncognitive symptoms, is likely to be the premorbid temperament disposition of the individual. While the researcher acknowledges that there is a danger in reducing the complexity of expressions of neurological disease to one component, this is done as an attestation to the irreducible uniqueness of individuals that are forced to share an inextricable neurological dilemma. Several studies explicate the possible causes and correlations of this disease and its symptomatology, but few focus on the possibility of an association between disposition and disease (brain) symptoms.

This study aims to contribute to the latter and in so doing acknowledge another possible dimension amongst the vast possibilities, which may account for the occurrence of specific noncognitive symptoms in individuals. It poses the following research questions: what is the nature and frequency of noncognitive disturbances in Alzheimer's disease, and on which dimensions are premorbid disposition and noncognitive symptoms related in Alzheimer's disease?

The goal of this study, therefore was to elucidate the relationship between noncognitive functional deterioration and distinct biological premorbid temperament traits in a group of Alzheimer's patients.

This chapter addresses the design of the study, procedures followed for sample selection, the rationale for the use of specific measuring instruments, and the analyses techniques used to interpret the data and shed light on the possible relationship between disposition and disease symptoms in a community based sample of Alzheimer's patients.

5.1 Design

This study utilised a correlational design. Data was obtained from Alzheimer's disease caregivers regarding the noncognitive symptoms and premorbid temperament traits of their wards. A noncognitive inventory (Behavioural Rating Scale for Dementia) was utilised to elicit information about current pathology and a temperament inventory (Formal Characteristics of Behaviour-Temperament Inventory) was used to gather information about premorbid temperament before the disease process. A primary caregiver completed the noncognitive inventory and the temperament inventory. In order to minimise retrospective bias, a secondary informant (who knew the patient before disease onset) completed the temperament inventory as well. The secondary informant was available for all of the Alzheimer's patients included in this study (63 secondary informants). The answers from the two information sources were correlated to determine if current behaviour biased judgement of premorbid disposition.

A screening schedule (Appendix A) and the CERAD Diagnostic Impression Protocol was administered telephonically to all interested participants, and those caregiver's that fulfilled the eligibility criteria (discussed below), thereafter completed a biographical questionnaire (Appendix B) about the patient's age, level of education, and gender. Caregivers were also asked about any other family members of the patient who may have had Alzheimer's disease. The cognitive status/functional state of the patient was determined using

caregiver information obtained from the Blessed Rating Scale. Biographical data, cognitive status, and premorbid temperament were correlated with noncognitive symptoms in order to determine whether premorbid temperament is related to the occurrence of specific noncognitive symptoms and may thus contribute to the heterogeneous profile observed in the noncognitive manifestations.

5.1.1 Sample

The sample in this study alludes to the primary caregivers of Alzheimer's patients who act as collateral sources of information, and Alzheimer's patients about whom the information and data is analysed and presented.

Over a period of two and a half years caregivers of Alzheimer's patients were contacted to participate in the study. The sample of caregivers was drawn from lists provided by the support group network of the Alzheimer's and Related Dementias Association (ARDA), names provided by neurologists, and other interested persons who volunteered after receiving information from third parties. The ARDA groups meet on a monthly basis and provide information and support to caregivers of patients with Alzheimer's and other dementias. During the time of data collection, the groups were active in seven South African provinces, Namibia, and Zimbabwe. On average four groups were active in the Eastern Cape, one in the Free State, nine in Gauteng, eight in Kwazulu-Natal, two in Mpumalanga, nine in the Western Cape, two in the North West province, one in Namibia, and two in Zimbabwe. The researcher contacted all group facilitators in order to obtain a large national sample. The groups from Namibia and Zimbabwe were excluded from the study because of cost and proximity dilemmas, although the participants from these groups showed a willingness to participate.

For each caregiver (primary informant) contacted, the researcher enquired about the availability of a secondary informant who knew the Alzheimer's patient before the disease onset. This was done to compensate for the challenge of retrospective bias that may be inherent in a study design of this nature.

5.1.2 Interrater concordance

One of the most challenging factors in studies dealing with premorbid temperament is the issue of retrospective bias. The relationship between premorbid temperament and noncognitive symptoms in Alzheimer's disease could either reflect "a premorbid diathesis for ...symptoms or a retrospective bias among the informants in which the current characteristics of the patient coloured the recollections of caregivers" (Strauss et al., 1997, p. 257). Studies show that the current behaviour or temperament often clouds judgment of previous traits either in the form of higher ratings on negative traits or higher ratings on positive traits, with caregivers idealizing the past relative to the present (Petry et al., 1988; Swearer et al., 1996). Alzheimer's disease is also characterised by an insidious disease onset and this compounds the issue of reliability of retrospective information because caregivers have difficulty distinguishing the disease characteristics from inherent disposition.

Various methods were used to counter the consequences of retrospective bias. Firstly, two informants were utilised. The primary informant is the person who lives with the Alzheimer's disease family member and knew him/her well in the past and thus, qualifies as a primary caregiver. In most cases, the person also lived with the patient prior to the diagnosis of Alzheimer's disease. The primary informant also provided information on the

current noncognitive symptoms. On the other hand, the secondary informant was chosen because of his/her knowledge of the person before the disease and is currently not living with the person. In this manner, the reliability of retrospective data could be ascertained.

Secondly, half of the primary informants were given the Behaviour Rating Scale for Dementia as the first instrument and the rest of the informants were given the Formal Characteristics of Behaviour-Temperament Inventory as the first instrument so that the order of completion was counterbalanced. This was done to counter the effects of current and premorbid bias as one instrument solicits information about the present (disease course) and the other about the past. Finally, when both informants were administered the Formal Characteristics of Behaviour- Temperament Inventory, they were asked to recall when the first symptoms appeared and thereafter, had to chose a time period several years (5 years) before that to describe what the patient was like. In this way, informants were given a specific grounding in terms of the recall period with all informants sharing some consistency in the period of recall.

It is important to note that caregiver characteristics such as gender, temperament, age may also influence their impressions of the Alzheimer's patients behaviour. However, the focus of this study is to inter alia explore the relationship between patients premorbid temperament and current noncognitive symptoms and the use of two informants was included in the design to minimise the influence of this confounder (caregiver characteristics).

5.2 Procedure

For the participants involved in the ARDA groups the researcher together with the national director of ARDA contacted all ARDA support group facilitators from the seven provinces, notified them of the study, and received the names of group members who were willing to participate. Participants referred by neurologists were also contacted and screened. After follow-up calls to 141 caregivers, 108 were available for the initial screening interview. Thirty-three caregivers from the original sample of 141 were not available or declined to participate.

The initial idea was to draw lists from the many groups and thereafter, use systematic sampling to obtain the target group. However, this would have reduced the sample to fewer than 30 people. Due to the nature of this study (community-based) and the research questions posed, a nonprobability convenience sampling technique was used. The lack of a registry of Alzheimer's patients and the stringent exclusion criteria that applied to this study necessitated the use of this technique.

The use of random sampling is strongly advocated in the methodology texts, however most neuropsychological studies use non-random samples of highly specialised subpopulations, because of the amorphous nature of brain-behaviour relationships. Although a significant level of generality is demanded from research output, which is achievable through the use of random sampling, there is a lack of consensus as to the necessity of this method of sampling in psychological research (Bordens & Abbott, 2002). Psychological studies aim to apply their findings implicitly through the models and theories and the necessity of using random samples is a moot point and less of a concern for the degree of generality beyond the sample.

5.2.1 Sample selection

The criteria for caregiver participation included the number of contact hours spent with the patient. Caregivers had to be staying with the patient because the requirement for this study was a sample of Alzheimer's patients who were community-based and not living in a nursing home.

The criteria for inclusion of the Alzheimer's patient was set out in the Screening Schedule (Appendix B), which elicited the following information from caregivers: a previous history of a medical, neurological and/or psychiatric condition, the nature of the diagnosis, the date of diagnosis, the confirmation of an Alzheimer's disease diagnosis, and pharmacological history.

5.2.2 Exclusion criteria

Implementation of the exclusion criteria minimised the influence of extraneous variables on the results, and included the following rationale:

- The basis for exclusion on a medical, neurological, or psychiatric condition was determined by the various ailments and their contribution to dementia. These conditions may lead to a differential diagnosis and contaminate the disease profile of the sample.
- Patients with advanced age were also excluded from the study (i.e. patients older than 80) because comorbid conditions associated with older people can complicate the clinical picture. Moreover, in this older patient group a wider range of pharmacotherapies are used and side effects may enhance or mask the noncognitive symptoms accompanying Alzheimer's disease.

- The primary caregiver had to live with the patient because knowledge about the patient's behaviour on a daily basis had to be comprehensive. The instrument used to elicit information about noncognitive symptoms included items that were specific in content and frequency of occurrence.
- For the reasons stated above patients who were involved in drug trials, and patients who were on a myriad of drugs for longer than a year were also excluded from the study. It must be noted that many patients are on one or two prescribed medications, however, this was factored into the study by asking caregiver's the reason for certain drug choices, eliciting information about the period of use, and using a measuring instrument that contains response choices spanning the disease course.
- Finally, a diagnosis of probable Alzheimer's disease was integral to achieving the study aims. Other studies analysed hospital records, brain scans, or EEG's to confirm a probable Alzheimer's disease diagnosis. This was not possible because of the community-based sample of Alzheimer's patients. The researcher involved only caregivers with family members who had two diagnoses of probable Alzheimer's disease from different health professionals. All participants included in this sample obtained a second opinion, which corroborated the first diagnosis of probable Alzheimer's disease. Furthermore, the researcher questioned caregivers about the presentation of symptoms using the CERAD Diagnostic Impression Protocol, which elicited general information about the patients overall cognitive manifestations and other illnesses that could have contributed to the dementing process. These impressions were collated with the information received on the Blessed Dementia Scale and a decision was made about inclusion in the sample using these varied information sources. This rigorous process was applied to compensate for the absence of neuroimaging records and laboratory tests, which were not available for all of the

community-dwelling sample. Moreover, in developing countries with limited resources, neurological scans (MRI) are not easily obtainable for all patients.

After the completion of the screening interviews, 63 caregivers who lived with an Alzheimer's patient were eligible for participation in the study. The forty-five caregivers of the listed 108 provided information about the Alzheimer's patient that excluded them as collateral sources of information. This included caregivers whose family member was in a nursing home, those who had no secondary informant, Alzheimer's disease patients who had a previous history of illness, patients who were older than 80 years, and those patients with a mixed diagnosis (e.g., Parkinson's and Alzheimer's disease), an unconfirmed diagnosis of Alzheimer's disease, and a general diagnosis of dementia.

In sum, 141 caregivers communicated an interest in the study by providing their contact details. An initial cohort of 108 communicated their willingness to participate. After the screening schedule, a final sample of 63 caregivers qualified from the list of 108. The latter were included in the study because they lived with the Alzheimer's patient, identified a secondary informant, and their wards had no previous record of major illnesses, were younger than 80 years of age, were not on any regimented drug trials, and had a second diagnosis of Alzheimer's disease. Sixty-three secondary informants were contacted to complete the temperament inventory and this information was used as a reliability check for premorbid estimation of a patient's temperament.

5.3 Data collection

Due to time and resource constraints, only participants in the Gauteng and KwaZulu-Natal were personally interviewed. All other participants were telephonically interviewed. Interviewees provided the time and date for the interview and the sessions were completed in approximately 55 minutes. Twenty-seven primary caregivers and 20 secondary informants were visited at their homes, and the instruments were administered personally. Thirty-six primary caregivers and thirty-one secondary informants completed the instruments telephonically. Three follow-up visits to Gauteng and KwaZulu-Natal were made to complete the data collection, and in some cases, an average of four follow-up calls were made to secondary informants telephonically obtain data from them.

Although all of the 63 participants provided details for a secondary informant, in 12 cases the secondary informant was not available to provide information. Data from 51 secondary informants were used in this study. The attrition rate for the secondary informant was to be expected as these informants were not primarily caring for the patient and often lived in another town, and their participation was subject to their availability.

The researcher was aware that these different techniques may have an impact on the responses elicited. To minimise any differences, the instruments chosen for the study were suitable for either type of interview and had been used in research employing both techniques (Tariot et al., 1996; Tariot et al., 1995). An attempt was also made to be consistent in the use of interview method thus, one method was used for both the primary and secondary informant of an individual patient and the time limit imposed in the telephonic interview was adhered to in the personal interview. Due to the instruments used (the questions are not prone to issues of social-desirability bias) and the nature of the

sample (caregiver's who voluntarily agreed to be part of the study), the use of these two techniques should have minimal effect on the results.

5.3.1 Measuring Instruments

Three instruments were used in this study namely the CERAD Behaviour Rating Scale for Dementia, the subscales from the Formal Characteristics of Behaviour-Temperament Inventory, and the Blessed Dementia Scale. In the following sections the above-mentioned instruments are discussed in terms of their reliability and validity, and their relevance to this study.

5.3.1.1 Behaviour Rating Scale for Dementia

This is a rating scale developed by the Behavioural Pathology Committee of the Consortium to establish a Registry for Alzheimer's disease (CERAD). This consortium consists of 24 medical centers and is involved in the standardisation of procedures for the evaluation and diagnosis of Alzheimer's disease (Neurology, 2002). The researcher communicated with the coordinator at CERAD to obtain the scale. Before permission was granted a concise summary and proposal for the study was submitted to the coordinator at Duke University Medical Center. After evaluation of the proposal, the consortium granted permission for the use of the CERAD protocols.

The Behavioural Rating Scale for Dementia is a standardised scale for caregivers of Alzheimer's patients and is conducive to either personal or telephonic administration. Due to its specificity, selected behavioural characteristics of Alzheimer's disease can be correlated with clinical aspects such as functional status, cognitive decline, gender, etc.

The instrument is considered appropriate for this sample as most studies show that it is designed for non-institutionalised Alzheimer's disease patients (Mack, Patterson, & Tariot, 1999). Furthermore, the scale was derived from components of the Behavioural Pathology of the Alzheimer's disease Rating Scale, the Columbia University scale for Psychopathology, and the Cornell Scale for Depression. The combined use and adaptation of items from three established questionnaires makes the Behavioural Rating Scale for Dementia a comprehensive evaluative instrument. Thus, in comparison to other similar instruments this scale is a comprehensive assessment tool for the spectrum of neuropsychiatric and neurobehavioural pathology in Alzheimer's disease patients, and is suitable for the investigation of the nature and frequency of a spectrum of noncognitive disturbances (Mack & Patterson, 1993; Mack et al., 1999; Tariot et al., 1995; Tractenberg et al., 2000).

5.3.1.1.1. Item composition

The scale was developed for the solicitation of information from observers, and the rating of scores are based on frequency rather than severity judgments. According to Tariot et al (1995) severity judgements are more challenging to determine and provide unreliable scores. The items represent relatively discrete aspects of behaviour and are worded in objective language to avoid bias and judgement on the part of the informant and examiner (Mack & Patterson, 1993). The long form of the this instrument, which was used in this study, consists of 46 items. The instrument is subdivided according to the following:

i) Thirty-eight items are rated according to frequency of occurrence.

If a respondent answers YES to occurrence during the one-month window period, the following scores can be given:

- 1 - occurred 1-2 days in the past month.
- 2- occurred 3 to 8 days during the past month.
- - occurred 9-15 days in the past month.
- - occurred 16 or more days in the past month.

If a respondent answers NO or unable to rate, the following scores are assigned to the response:

- 0 – has not occurred since illness began.
- 9 - unable to rate.

If the respondent answer NO to behaviours observed during the window period, the interviewee inquires about the occurrence prior to the window period and assigns the following score:

- 8- occurred since illness began, but not in the past month.

Examples of questions that require these frequency ratings include:

- a) Has {S} said that {S} feels anxious, worried, tense, or fearful? For example, has {S} expressed worry or fear about being left alone? Has {S} said {S} is anxious, afraid of certain situations? If so, describe.
- b) Has {S} shown physical signs of anxiety, worry, tension, or fear? For example, is {S} easily startled? Does {S} appear nervous? Does {S} have a tense or worried facial expression? If so, describe.

- c) Has {S} shown sudden changes in emotion? For example, does {S} go from laughter to tears quickly?

In all test items, the term {S} is replaced by an appropriate substitute as it denotes the individual with Alzheimer's disease. The examples provided are only presented to the caregiver if clarity of a particular question is obscured. If a respondent understands the question, the examples are not given.

ii) Eight items, which deal with symptoms related to diurnal confusion, interest and motivation, weight and appetite changes, and clingy behaviour, do not require a frequency estimate and are rated as absent or present since illness began, and can be scored as:

- 0 - No, has not occurred.
- 1 – Yes, has occurred in past month.
- 8 - Occurred since illness began, but not in past month.
- 9 - Unable to rate.

Examples of questions that require these frequency ratings include:

a) Does {S} seek out more visual and physical contact with caregivers than before {S's} dementia began? For example, has {S} seemed 'clingy'? Does {s} follow you about and seem to want to be in the same room with you?

iii) Fourteen items of the inventory have a probe because the frequency ratings do not adequately address ideational items. This follow-up question is used to determine whether the misperception is a clear fixed distortion of reality or a vague, transient perceptual experience. The items concerning hallucinations also have an additional component that

requires the informant to describe the behaviour thus enabling the examiner to rate in terms of clarity of the hallucinatory experience.

Examples of questions that require these frequency ratings include:

a) Has {S} done or said anything that suggests {S} thinks {S's} spouse is unfaithful?

Probe: *If yes, ask:* If you try and correct {S}, will {S} accept the truth?

b) Has {S} seen things or people that were not there? *If yes, describe.*

If yes, rate for clarity: Vague 0, Clear 1

iv) Finally, item 46 is an open ended question and is used to elicit information that is not otherwise represented in the scale.

5.3.1.1.2 Reliability and Validity

Two total scores and six subscale scores represent the scoring estimates of the BDRS. The sum of all the ratings of items (0-4 for 26 items, 0-5 for 11 items, and 0-1 for 8 items) comprises the total weighted score. The open-ended item 46 is the only exclusion from this total. The value of the total weighted score ranges from 0-167, and this score provides an overall picture of the frequency and severity (11 items) of psychiatric and behavioural symptoms in Alzheimer's disease. The second total score represents the total number of items rated as present in the past month and does not reflect the frequency but rather the number of varying behaviours shown by a subject. This continuum ranges from 0-45. The subscales comprise the additional six ratings and are scored as follows:

- The Depressive symptom subscale is made up of seven items scored 1-4 and 1-5 with the value ranging from 0-29.

- The *Inertia* subscale comprises three items and has a range of 0-3.
- The *Vegetative* subscale score is obtained by summing the ratings on four items and scores range from 0-4.
- The *Irritability/Aggression* subscale score is the sum of ratings of items 18-22 and the value ranges from 0-20.
- *Behavioural Dysregulation* is the sum of ratings attributed to five items and the scale has a range of 0-17.
- The *Psychotic* symptom subscale comprises six items scored on a scale from 0-5 and the value of this ranges from 0-30.

Mack et al. (1999) found that the subscales correlate significantly with the total weighted scores, the total weighted score is significantly associated with the number of items rated present. A high internal consistency is reflected by the α values of .87 and .85 for the total weighted score and total of items rated from 1-4, respectively. The test-retest total estimates among differentially impaired Alzheimer's disease groups range from .70 to .89 thus, demonstrating the reliability of the instrument across severity parameters. Due to the community-dwelling sample and the selection process in this study, it was not possible to obtain information from a cross section of differentially impaired subjects therefore, this instrument was chosen because of its robustness in terms of moderate disease severity and noncognitive symptoms.

In terms of consistency between subscales, three (Depressive, Irritability/aggression, and Psychotic subscale) show a moderate to high internal consistency, whereas the Inertia, Behavioural Dysregulation, and Vegetative subscales have low α coefficients (Mack et al., 1999). Furthermore, the correlations between the scales are significant and range from

.10 to .44. The criterion for the inclusion of the three scales with low consistency is based on their clinical significance.

Using factor analysis to investigate inter-item relationships, Tariot et al. (1995) show that 4 factors (depression, irritability/aggression, vegetative symptoms, and apathy) reflect the known categories of noncognitive features that are seen in Alzheimer's disease samples. The other two factors namely psychotic features and behavioural dysregulation show a less robust relationship but reflect conditions that are attributable to dementia of the Alzheimer's type. In a comparative study, Patterson et al. (1997) found that Alzheimer's disease patients differ significantly from normal elderly control subjects on BRSD ratings.

A follow-up study by Tractenberg et al. (2000) confirms a higher prevalence rate of noncognitive symptoms for Alzheimer's disease patients when compared to the endorsement rates of normal elderly controls. At baseline the Alzheimer's disease subjects mean score on the BRSD was 29.9 (20.0) with a range of 0-117, whereas the control group had low total scores with a mean of 4.7 (8.3) and a range of 0-53. Tariot et al (1995) also shows that patients who are described as having undergone personality changes have an increased average number of items rated as present. They suggest that this also provides a basic validity estimate of the instrument. Tariot (1996) concludes that the instrument has satisfactory content, construct, discriminant, predictive, and convergent validity as demonstrated by numerous studies.

A caveat on the reliability estimates derives from the notion that pathological behaviours are not stable and therefore, reliability of scores may be influenced by this. According to Mack et al. (1999) shorter retesting intervals reduces the impact of behavioural instability, but enhances the odds that a respondent may recall a previous answer and this influences

reliability estimates. Nevertheless, the availability of scale scores for specific clusters of noncognitive symptoms makes this instrument relevant to the investigation of possible correlates of specific noncognitive symptoms

5.3.1.2 Formal Characteristics of Behaviour-Temperament Inventory

The choice of an appropriate temperament inventory proved challenging. Most inventories are designed in self-report formats, and Alzheimer's patients do not have the capacity to report on their own behaviours thus, necessitating the use of collateral sources of information. After a lengthy correspondence with Strelau, Newberry, and Zawadzki (personal communication, July 31, 2000; August 13, 2000; August 29, 2000; August 30, 2000; September 11, 2000; October 2, 2000; December 17, 2000) it was decided that the Formal Characteristics of Behaviour- Temperament Inventory would be used instead of the Pavlovian Temperament Inventory (Strelau & Zawadzki, 1993).

This decision is based on the knowledge that the instrument is constructed on the assumption that temperament refers not to content but to formal aspects of behaviour. Moreover, in addition to the Eysenck Personality Questionnaire, for example, the Formal Characteristics of Behaviour-Temperament Inventory includes measures of perseverance traits that are not included in other inventories, and has scales that tap into a wider content. The activity scale, for example, refers not only to motor actions but to goal directed behaviours as well and this appears to have relevance for the chosen Alzheimer's sample.

Drawing on the theoretical literature one can hypothesise that due to the involvement of frontal circuits in Alzheimer's disease, assessment of goal directed behaviour is integral to

this study. Moreover, this inventory was developed using the postulations of the Regulatory Theory of Temperament and identifies temperament according to its primary traits thus, allowing the measurement of its functional importance and distinctiveness. This corroborates the goal of the study, which attempts to elucidate the relationship between functional deterioration during the course of Alzheimer's disease with distinct biological premorbid traits. The robustness of the scale is evident because of its significant correlations with other biologically based temperament inventories (Strelau & Zawadzki, 1995).

The Formal Characteristics of Behaviour-Temperament Inventory was constructed as a self-report questionnaire. On the advice of Strelau and Zawadzki (personal communication, 13 August 2001) it was decided that the questions would be changed to reflect the third person singular so that informants could rate patient behaviours. According to Strelau (personal communication, 13 August 2001) questions on the Pavlovian Temperament Inventory were changed to the third person and administered to caregivers of patients with bipolar affective disorders and the results corresponded with the temperament dimensions as measured by the Formal Characteristics of Behaviour-Temperament Inventory and are in accordance with the hypotheses on which this inventory was developed.

Hofstee (1991) is in agreement with the translating of these instruments into the third person and suggests that this is a more satisfactory manner than asking informants to rate persons directly on traits using an unchanged self-report format. He contends further that because of the different social roles ascribed to people different views of temperament traits may arise. These discrepancies can be addressed through the use of many raters, whereas a self-report cannot be validated in this manner. He suggests that self-reports

should only be used if observer ratings are not available and only as an “auxiliary variable, boosting the reliability and validity of the observer ratings as a prime measure “ (Hofstee, 1991, p. 187). Nonetheless in this study, the methodological consequence of self and informant bias is benign, because Alzheimer’s patients have limited capacity to make judgments on their temperamental dispositions, especially the premorbid approximations. However, it should be pointed out that some of the items on the scale refer to traits that are more readily evaluated by introspection and self-awareness and these scale items are most likely to show greater interrater disagreement.

5.3.1.2.1 Item composition

The Formal Characteristics of Behaviour-Temperament Inventory consists of six subscales constructed on the hypothesis that temperament encompasses formal aspects of behaviour that emerge as energetic and temporal attributes (Strelau & Zawadzki, 1993). Each of these subscales represents a robust temperament dimension with four traits (sensory sensitivity, endurance, emotional reactivity, and activity) reflecting the energetic characteristics, and two traits (briskness and perseverance) alluding to the temporal dimension of behaviour.

Informants are asked to make a general assessment of what the patient was usually like without contemplating their previous answers. There are many versions of this inventory and the international version was used in this study. The following six subscales, with 20 items each comprise this international version:

- *Perseverance (PE)* - penchant for continuous and repetitive actions after cessation of the stimuli responsible for these actions.

- *Emotional Reactivity* (ER) - penchant for intense reactions to emotion - generating stimuli, manifested as high emotional sensitivity and low emotional endurance.
- *Endurance* (EN) - the capacity for appropriate and adequate reactions in situations of long-lasting or high stimulative activity and situations of intensive external stimulation.
- *Activity* (AC) - penchant for actions of a high stimulative value.
- *Sensory sensitivity* - response to low stimulation in all sensory modalities.
- *Briskness* – the behavioural capacity for mobility, speed and tempo in response to stimuli.

5.3.1.2.2 Reliability and validity

According to Strelau and Zawadzki (1993) alpha coefficients of the subscales range from .77 to .85, and intercorrelations are satisfactory across five different samples ($n=2023$) providing support for the replicability of results, and the reliability of this instrument as a measure of primary temperament traits. With reference to the psychometric properties of the scale, Strelau and Zawadzki (1993) conclude that the scores on the six subscales follow a normal distribution with skewness and kurtosis indices in an acceptable range.

The Formal Characteristics of Behaviour-Temperament Inventory has demonstrated acceptable construct validity in a large study. In a study utilising samples of 1500 people, Strelau and Zawadzki (1995) correlated the subscale scores with 27 other temperament dimensions measured by seven different temperament inventories. They found that the construct emotional reactivity correlated highly with emotion-oriented scales, activity was associated with extraversion and strength of excitation, perseverance was negatively linked with strength of excitation and positively with emotional dimensions and neuroticism, and endurance had positive association with strength of inhibition. Furthermore, they

found no significant association between traits of temperament and most of the personality traits as measured by the NEO-FFI (e.g., openness, agreeableness, and conscientiousness), and the 16PF.

This supports the theoretical assumptions on which the scale was constructed, namely that nontemperamental measures of personality characteristics should not be linked to temperament because the Regulative Theory of Temperament proposes that temperament and personality are separate constructs. The discriminant validity was also indicated by the lack of association between the subscales and the 16PF measures of intelligence, shrewdness, and self-sufficiency.

5.3.1.3 Blessed Dementia Scale

This scale, which was originally developed by Blessed et al. (1968) is widely cited in literature as a quantitative measure of the severity of deterioration in Alzheimer's disease. It is commonly used in cross-sectional studies because of its high reliability and validity in short term evaluations and its "brevity and ease of administration" during the assessment (Harwood et al., 2000, p. 397).

For the purposes of this study, a modified version of Part A of the scale was used (Mack & Patterson, 1993). Caregivers are asked to rate on a 3- or 4- point scale the patient's premorbid cognitive ability in comparison with the preceding six months and the patient's ability to perform everyday tasks. The scores range from 0 to 17, with higher scores reflecting greater incapacity. Researchers often use the BDS as a measure of disease severity, cognitive impairment, or functional incapacity (Gauthier, Gelinas, & Gauthier, 2002; Teri et al., 1988).

Studies show that the Blessed Dementia Scale correlates highly with post-mortem changes and level of cortical involvement (Hesdorffer, Sano, & Mayeux, 1990; Teri et al., 1988), and this confirms the earlier results of Blessed et al. (1968) who found that there is a significant association between biological markers (plaque counts) and incapacity among patients with senile dementia. Chen et al. (1998) also demonstrate the association between BDS and cortical deterioration in their study, which shows significant positive relationship between specific cognitive disabilities such as executive deficits and BDS scores. When compared to the Mini Mental Status Exam, scores on the Blessed Dementia Scale show high correlations with this measure of cognitive impairment, and positive significant associations with noncognitive problems reported by caregivers (Harwood et al., 2000; Swearer et al., 1996; Teri et al., 1988).

To reiterate, the aim of this study was to elucidate the relationship between noncognitive functional deterioration and distinct biological premorbid temperament traits in a group of Alzheimer's patients. The data were analysed using both descriptive and multivariate analyses.

5.4 Data analyses

The data were analysed using both descriptive and inferential statistics. The descriptive analysis was used to summarise the frequency of noncognitive aspects thereby aiding the description of a large quantity of data (Welkowitz, Ewen, & Cohen, 2000). This was followed by the calculation of alpha coefficients, which indicate consistency among scales, skewness, kurtosis and standard error scores, and other psychometric measures. A description of the method for collating the primary and secondary informant data from the

Formal Characteristics of Behaviour-Temperament Inventory into one composite score follows. Finally, this section describes the multivariate method of canonical analysis that was used to explore the relationship between premorbid temperament and noncognitive symptoms in Alzheimer's disease.

5.4.1 Descriptive statistics

Biographical data such as mean and standard deviations for age, education levels, gender, scale means, and frequency of occurrence of noncognitive symptoms were calculated. This provides a description of the sample characteristics and average ratings obtained on the scales.

Concordance between primary and secondary informant's descriptions of premorbid temperament along all dimensions was analysed using intraclass correlations with Bonferroni corrections. An alternative technique (Cohen's Kappa) was considered, but with this technique it is not possible to determine statistical significance (Bordens & Abbott (2002). Furthermore, according to Strauss, Pasupathi, and Chatterjee (1993) the correlational technique takes into account the difference in mean scores and variances and is a useful measure of interrater reliability. The mean differences between raters in the domain scores were calculated and the combined mean was used in the analysis. In order to minimise errors of interpretation the means and standard deviations of the two sets of scores were compared. In this way the researcher can determine if the correlation is a true reflection of agreement or an anomaly that arises when the magnitude of scores from the two sets increase and decrease similarly, but differ in absolute value (Bordens & Abbott, 2002).

5.4.2 Canonical analysis

This technique was used because it serves as an apt tool to answer the questions about the relationship between premorbid temperament and noncognitive symptoms of Alzheimer's disease. Two sets of variables (with many scale scores) were analysed in order to determine the number of dimensions that one set (noncognitive symptoms) shares with the other set (premorbid temperament). The canonical analysis was performed using the SAS computer package (CANCORR procedure).

This technique has a number of limitations. According to Tabachnick and Fidell (1983) the associations between linear variable composites do not necessarily lead to the interpretability of principal dimensions. Moreover, unlike other techniques, canonical analysis restricts interpretation to orthogonal factors, and intercorrelations within the sets are not identified. However, to answer the research question posed in this study, the researcher considered this technique because of its complexity and its incorporation of multiple relationship dimensions. The use of linear regression was considered, however this empirical study is explanatory and the following advice was heeded:

We take a dim view of regression in explanatory research for various reasons...but mostly because we feel that more orderly advance in behavioural sciences is likely when researchers, armed with theories, provide apriori theoretical ordering that reflects causal hypothesis rather than when computers order IVs post and ad hoc for a given sample ... Probably the most serious problem with the use of regression is when a relatively large number of IVs is used...and the ad hoc order produced from the set of IVs is likely not to be found in other samples from the same population (Cohen & Cohen, 1983, p. 124).

Prior to the use of canonical analysis the following norms were considered:

- The skewness and kurtosis values and associated standard errors were carefully assessed to ensure that the variables were normally distributed. This was of particular importance because of the small sample size.
- Outliers or extreme datum were determined and controlled for. In the event of nonnormality (skewed distributions) and outliers transformations and other methods for multivariate outliers were used to transform the data and fulfil the prerequisite of normality.
- Aspects of multicollinearity, singularity, and linearity were identified and eliminated or corrected using various techniques (Miles & Shevlin, 2001; Tabachnick & Fidell, 1983).

Steps 1 to 10 of the analysis process are outlined below.

1. A correlation matrix is generated. This matrix can be subdivided into four sections: correlations between dependent variables, correlations between independent variables, and two matrices between independent and dependent variables.
2. The canonical correlations obtained from the four elements provide a coefficient that is interpreted as a Pearson product-moment coefficient (r).
3. When r is squared it reflects the overlapping variance between pairs of canonical variates.
4. Eigenvalues are calculated to denote overlapping variance. They are considered equal to the squared r (Tabachnick & Fidell, 1983).
5. Significance tests (Chi-squared or F distributions) are conducted to determine the significance of the canonical correlations. Only variates that are significant are considered for interpretation.

6. The two matrices of independent and dependent canonical coefficients are used to ascertain the scores on canonical variates. This establishes a matrix of canonical structure that shows the correlation of the original variables with the canonical variates.
7. In order to estimate the direct contribution of each variable to the composite variate, a matrix of canonical coefficients is calculated.
8. Assessment of variance from the significant variates is determined by calculating the amount of variance that a canonical variate extracts from its own set of variables (pv).
9. Finally, a redundancy analysis is done to determine variance obtained by a canonical variate multiplied by the canonical correlation of the pair.
10. Interpretation of variates involves the assessment of correlations for all variates found to be significant. In most cases loadings between variables and variates below .30 are disregarded.

5.5 Conclusion

The power of neuropsychological research is reliant on the knowledge of basic organization of functional systems, its adaptability to atrophy, and its threshold of resilience or vulnerability to disease states. In this study information on premorbid temperament and current noncognitive symptoms of Alzheimer's disease patients was elicited from a carefully chosen cohort of Alzheimer's disease caregivers.

Various statistical techniques were used to derive results on the occurrence of noncognitive symptoms, concordance of ratings among informants, and relationship between dimensions of temperament and disease symptoms. The choice of instrumentation fulfils the purpose of distinguishing between dimensions of noncognitive

symptoms and eliciting primary functional temperament traits. In this manner the researcher ensures both the measurement of temperament on a continuum and the assessment of nominal neuropsychiatric and neurobehavioural signs, and seeks to explain the relationship between the two. In addition, this study provides the implicit benefit of providing insight about how functional states emerge from the structural substrates of the brain, relative to the imposition of a neurological disease. The latter premise is explored in the following chapters.

CHAPTER 6

RESULTS

In this chapter the results of the empirical study are reported and explained. Firstly, the descriptive statistics are provided for the caregivers and the Alzheimer's patients. Secondly, an item analysis of the Behaviour Rating Scale for Dementia is given, followed by the qualitative descriptions of some noncognitive correlates, and the descriptive statistics for the scale scores. Thirdly, the concordance statistics are given for the interrater reliabilities using intraclass correlations. Lastly, the relationship between dimensions of premorbid temperament and noncognitive symptoms are elucidated using canonical analysis.

6.1 Characteristics of the sample

The ARDA support group network and neurologists in all the provinces of South Africa were utilised as a contact base over a two and a half-year period. The use of the latter was feasible because of the researcher's membership and involvement with ARDA activities, and the former was accessible because of the researcher's familiarity with neurologists through involvement in pharmacological geriatric trials. This method was used because of a lack of a general registry for Alzheimer's patients and the 'research fatigue' that Alzheimer's patients visiting dementia clinics, which are affiliated to institutions, may have experienced. During this time, the researcher initiated contact with 141 caregivers of Alzheimer's patients. After careful screening, 63 caregivers fulfilled the eligibility criteria for the study. The exclusion of other possible candidates resulted from their reluctance to participate or the stringent criteria outlined in the preceding chapter.

Data was elicited from caregivers pertaining to their own relationship with the patient and other relevant information about the Alzheimer's patient themselves.

6.1.1 Biographical characteristics

This study utilised information from caregivers to determine the premorbid temperament, noncognitive symptoms, and cognitive status of Alzheimer's patients in their care. In the following sections the biographical information for both caregivers and Alzheimer's patients are presented.

6.1.1.1 Caregiver status

For all of the 63 Alzheimer's disease patients a primary caregiver was available to provide information on a patient's premorbid temperament, current noncognitive symptoms, and cognitive status. The primary caregiver in 78% of the cases was a spouse followed by the patient's children in 18% of the cases. In the remaining four percent of the cases, the primary caregiver was a nurse or nurse aide who lived with the patient. Data on the patients' premorbid temperament was also procured from secondary informants. The secondary informants were siblings (28%), children (43%), or friends (29%) who knew the Alzheimer's disease patient before the illness.

6.1.1.2 Alzheimer's patients: Biographical information

Table 6-1 indicates that the mean age of the Alzheimer's disease participants was 74, 4 (5.5). Caregivers provided information for 35 male and 28 female wards members who

were diagnosed with Alzheimer's disease. The mean number of years engaged in education was 12, 7 (3.9).

Table 6-1 Demographic characteristics of Alzheimer's patients

Variables	Mean (SD)
Age	74.4 (5.5)
Education	12.7 (3.9)
Blessed Dementia Scale	6.0 (2.1)

The Blessed Dementia Scale (BDS) elicited information about the severity of the dementia and the functional status of the patient. This information was procured from collateral sources because the patients themselves were unable to answer the questions. High correlations between the Blessed Dementia Scale and Mini Mental Status Exam scores have been reported in the literature (Harwood et al., 2000). This measure is therefore, a reliable reflection of the patient's cognitive state as well.

As illustrated in Table 6-1 the mean score for this sample of Alzheimer's patients on the Blessed Dementia Scale was 6.0 (2.1), thereby suggesting that the sample composed of mainly moderately affected individuals with more discernible neuronal deterioration than a mildly affected group (Blessed et al., 1968; Teri et al., 1988).

In 52% of the cases the caregivers stated that English is the first language of the patient, 44% of the cases stated Afrikaans as a first language, and four percent of the sample can be characterised as foreign language speakers (French, Portuguese, and Dutch). As illustrated in Table 6-2, twenty-seven patients lived in Gauteng (15) and KwaZulu-Natal (12), and the remaining thirty-six were from the Western Cape, North-West, Mpumalanga,

Free State, and the Eastern Cape. All participants, however, were satisfactorily proficient in English and all instruments were administered in English.

In 60% of the cases, a neurologist provided the first diagnosis, followed by a general practitioner (19%), a psychiatrist (13%), and neuropsychologist (8%). For all participants considered eligible for the study, a second confirmatory diagnosis of Alzheimer's disease was available. The results showed that 32% of the Alzheimer's patients (32%) had some family member (grandparents, parents, siblings, aunts, or uncles) with a diagnosis of Alzheimer's disease. Twenty-six (41%) had no family member diagnosed with Alzheimer's disease and in the case of 17 (27%) patients, caregivers had insufficient knowledge about the ancestry of the patient.

Table 6-2 Patient profiles

Variables	%
Language	
English	52%
Afrikaans	44%
Other	4%
Area (Provinces)	
Gauteng	24%
KwaZulu-Natal	19%
Mpumalanga	14%
North West	13%
Western Cape	13%
Eastern Cape	12%
Free State	5%
First Diagnosis	
Neurologist	60%

General Practitioner	19%
Psychiatrist	13%
Neuropsychologist	8%

Family history of disease

Present	32%
Absent	41%
Unknown	27%

6.2 Neuropsychiatric and neurobehavioural correlates

To address the research question about the nature and frequency of symptoms displayed, caregiver ratings of symptoms that occurred in the past month were collated, and these are presented in the graphs below. At least one noncognitive symptom was present in all Alzheimer's disease patients, with specific behaviours showing greater frequencies of endorsement. On average 15 items were rated present per individual. The noncognitive profile of over 50% of the sample included six and more items, thus indicating that noncognitive symptoms are common in this sample of Alzheimer's patients.

The following sections contain a graphical item-by-item analysis, a summary of descriptions of specific behaviours, and the descriptive statistics for the Behaviour Rating Scale scores.

6.2.1 Endorsement of specific disturbances

Items relating to self-misidentification, belief that one's spouse is an impostor, one's spouse is unfaithful, one's spouse is plotting abandonment, exaggerated complaints about health, attempts to leave home, expressions of guilt and blame, suicidal ideation, and

weight changes were rated as present in less than a third of the sample. In the majority of the sample, items that were unrated included disturbances pertaining to sexual behaviour, purposeful wandering, and a belief that one's house is not one's home.

Figures 6-1, 6-2, and 6-3 show the frequency of items endorsed by subjects according to a triadic categorisation namely disturbances of thought and perception, mood and neurovegetative disturbances, and behavioural dysregulation.

The number of participants manifesting with psychotic and misidentification symptoms ranged from 5% (auditory hallucinations) to 23% (feeling threatened and suspiciousness).

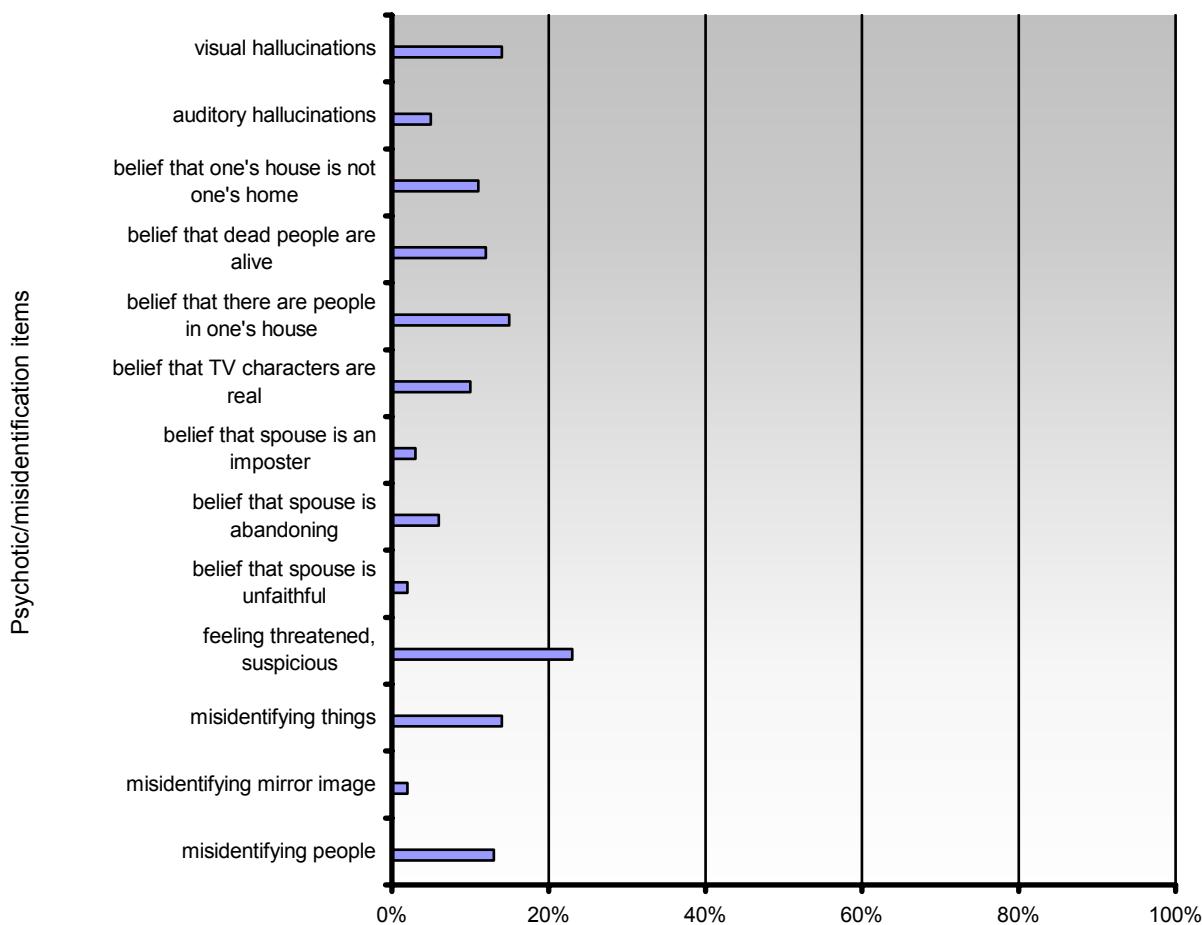


Figure 6-1 Disturbances of thought and perception percentage

Misidentification items had the lowest endorsement compared to all scaled items. The most common reported visual hallucination pertained to children, who the subject saw in a room.

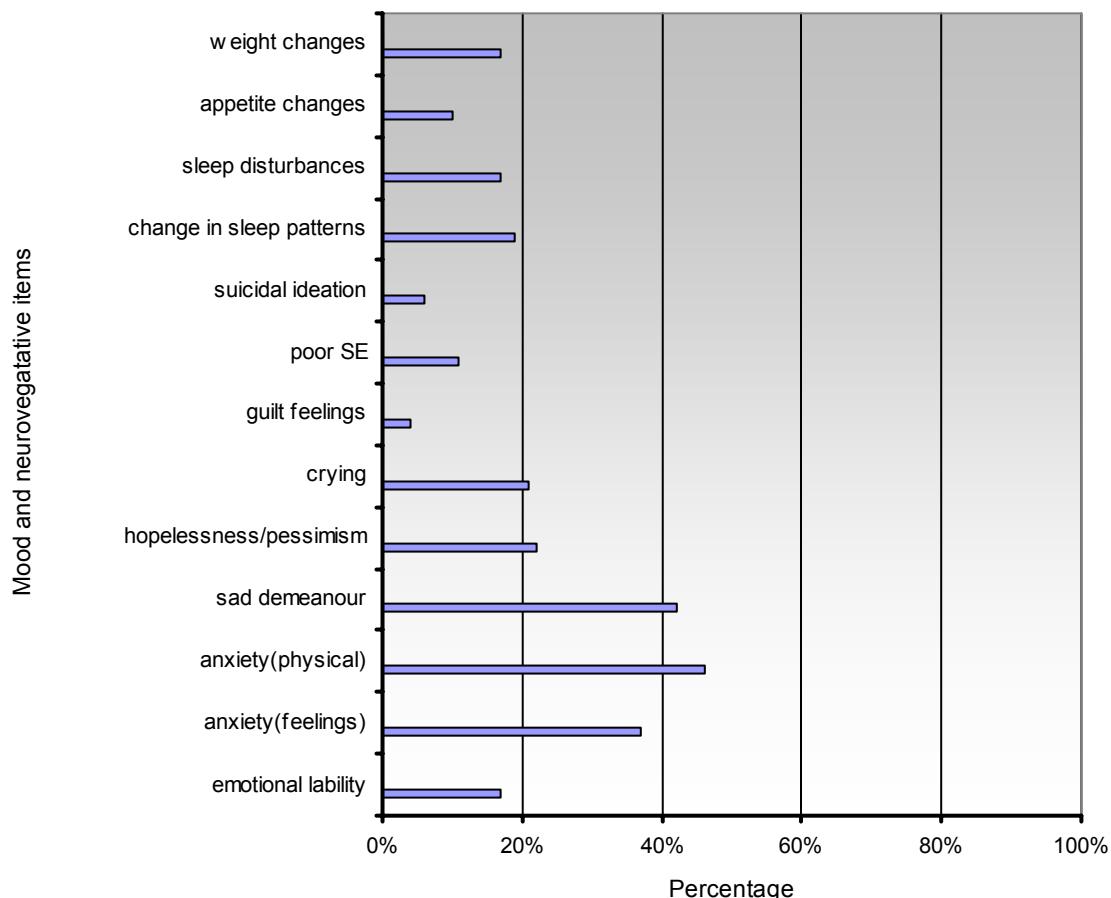


Figure 6-2 mood and neurovegetative disturbances

Mood related symptoms occurred in over 20 % of the sample, with characteristics of sadness and overt anxiousness occurring in approximately 50% of the Alzheimer's disease patients. One can hypothesise that mood related symptoms such as anxiety and depression may occur early in the disease process and diminishes over time because of the decline in cognition and thus, insight or awareness into their condition. This may account for the high occurrence reported in this group of moderately affected patients.

The neurovegetative changes occurred in less than a fifth of the sample with sleep alterations more frequent (19%) than weight (17%) or appetite changes (10%).

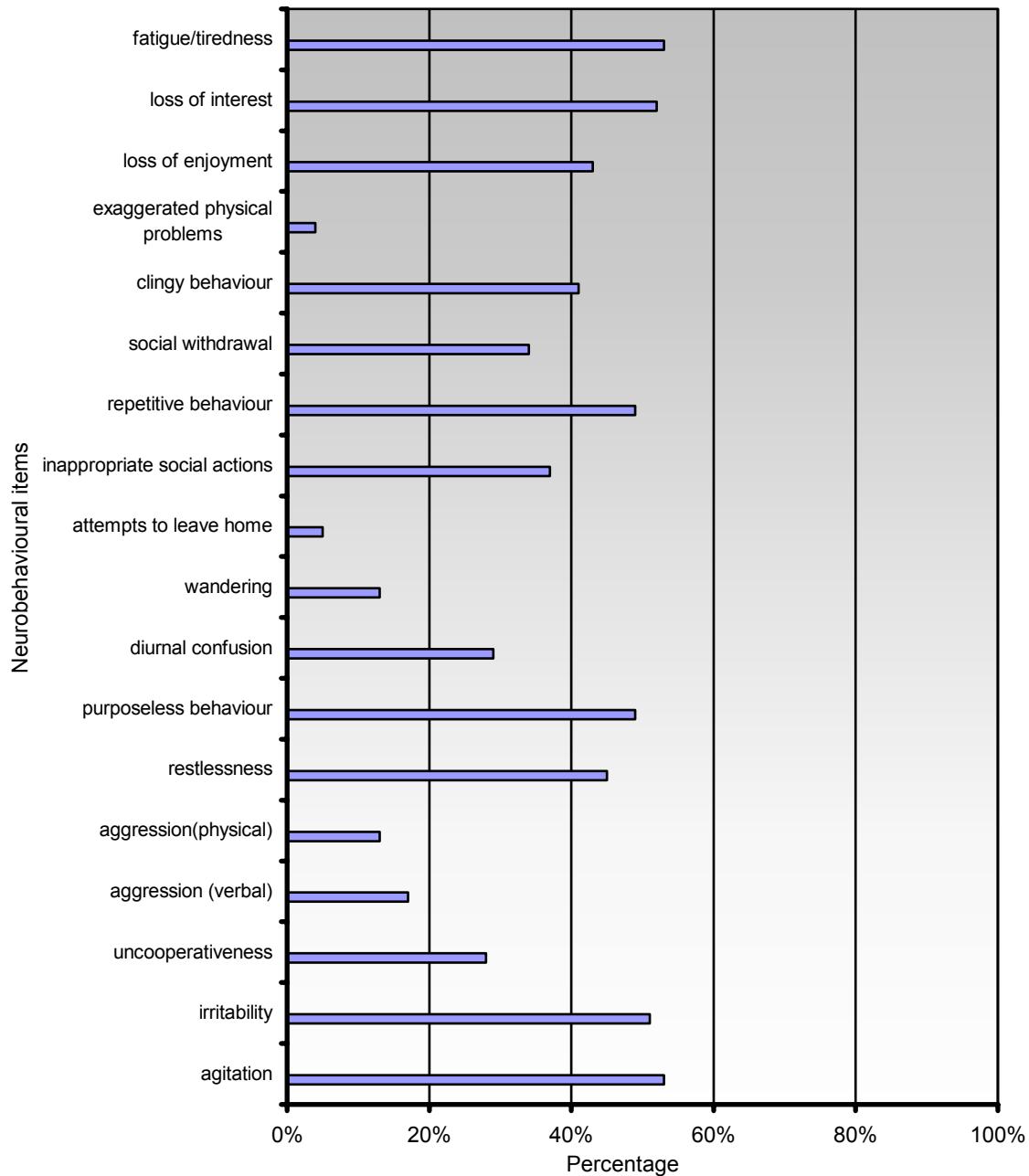


Figure 6-3 Behavioural dysregulation

In the group of Alzheimer's disease patients, caregivers observed a spectrum of dysregulatory behaviour. A change in energy and initiative components of the person's behaviour was reported in 53% and 52% of the sample, respectively. However, this ebb of

inertia was interspersed with moments of excessive kinaesthetic flow, which occurred when usually docile patients engaged in purposeless wandering and repetitive behaviours that perseverated over a period. It would seem therefore, that the behavioural disturbances display a pattern of temporal and energetic juxtaposition.

Levels of irritation and agitation were reported in over half of the sample and this appears to contribute to the challenging behaviours caregivers have to deal with, when patients act out in aggressive and uncooperative styles.

In sum, there was a wide spectrum of noncognitive symptoms in the patients' profile. Furthermore, the frequencies of endorsement varied across items. The conclusion from this data supports the idea that noncognitive variables are common in the disease profiles of moderately impaired Alzheimer's disease patients, but there is a relative heterogeneity in the symptom presentation, with symptoms classified under the rubric of neurobehaviours (behavioural dysregulation) being more common than those classified as neuropsychiatric (mood and psychotic symptoms).

6.2.2 Description of specific behaviours

The open-ended item 46 yielded new information for only seven subjects. All other responses provided for item 46 were amenable to recoding and rating under existing items. Three subjects displayed phobias for snakes and continuously shut all doors and windows that were open. Two would repeatedly talk to themselves and one subject complained of a rancid odour that permeated his home. Outlined below are three brief vignettes of individual idiosyncrasies in presentation profile.

Vignette 1: A 66 year-old participant (Mrs A) watched rugby obsessively so that she could see Joost van der Westhuizen. Her recognition of him was intact even though she could not remember most of her family members. Her interest in rugby prior to the dementia was at best marginal. One of her prized possessions was a scrapbook in which she pasted pictures of him that she found in magazines and newspapers. If she misplaced this book, which occurred often, Mrs A would sulk for hours and then proceed to sit in front of the television in the hope of seeing him again.

Vignette 2: A 70 year-old participant (Mrs B) recognised Marike de Klerk on television during the time of her murder. Mrs B believed that the deceased was a childhood friend who had grown up with her. She was adamant that her family go to the home of the deceased and pay their respects. Mrs B continuously reminisced about de Klerk and was on occasion seen having a conversation with de Klerk, as if she were present. During the next few months, Mrs B would sporadically talk about her friend de Klerk and mention that she was feeling sad, but could not relate this sadness to de Klerk's death.

Vignette 3: A 69 year old foreign diplomat (Mr C) was obsessed with obtaining news and would walk up to strangers and ask them about some current or remote political, social, or sports event. Before the dementia, he held a high position as a foreign diplomat and mainly spoke a foreign language before the dementia. After the onset, he began speaking in Zulu to all persons, and was hostile towards family and friends but very sociable to strangers.

These vignettes illustrate the peculiarities that begin to manifest and the challenges that these behaviours may present to caregivers. Interestingly, the narratives that the caregivers used to describe the behaviour of patients conjured impressions of specific

profiles of behaviours. For example, obsessive and rigid traits seem to permeate these descriptions and hint at frontal pathway deterioration and a general breakdown of the patient's 'theory of mind'. The following chapter addresses this in more detail.

Twelve questions of the rating scale require descriptions of the manifestations that caregivers observed. Table 6-3a and 6-3b contain examples of these neurobehavioural and neuropsychiatric displays.

Table 6-3a Content of anxiety and sleep disturbances

Noncognitive items	Examples
Anxious/fearful situations	<p>Fear at being abandoned if caregiver is late or out of sight.</p> <p>Fear at being left alone in unfamiliar surroundings.</p> <p>Person could not walk down a little hill without being panic stricken and afraid of falling into a dam.</p> <p>Fear at being left alone with unfamiliar people.</p> <p>Strong aversion to water, having a bath or shower.</p> <p>Anxious about the weather and if the sky was blue with no clouds he would insist on walking around with an open umbrella.</p>
Physical signs of anxiety	<p>Nervous when caregiver is out of sight and screams especially when in a public place.</p> <p>Pacing and babbling.</p> <p>Fearful facial expressions and disruptive behaviour.</p> <p>Panic expressed in excessive movement/talking.</p> <p>When family member is talking to someone, the patient would laugh inappropriately and attempt to push the stranger away or scream at them to leave.</p>

Sleep disturbances	Excessive daytime napping. Getting up at odd hours at night and assuming it is day and opening doors and windows. When awake at night, spends the time cleaning the bathroom and toilet walls.
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Table 6-3b Content of psychiatric and behavioural manifestations

Noncognitive Items	Examples
Incidences of wandering	Person found at the end of his street, totally disorientated, and unable to find his way home. Person found wandering many kilometres away from home after boarding a bus to an unspecified location.
Auditory hallucinations	Hears noisy children in the room. Hears people from the past or television characters speaking.
Visual hallucinations	Observes children in rooms and around the house and spends most of the day trying to shoo them away. Converses with deceased people from the past. Believes that television characters are real and having conversations with the patient specifically. The patient responds in a monologue or whispers as if answering questions from these characters. Became agitated and saw tarred footprints on the carpet, as if some entity was walking in the lounge.

6.2.3 Six composite noncognitive measures

As explained in chapter five the Behaviour Rating Scale for Dementia includes aggregated values according to composite subscale scores. The calculation of Cronbach alpha determined the internal consistency of the subscale scores. The coefficients varied between .68 and .83, which indicated acceptable levels of internal consistency (Nunnally & Bernstein, 1994). The skew and kurtosis values for all subscales except the psychiatric subscale were close to the value one but less than the value two. This is acceptable according to the rule of thumb, which punctuates the possible effects and significance of distributions on parameter estimates between these two values (Miles & Shevlin, 2001). The psychiatric subscale has a moderate degree of skewness (1.11), however the skewness values are less than twice the standard error ($SE = .56$). The distribution for this subscale therefore, did not differ significantly from the expectations of normally distributed scores.

The subscales yield six scores and Table 6-4 provides the sample means and standard deviations for each of the Behaviour Rating Scale for Dementia subscales.

Table 6-4 Mean and standard deviations for subscales

Subscale Measures	Mean (SD)
Psychotic Symptoms	6.2 (3.3)
Behavioural Dysregulation	10.7 (2.5)
Vegetative Symptoms	1.3 (1.7)
Depressive Symptoms	9.8 (4.1)
Inertia	1.9 (1.1)
Irritability/Aggression	10.9 (3.7)

Pearson correlation coefficients were used to evaluate the association between noncognitive indices and patient characteristics.

Table 6-5 Relationship between noncognitive symptoms and patient characteristics

Noncognitive pathology	BDS	Age	Gender	Education
DEP	.25*	.03	.06	.11
I/A	-.34**	.01	.09	.12
VEG	-.07	.21*	.13	.02
IN	.10	.15	.10	-.08
BD	-.09	.02	-.14	.14
PSY	.13	-.10	.04	.03

p<0.05, ** p<0.01

DEP-Depression, I/A- Irritability/Aggression scale, VEG-Vegetative, IN-Inertia, BD-Behavioural dysregulation, PSY-Psychotic. BDS- Blessed Dementia Scale

As Table 6-5 illustrates, lower levels of cognitive functioning is significantly associated with aggressive actions, and higher levels of cognitive functioning with manifestations of depressive symptoms. Advancing age appears to influence the neurovegetative manifestations of the disease.

6.3 Descriptions of premorbid temperament

In fifty-one cases, Alzheimer's patients had premorbid temperament ratings from a primary caregiver and a secondary informant. Computation of mean differences between the ratings and intraclass correlations determined the interrater reliability. Comparison of means and standard deviations facilitates the alleviation of errors of concordance that may arise when two sets of scores correspondingly increase and decrease in magnitude across observations. Bordens and Abbot (2002) suggest that comparison of two sets of means

acts as a guide for interpreting the high Pearson r scores. In other words, if the means are similar and the Pearson r is high then the researcher can conclude with more confidence that the two scores are similar.

Among the specific temperament domains, no significant mean differences were observed between the raters. The intraclass correlations were significant for five of the six domains, with Endurance the temperament domain that was not significant ($r = .23$, $p < 0.05$). The other domains had higher correlations, with Briskness ($r = .53$, $p < 0.05$), Activity ($r = .57$, $p < 0.05$), Emotional Reactivity ($r = .49$, $p < 0.05$), perseverance ($r = .42$, $p < 0.05$), and sensory sensitivity ($r = .61$, $p < 0.05$) showing significance. The basis for rater disagreement on the Endurance domain could be attributable to the introspective nature of the questions on that subscale. Informants had to provide the best estimate of the patient's introspective processes and this could yield discrepancies in answers. However, based on the overall agreement between observers and no significant differences between the means, a combined mean score was used in all subsequent analyses and in instances where only one rater was available (12 cases), the individual rating was used. The concordance between primary and secondary informants may reflect reliable estimates of the patient's premorbid disposition with retrospective bias being a minimal confounder.

6.4 Canonical correlation analysis

To analyse the relationship between two sets of variables, the multivariate technique of the canonical correlation routine was used. The first set of variables, comprising six dependent or criterion variables, included the subscales of the Behaviour Rating Scale for Dementia, and the second set of eight independent or predictor variables derive from the subscales of the Formal Characteristics of Behaviour-Temperament Inventory, Blessed

Dementia Scale (cognitive status), and age scores. Gender and education level were omitted from this analysis based on their low correlations with all of the noncognitive scales. Before the analysis procedure, variable distributions were evaluated for skewness. Although some variables had slightly positive skewed distributions, these were insignificant and logarithmic or square root transformations were unwarranted.

The analysis entailed a series of steps namely, the generation of i) an intercorrelation matrix, ii) canonical variates, iii) squared canonical correlations, iv) canonical coefficients v) within set variance and redundancy for significant variates and, vi) interpretation of relevant dimensions of set one and set two. A discussion of the above-mentioned processes is included in the following paragraphs.

6.4.1 Pearson product-moment correlations

The matrix of intercorrelations between the two sets revealed moderate and high correlations (r) among some variables (Table 6-6).

Table 6-6 Correlation Matrix of set 1 and set 2

IV's	DEP	I/A	VEG	IN	BD	PSY
BR	-.03	.07	.14	-.18	.12	.05
PE	.41	-.18	.03	.19	.06	.53
SS	.23	.33	.09	.05	.39	.25
EN	-.03	.10	-.09	.11	-.07	-.16
ER	.17	.62	.07	-.03	.38	.06.
AC	-.10	.04	-.16	-.28	.17	.29
AGE	.03	.01	.21	.15	.02	-.10
COGSTAT	.25	-.34	-.07	.10	-.09	.13

BR-briskness, PE-perseverance, SS-sensory sensitivity, EN-endurance, ER-emotional reactivity, AC-activity, COGSTAT-cognitive status.

DEP-Depression, I/A- Irritability/Aggression, VEG-Vegetative, IN-Inertia, BD-Behavioural dysregulation, PSY-Psychotic.

Table 6-6 indicates that Irritability/Aggression and Emotional Reactivity were highly correlated with a coefficient of .62. Psychiatric (.53) and depressive symptoms (.41) shared moderate associations with a perseverative temperament. The temperament trait of sensory sensitivity shared positive correlations with behavioural dysregulation and emotional reactivity, with coefficients of .33 and .39, respectively.

6.4.2 Canonical variates and correlations

The canonical analysis yielded six pairs of canonical variates. Table 6-7 shows the correlations of the variates together with the squared canonical correlations and their eigenvalues.

Table 6-7 Canonical correlations

Variate	Canonical correlation (r_{Cj})	Squared canonical Correlation (r_{Cj}^2) / Eigenvalues
1	.78	.61
2	.69	.48
3	.43	.19
4	.28	.07
5	.19	.04
6	.08	.02

The first pair of canonical variates yielded the maximum correlation and the r_{Cj} was .78, and the second pair showed a canonical correlation of .69. This indicated a strong

association between pairs of canonical variates, because the r is interpretable as a Pearson product-moment coefficient. For the first pair of variates, calculations yielded a .78 correlation and an overlapping variance of 61% (eigenvalue of .61). The last pair of variates correlates at .08 and has an overlapping variance of 2% (eigenvalue of .02).

The patterns of association between and within the two sets are important in identifying the linear combinations of variables. Therefore, Bartlett's test of significance allowed for the possibility of a rejection of the null hypothesis, which states that the sets of data are unrelated. When all sets of canonical variates were included, the tests of significance showed that X^2 (48) = 124.58, $p<0.001$. When the first variate was removed, X^2 was still significant: X^2 (35) = 91.07, $p<0.001$. With the first and second removed the calculated values for the remaining variates did not attain significance. Although the six dependent and eight independent variables yielded six pairs of variates, the significance tests showed that only the first and second variate pairs were amenable to interpretation.

Two sets of canonical coefficients, one for dependent/criterion variables [Y] and another for independent/predictor variables [X], were calculated and these allowed for the estimation of correlations between variables and canonical variates. Table 6-8 and Table 6-9 are matrices of canonical coefficients for both sets of variables.

Table 6-8 Matrix of canonical coefficients: Noncognitive correlates

BRSD	Y1	Y2	Y3	Y4	Y5	Y6
DEP	-.30	.69	.63	.06	.52	.09
I/A	.87	.24	.25	.11	.21	.11
VEG	.08	-.05	.09	-.33	-.10	-.17
IN	-.02	.13	.11	-.18	-.08	-.36
BD	.66	.43	.25	.14	.26	.20
PSY	.22	-.55	.14	.47	.24	.24

BRSD-*Behaviour Rating Scale for Dementia*

DEP-*Depression*, I/A- *Irritability/Aggression*, VEG-*Vegetative*, IN-*Inertia*, BD-*Behavioural dysregulation*, PSY-*Psychotic*.

Table 6-9 Matrix of canonical coefficients: Premorbid temperament/Cognition/Age

FCB-TI/BDS/Demographic	X1	X2	X3	X4	X5	X6
BR	.30	-.05	.02	.37	.17	.25
PE	.13	.63	.17	.19	.23	.04
SS	.24	.27	.19	.06	.41	.12
EN	-.06	.29	-1.01	.24	.13	.12
ER	.69	-.31	.37	.26	.19	.14
AC	.25	.38	.12	.1.02	.27	.11
AGE	-.17	.19	.07	.20	.02	-.42
COGSTAT	-.31	.08	.37	.04	.29	.27

FCB-TI- Formal Characteristics of Behaviour-Temperament Inventory

BDS- Blessed Dementia Scale

BR-*briskness*, PE-*perseverance*, SS-*sensory sensitivity*, EN-*endurance*, ER-*emotional reactivity*, AC-*activity*, COGSTAT-*cognitive status*.

The matrices indicate the direct contribution of each variable to the composite. The pairs of variates have moderate to high coefficients, and this suggests that the noncognitive correlates are associated with premorbid temperament traits along multiple dimensions.

In the table below, the correlations were extracted from a canonical structure, and the canonical variable loadings show the association between the original variables and the variates.

Table 6-10 Correlations, standardised coefficients, canonical coefficients, and redundancy statistics for significant variates.

Temperament set	Variate 1		Variate 2	
	Correlation	Coefficient	Correlation	Coefficient
BR	.27	.30	-.27	-.05
PE	.29	.13	.81	.63
SS	.66	.24	.43	.27
EN	-.19	-.06	.28	.29
ER	.88	.69	-.29	-.31
AC	.17	.25	-.72	.38
AGE	.25	-.17	.08	.19
COGSTAT	-.78	-.31	.23	.08
% Variance (<i>pv</i>)	.28		21	
Redundancy (<i>rd</i>)	.17		13	
 Noncognitive set				
DEP	-.54	-.30	.80	.69
I/A	.80	.87	.15	.24
VEG	.18	.08	-.19	-.05
IN	-.26	-.02	.26	.13
BD	.63	.66	.67	.43
PSY	.25	.22	-.20	-.55
% Variance (<i>pv</i>)	24		20	
%Redundancy (<i>rd</i>)	15		11	

From Table 6-10, the individual variates are interpretable as pairs, with each variate representing dimensions of the predictor variable that correlate with dimensions of the criterion variables. Only correlations in excess of .3 are amenable to interpretation because loadings on variate pairs are correlations and squared correlations of estimates below .3 would yield marginal measures of overlapping variance.

Dimensions of the noncognitive variables that contributed to the first variate include irritation/aggressive behaviours, overall behavioural dysregulation, and depressive signs. Emotional reactivity, sensory sensitivity, and cognitive status comprised the temperament and disease dimensions that were relevant to variate one. As a pair, the first variate indicates that Alzheimer's disease patients with a proclivity for aggressive behaviours and inappropriate behaviours but lower depressive profiles, were premorbidly more emotionally reactive, had low sensory thresholds (high sensitivity), and greater deficit in cognitive status. The second significant variate showed that patients with Alzheimer's disease who tended to manifest with depressive and dysregulatory behaviour appear to have had a premorbid perseverative temperament with low neuronal sensory thresholds (high sensitivity) and the tendency to maintain and attain a low level of stimulation (low activity).

In terms of the variance and redundancy statistics reported in Table 6-10, the noncognitive dimensions extract 24% of the variance from their own set in the first variate, and 20% from their own set in the second variate. Together, they account for 44% of the variance in the noncognitive set. Among the predictor variables, 49% of variance is extracted from this independent set.

The redundancy statistics indicate that the first noncognitive variate reduces 15% of the uncertainty in the temperament set, and the second noncognitive variate reduces the uncertainty by 11%. By combining the two one can deduce that the noncognitive dimensions explain 26% of the variance of the temperament set on the two significant variates, thus implying that having specific temperament traits may precede the occurrence of specific noncognitive manifestations. Similarly, the first temperament variate reduces 17% of the uncertainty in the noncognitive set, and the second temperament variate reduces the variance of the noncognitive set by 13%. Together they account for

30% of the variance in the first set. Overall, these statistics indicate that the canonical analysis is more robust for the first set of variables and the lower redundancy in the second set indicates that the interpretation should proceed with necessary caveats.

6.5 Conclusion

The analysis of data yielded the following results:

- Patients with Alzheimer's disease display a wide spectrum of noncognitive symptoms.
- Some symptoms occur more frequently in patients. For example, symptoms that are neurobehavioural are more commonly reported than the neuropsychiatric sequelae, suggesting that the profile of noncognitive symptomatology is heterogeneous.
- The qualitative descriptions of specific manifestations suggest common themes as well as some idiosyncrasies unique to patients.
- Concordance between raters is high and this indicates the absence of bias among primary observers who knew the subject in a premorbid and current role.
- Canonical analysis yielded two significant variates and related specific noncognitive dimensions to different temperament traits, thereby highlighting the predictive influence of temperament on noncognitive manifestations. The significant variates indicated dimensional relationships between depressive symptoms, irritability/aggression and behavioural dysregulation and sensory sensitivity, emotional reactivity, perseveration, activity, with cognitive status being the moderating disease variable.

Chapter 7 elaborates on the interpretation of results and includes discussions on the possible mechanisms underlying the dimensional relationship between premorbid temperament and noncognitive correlates utilising the delineation of disease process and underlying dysfunctional substrates.

CHAPTER 7

DISCUSSION

The results of this empirical study indicate the following:

- Noncognitive sequelae are present in the disease profile of Alzheimer's patients and the findings of this study support the literature indicating a higher prevalence of neurobehavioural in comparison with neuropsychiatric disturbances.
- The noncognitive symptoms are related to specific patient characteristics such as age and cognitive status.
- There is a significant association between primary and secondary caregiver ratings on premorbid temperament. This indicates that retrospective bias has a limited influence on premorbid and current ratings.
- There is a significant association between premorbid temperament traits and the occurrence of noncognitve symptoms.

The following discussion addresses the above results in the context of the specific theoretical approaches that have been outlined in the preceding chapters.

7.1 Noncognitive manifestations

Neurobehavioural symptoms seem to occur more frequently than neuropsychiatric symptoms in this group of Alzheimer's patients. Moreover, specific symptom clusters share significant links with certain patient characteristics. For example, neurovegetative disturbances are significantly associated with age, indicating that advancing age adds to the cumulative effects of the disease in disrupting regulatory behaviours. In terms of noncognitive symptoms, specific neurobehavioural and neuropsychiatric manifestations

are related to the level of cognitive functioning. The latter appears to be inversely associated with cognitive status and the former positively associated. This variable relationship may shed light on the underlying manifestations of noncognitive disturbances.

7.1.1 Neuropsychiatric symptoms and cognitive status

The neuropsychiatric manifestations may be related to the neurological substrates that are dysfunctional and these may cause specific cognitive deficits. In the case of depression, impairment in specific domains may influence a patient and the underlying frustration at his/her inability may induce this type of reaction (Harwood et al., 2000). Support for this conjecture is derived from findings obtained for anosognosic Alzheimer's disease patients. This group of patients has shown an unusually low incidence of depressive symptoms, which suggests a link between observed depressive symptoms and awareness of declining abilities (Green, 2000; Zec, 1993). Moreover, neuropsychiatric phenomena have been linked to the preservation of particular cortical areas and associated neurochemicals (Harwood et al., 2000). The existence of depressive symptoms early as opposed to late in the disease course may suggest that this is a reactive response to awareness of one's declining abilities (Cummings & Black, 1998; Payne et al., 1998). Insight and awareness diminishes with disease severity thus, the reactivity to declining abilities also diminishes. This contention provides a psychological substrate for the occurrence of depressive symptomatology.

Further evidence for a psychological substrate comes from studies comparing the clinical profiles of late-onset Alzheimer's disease patients with early-onset Alzheimer's disease patients. Lawlor et al. (1994) found that early-onset age predicted the severity of depressive symptoms more robustly than late-onset age. Several studies have shown that

dementia onset at an early age is accompanied by greater atrophy and neurochemical disturbances, and the greater impairment in function may adversely influence the younger Alzheimer's patient as long as awareness and insight into the progressive deficits is retained (Green, 2000).

7.1.2 Neurobehavioural symptoms and cognitive status

In terms of the neurobehavioural symptoms and declining cognitive ability, the results show that the irritability/aggression subscale scores share a significant inverse relationship with the level of cognitive functioning. It appears that patients with greater cognitive impairment and widespread atrophy may be more likely to act out and engage in repetitive and disruptive behaviour because of a disruption in general information processing mechanisms. Based on the deduction that greater cognitive inability translates into more acute neuropathology, the atrophy of the prefrontal cortex may be the underlying substrate for dysregulatory behaviour.

The degenerative progression of Alzheimer's disease disrupts the adaptive algorithmic sequences that have developed over the life span and insidiously allows the devolution of the self. Interestingly, the pathological degeneration follows a pattern that is opposite to that of myelination during brain development. In other words, the atrophy commences in sparsely myelinated areas and proceeds to areas of dense myelination paralleling a hierarchical devolution beginning with lower order functions and ending with deterioration in frontal cortex and a complete unravelling of behaviour and affect (Braak & Braak, 1997). The correlates of this unravelling process are an inability to maintain complex interactions, regulate emotions, and conform to societal expectations, all of which reflect aspects of executive functioning. Studies have shown that the

components of disinhibition (restlessness, irritability, agitation) were significantly associated with executive abilities in subjects with moderate and severe Alzheimer's disease (Chen et al., 1998; Paulsen et al., 2000).

In this sample, the neurobehavioural symptoms of irritability and agitation co-occurred with the neuropsychiatric manifestations of anxiety and depressive characteristics. Mega et al. (1996) shows a similar profile and suggests that the co-occurrence of neurobehavioural and neuropsychiatric symptoms illustrates that the antecedents of these manifestations may be multifactorial and related to both underlying neuropathology and a psychosocial attempt to emulate premorbid communication with the environment. Agitated activity, for example, may be a self-soothing mechanism for the patient. In addition, motor activity may be a patient's way of providing self-stimulation in order to overcome the paucity of environmental stimuli (Niesten & Siegal, 1996). The anger, anxiety, emotional lability, and inappropriate behaviours may be masks of despair, a form of primitive communication emerging from an unravelling self (Lawlor, 1996).

The results of the frequency analysis therefore, shows that noncognitive symptoms manifest in varying degrees among Alzheimer's patients, and its significant correlation with patient characteristics such as cognitive status indicates that its multifactorial aetiology may derive from both neurological and psychological substrates.

7.2 Retrospective bias

One of the most challenging aspects of research on premorbid assessment is the need to hark back in time and sketch portraits of individuals prior to the disease onset. This

challenge is compounded by the incapacity of Alzheimer's patients to narrate their own life history and introspect about their own character and predispositions.

The results of several studies provide evidence for and against retrospective bias colouring the images and impressions of premorbid disposition (Brandt et al., 1998; Malinchoc, Rocca, Colligan, Offord, & Kokmen, 1997; Strauss et al., 1997; Swearer et al., 1996). Bearing in mind the equivocal results and the challenge posed by possible recollection bias in caregiver ratings, this study attempted to minimise reporting biases by employing a reliable instrument and by procuring information about premorbid disposition and current behaviour from different informants. The findings of the present study show that the premorbid recollections of different observers correlate significantly, and primary caregivers who live with the patient are able to distinguish between their recollections of a person's demeanor in the past without the impingement of current problematic behaviours. The researcher, however, bears in mind that the difficulty in determining the extent of the preclinical phase may introduce an ad hoc type of recollection bias.

Manifestations of specific noncognitive symptoms can be attributable to particular premorbid temperament characteristics and not only to recollection bias. The premorbid temperament traits that appear to be significant prognostic factors are discussed below.

7.3 Premorbid temperament and noncognitive symptoms

Individual differences in temperament in nonpathological samples are associated with biological substrates (Boyce et al., 1991). The theories of inter alia Pavlov, Eysenck, Zuckerman, and Strelau explore and expand on these based on the underlying premise that differences in temperament are driven by the idiosyncratic functional organisation of

the central nervous system. Temperament also features as a possible salutogenic factor that protects against certain psychopathological behaviours in nonclinical samples (Cederblad et al., 1995). In neurological patient groups, temperament traits serve as possible predictors of onset of such diseases as Parkinson's or Alzheimer's, as well as playing a role in molding the symptom profile of these diseases (Furukawa, Hori, Yoshida, Tsuji, Nakanishi, & Hamanaka, 1998; Glosser et al., 1995; Meins & Dammast, 2000). As an elaboration of the latter premise, the following sections attempt to elucidate the multidimensional role of temperament in predicting noncognitive symptoms in Alzheimer's disease.

In our attempts to understand the relationship between premorbid temperament and behaviour within a disease context, one is reminded that the relationship is not confined to a unitary neural-behavioural interchange, but rather interactions of multilevel and multidimensional neural and behavioural systems. The empirical evidence supports the contention held among researchers that the interplay on a neural and behavioural continuum is multidimensional.

7.3.1 A multidimensional lens: Legacy of a neuropsychological approach

A neuropsychological approach takes into account the dimensional and categorical explanations as espoused by the psychological and medical models, respectively. The psychological model assumes that symptoms lie on a continuum for a given trait, and the medical model assumes that pathology is defined in the absence of normal behaviour. Claridge (1997) argues that there is an inextricable link between normality and disorder, illness and health in psychological terms, and in order to unravel the disorder it is necessary to comprehend the nuances of normality. In other words, the dimensional as

opposed to the discontinuous view may provide a structural and descriptive illustration on predisposition and behaviour. For example, the dimensional view provides some insight about the extent to which a person's depressive state or their aggressive manifestations may stem from a perseverative temperament or by its underlying biological substrate such as an inherently low threshold of arousal and high reactivity. Several authors, who argue that noncognitive symptoms in Alzheimer's disease are merely an exaggeration of premorbid traits, have used the dimensional approach (Bozolla et al., 1992; Chatterjee et al., 1992; Kolanowski et al., 1997; Welleford et al., 1995).

7.3.1.1 Noncognitive symptoms: Merely caricatures of premorbid traits

In Alzheimer's disease, according to Chatterjee et al. (1992), persons who occupy the extremes on the temperament continuum are considered more vulnerable to noncognitive manifestations as the extremes or nonnormative behaviours are likely to emerge because of the diseased profile. The dimensional approach regards abnormal behaviour as an extreme manifestation of specific traits. In contrast, the medical model considers individuals designated with pathological labels as qualitatively distinct groups. There is growing recognition that symptoms underlying Alzheimer's disease are merely an exacerbation of stable, inherent temperament tendencies that are measurable along dimensions (Zuckerman et al., 1984).

Utilising the dimensional approach, the assumption that patients at extremes on the temperament continuum premorbidly are more likely to display pathologic signs can be applied as an explanation for certain patients displaying specific noncognitive symptoms. In other words, a patient's temperament interacts with the neurologically imposed stereotypic profile, thus creating differential increments at which noncognitive symptoms

are likely to emerge. Studies have shown that many demented patients maintain a semblance of their unique patterns of traits and therefore, their premorbid traits act as catalysts for any manifestations that may occur, and the premorbid temperament "gives drama and intensity to life-long traits" (Kolanowski et al., 1997).

This pathoplastic aspect of temperament is addressed by Berrios (1989), who attempts to explain the occurrence of noncognitive symptomatology. He suggests that the exaggeration of premorbid traits caused by disease processes only explains the quantitative alterations in noncognitive symptoms, whereas the qualitative changes (hallucinations, delusion) have no obvious counterpart in premorbid actions. In other words, pathoplasticity may serve as explanations for neurobehavioural symptoms but not for neuropsychiatric manifestations. The latter, according to Berrios (1989) may be explained by recourse to the occurrence of cortical disinhibition. The neuropsychiatric manifestations may be the 'released behaviour' that arises when higher inhibitory functions cannot contain the processes arising from lower cortical areas. This mechanism, however, cannot fully explain the neuropsychiatric phenomenon in the absence of neuroanatomical knowledge about the specific structures of the brain whose release is assumed to cause hallucinations and delusions.

7.3.1.2 The flip side of the coin: Salutogenic properties of extreme traits

Further criticism of the view that noncognitive symptoms are merely exaggerations of extreme premorbid disposition arises from the research of Cederblad et al. (1995). They utilized categories of sub and super dimensions with the former classified on the low end of the continuum and the latter on the high end of the continuum. They hypothesised that persons occupying the extremes of the continuum are less likely to be vulnerable to

pathological conditions and maladaptive stress reactions when compared to persons who occupy a middle position on the continuum. They motivate their idea that extremes on a continuum act as salutogenic factors by assuming that persons on the extreme are more likely to alter the aversive environment or seek out a more suitable niche environment when compared to persons in the middle position. They use dimensions of super- and sub- capacity, validity, solidity, and stability. They associate their dimensions of super-validity and super-solidity to low emotionality (low arousal to stimulation), low impulsivity, high persistence, high exploratory, and high energy behaviours. Sub-stability is associated with high reward dependence, high sociability, high adaptation level, and openness. Depression is associated with validity (level of energy); and high energy correlates with super-validity, active, energetic, persevering, and tenacious traits (sub-validity associated with cautious, tense, and hesitant). They conclude that super-validity is a salutogenic factor or custodial factor for mental health against depression.

According to Cederblad et al. (1995), psychosis correlates with a person's capacity (intelligence) and solidity (flexibility). A high capacity translates into a high intelligence and super-solidity translates into low flexibility and good impulse control. On the other hand, sub-solidity translates into extreme flexibility, impulsive, and a need for novelty and avoidance of monotony. They conclude that super-solidity is a salutogenic factor against psychiatric disturbances. Overall, they conclude that protection from psychosis comes from super-validity (low emotional reactivity), super-solidity (low impulsivity), and capacity. These factors increase the coping capacity of an individual because the adaptive temperament disposition functions as a coping resource. Certain extreme temperament traits therefore, seem to be advantageous and may act as protective-reactive or protective-enhancing. Of note, their hypothesis was based on subjects that were not neurologically impaired but at different risk levels for psychopathology. The interjection of a brain

disease, however, may reduce the salutogenic benefits of temperament extremes. Alzheimer's patients lose the ability to negotiate their environment as the disease progresses. Hence, the salutogenic benefits of extreme traits may be dependent on the disease stage and its accompanying cognitive consequences and not merely a positioning on a continuum.

Adding to the general criticism of the account of noncognitive symptoms as exaggerated manifestations, Strelau (1987b) considers the interaction between predisposition and behaviour to be more complex and involving systems that regulate arousal and reactivity. It is the interaction of these systems together with disease processes, which may produce certain noncognitive profiles in Alzheimer's patients. The following premise is discussed below, utilizing the general principles of the Regulative Theory of Temperament (Strelau, 1994).

7.3.2 Theoretical stance revisited

One of the central themes that permeate the temperament theories discussed in chapter four pertained to the concepts of arousal or activation. Furthermore, according to Klonowicz (1986, 1987) and Strelau (1987b) reactivity as a key component of arousal mechanisms, is a fundamental mediator of environmental, biological and behavioural relations. In the following sections, the discussion focuses on the nature of reactivity and its implications in the context of the empirical findings.

7.3.2.1 Reactivity

In the context of this study, one considers reactivity to mediate relations between the disease influences (environmental), biological predisposition (temperament) and behaviour outcomes (noncognitive symptoms). To recapitulate, the reactivity concept is primarily derived from Pavlov's nervous system types such as strength of excitation. Strength of excitation incorporates the idea that there are individual differences in the level of excitation to stimuli of a given intensity. Many underlying anatomical substrates have been proposed as the driving mechanism for these processes: Robinson (1987) stipulates that strength of excitation corresponds to the activities of the diffuse thalamocortical system; Meccaci (1987) speaks of the reticular formation; Gray and McNaughton (2000) focus on the behavioural inhibition and activation systems, and Zuckerman (1995) considers the neurochemical interactions. Strelau (1987b) however, argues that the underlying physiological functional systems are complex and although all these systems may contribute to an individual's intensity and magnitude of reactions, the dominance of a particular anatomical system or neurochemical is determined by type of activity and situation.

The reactivity continuum consists of two extremes: high reactivity (high sensitivity) and low reactivity (low sensitivity). Due to the complex and multilevel physiological mechanisms that determine an individual's magnitude and intensity of reaction and the outcome of Alzheimer's on these processes, it is incumbent on the reader to understand the role of reactivity in regulating the impact of stimulation.

7.3.2.2 Reactivity and the resting level of arousal

According to Strelau (1987b) and Klonowicz (1987) the level of arousal is higher in high reactive individuals when compared to low reactive individuals. By implication, one can deduce that reactivity controls the level of arousal and a high level of resting arousal enables the individual to detect stimuli easily because the cortex has sufficient tonus. The impact of the stimuli magnitude and novelty is greater for people with high reactivity and higher resting arousal levels.

7.3.2.3 Impact of altered stimulative values

Among Alzheimer's patients who showed a high reactive profile, it is assumed that the impact of stimulation would collude with the pathological correlates of the disease. This assumption is based on the knowledge that individuals have a requisition-competence ratio, which helps with filtering input in proportion to a person's handling capacity (Strelau, 1983). The higher the reactivity levels, the more susceptible the system processes to entropy and disruption of balance. Moreover, in higher reactives, changes in performance and energy expenditure are commensurable with increases in the stimulation load. Due to this susceptibility, high reactive Alzheimer's disease patients would be unable to process input and with altered filtering mechanisms, the stimulation load on brain processing would probably cause certain pathological symptoms to manifest.

These manifestations may reflect an imbalance in the requisition-competence ratio. On a practical level, caregivers interact with patients who are mild or moderately affected utilising similar premorbid communication patterns. However, with a high reactive, the disease would most likely disrupt the requisition-competence balance and this change in

stimulative value could result in difficult and challenging behaviour. This implies that in certain situations caregivers may benefit from a modification in patterns of interaction depending on premorbid temperament of the patient. Among low reactives, the ratio is not as susceptible to imbalances, although decreases in stimulation load can cause imbalances in the system (Strelau, 1987b). However, a more drastic attenuation of stimuli is needed for restoring the balance in high reactives when compared to low reactives. In other words, discrepancies between optimal and actual levels of stimulative intensity is more likely to impact on the high reactive rather than the low reactive, and adverse behavioural outcomes may underscore the disruptive processes (Eliasz, 1987).

7.3.2.4 Exteroceptive influences and self-regulation

Persons with Alzheimer's disease have to endure potentially noxious stimulation (overload or underload) because of the malfunctioning of their cognitive filtering mechanisms. The degree of nonspecific bombardment of the cortex by stimuli depends on a person's level of reactivity, and they compensate for the deficits arising from inadequate task demands and capacity according to their reactivity level (Strelau, 1983).

Self-regulation mechanisms are in place to control the stimulation in order to maintain the optimal level of stimulation and arousal, and these mechanisms function at a physiological and behavioural level. The latter engages trigger mechanisms that activate transient alterations in stimulation processes in order to deal with change increments in inputs.

Studies on animals reflect the self-regulatory mechanisms and show that rats deprived of stimulation select a more stimulating environment, whereas over-stimulated rats choose a more mundane environment (Klonowicz, 1987). The intensity of the seeking behaviour (in

this case pressing a button) is associated with the need for stimulation, which depends on reactivity levels. Perhaps high reactive Alzheimer's patients, who experience an increased level of chaotic input stimuli, react in dysregulated ways to shut off the input. Moreover, high reactives are more susceptible to changes in the social milieu and this is accompanied by a general lack of adaptive behaviour to altered environmental stimulation (Eliasz, 1987). The higher the reactivity the more attention is paid to others and the need for caregiver supervision among Alzheimer's patients creates contexts in which the patient and caregiver interact very closely. Consequently, a high reactive would be more likely to misinterpret the interactions and because of their limited capacity to function appropriately within broad ranges of stimulus intensities are more likely to manifest with challenging behaviours such as aggression and general behavioural dysregulation. Hence, the impact of temperament on noncognitive manifestations may depend on the balance between the need for stimulation (inherent) and the stimulation received from the environment (acquired and malleable to disease processes).

7.3.2.5 Functional structure of behaviour

Behaviour that is goal directed utilises two pivotal operation systems to organize the optimal output. The first is considered the basic operations and the second the auxiliary operations. According to Strelau (1987b) in low reactives the basic operations dominate over the auxiliary operations and in high reactives the relationship is reversed.

From the assumptions underlying the notion of reactivity and response to stimulation, the psychological significance of this pertains to a protective role of auxiliary operations. For example, the auxiliary mechanisms sustain the target activity and minimise stress and circumstances that appear to create tension. Moreover, high reactives fatigue easier than

low reactives in terms of work capacity and low reactives make fewer attempts at planning and control. In other words, the more reactive a person is, the greater the need for protection from adverse stimuli because of the lower capacity to deal with stress and the higher capacity to tire more easily when dealing with novel situations. Hence, an Alzheimer's patient with high premorbid emotional reactivity may react more adversely as the disease progresses because of his/her capacity to deal with environmental stimuli. Caregivers of such patients may have to regulate the environmental demands more stringently as the function of behaviour is more dependent on the progression of disease because as the disease progresses the Alzheimer's patients cognitive capacity to deal with environmental stressors also deteriorates.

7.3.2.6 Interoceptive influences and self-regulation

Unlike the self-regulation that responds to environmental stimulation, interoceptive influences involve another stimulation source namely individual behaviour. The modification of activity and the preference for certain contexts depend on the stimulation value of those contexts and a person's level of reactivity (Eliasz, 1987; Robinson, 1987). In less stimulating contexts, high reactives modify activity levels and respond with more stimulating activities. Conversely, low reactives expend higher levels of activity commensurate with the higher stimulation values of the context. It would appear that low reactives are more attuned to their environments, whereas high reactives display a lesser aptitude for behavioural regulation in relation to changing environmental stimulation. In other words, activity modification is dependent on reactivity, which in turn determines an individual's capacity for regulation, and the optimal functioning of reciprocal feedback lopes between intrinsic and extrinsic stimulation (Klonowicz, 1987).

7.3.2.7 Reactivity and anticipation

In addition to a difference in arousal levels between high and low reactives, Klonowicz (1987) postulates that high and low reactives differ in emotional tone of arousal with high reactives displaying a negative emotional bias. It appears that the negative bias displayed by high reactives may be the result of their resistance to the differential between their optimal arousal and current levels of arousal. This generalization, however, depends on the principle of Occam's razor. The juxtaposition of simplicity and complexity reflects Bateson's (1979) notion of Occam's razor or the rule of parsimony, which states that the simplest solution/hypothesis is adequate to explain certain phenomenon.

In this case, however, the phenomenon under consideration has complex links with neurophysiology, particularly the reciprocal regulative principles of feedback, therefore a more complex explanation is warranted. Klonowicz (1987) hypothesises that interactions with the environment produce different levels of uncertainty and anticipation in high and low reactives. This results in the differentiation of emotional tone that is observed between the two groups. Interestingly, Klonowicz (1987) found that anxiety and uncertainty decrease proportionately in both groups, but that high reactives are more sensitive to the effects of information when compared to low reactives. She concludes that high reactives have a greater capacity for anticipatory stress and a smaller repertoire of coping resources, thus the stress is often interpreted as aversive stimuli and the reactions are imbued with a negative emotional tone.

7.3.2.8 Summary

The reactivity principle according to the Regulative Theory of Temperament is therefore a central concept in theories of temperament and personality that espouse a biological base. Individual differences in behaviour can be explained utilising the idea of reactivity as a mechanism that influences modes of regulation. Figure 7-1 summarises the main principle of reactivity and its influence on behavioural outcomes.

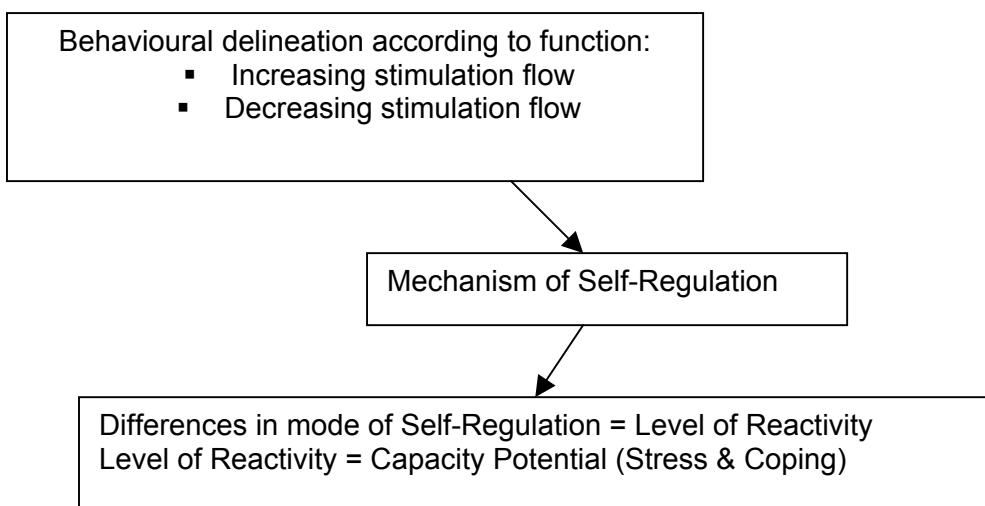


Figure 7-1: Reactivity mechanisms

7.4 Empirical and theoretical coupling

As a pair, the first variate indicates that Alzheimer's disease patients with a proclivity for aggressive behaviours and inappropriate behaviours but lower depressive profiles, were premorbidly more emotionally reactive, had a low sensory threshold (high sensitivity), and impaired cognitive abilities. The second significant variate shows that patients with Alzheimer's disease who tend to manifest with depressive and dysregulatory behaviour appear to have a perseverative temperament with a low neuronal sensory threshold (high sensitivity) and a propensity to maintain and attain a low level of stimulation (low activity).

level). These significant results will be discussed in relation to the general Regulative Theory of Temperament principles mentioned above.

7.4.1 The premorbid antecedents of aggressive symptoms

Higher levels of inner instability and nervous tension are regarded as unspecific vulnerability factors for various mental disorders (Andrews, 1996). Therefore, individuals with Alzheimer's disease and high levels of emotional reactivity and sensory sensitivity may be at special risk for a broad range of subsequent neurobehavioural and neuropsychiatric pathologies. Emotional reactivity, according to Strelau (1987b), regulates the intensity of reactions and is expressed as negative affect intensity. Extrapolations from this assumption would suggest that high levels of emotional reactivity would translate into more intense reactions and the reverse would hold for low levels of emotional reactivity.

7.4.1.1 Low thresholds

The canonical analysis reveals that emotional reactivity and sensory sensitivity correlate positively with irritability and aggressive symptoms thereby indicating that high reactives would more likely respond intensively to what they would punctuate as aversive stimuli. To reiterate, according to biological based theories of temperament persons classified as augmenters, introverts, weak nervous system types, and high reactives (high sensory sensitivity) are considered to have a low arousal threshold (Strelau, 1987b). Consequently, they have a lower capacity to deal with altered stimulative values. In other words, high emotional reactivity levels in the presence of high sensitivity (low thresholds) would likely result in intense behaviours being triggered more easily because of the low arousal thresholds.

Several studies have shown that many of the Regulative Theory of Temperament traits are significantly associated with other temperament and personality dimensions (Strelau & Zawadzki, 1995; Zuckerman, 1987a). Significant correlations were found for the emotional reactivity scale of the FCB-TI and the NEO-FFI neuroticism scale and due to the paucity of research dealing with specific temperament dimensions one has to utilize these studies as comparative parameters. One such study by Kolanowski et al. (1997) found a significant association between premorbid neuroticism and aggressive behaviours and between extraversion and aggression. If one assumes a correlation between neuroticism and emotional reactivity, then Kolanowski's et al. (1997) results would support the findings in the present study. On the other hand, the second significant association reported by Kolanowski et al. (1997) contradicts the results of the present study. The Regulative Theory of Temperament proposes that persons with high emotional reactivity and low sensory thresholds are more likely to be introverted and more prone to the inimical effects of altered stimulative value and more likely to act out when compared to people with low emotional reactivity.

A possible explanation from an Regulative Theory of Temperament perspective involves the following: in relation to the stimulative value of the behavioural output, it is likely that the extroverts with Alzheimer's disease respond with behaviour that has a high stimulative value such as aggressive acts and behavioural dysregulation such as pacing. One would assume that the deterioration in cognition alters the intensity and magnitude with which input is perceived and processed, and persons who are categorized as extroverts may display these behaviours as attempts to provide self stimulation to overcome the lack of environmental stimulation, which is required because of their high arousal thresholds (Neistein & Siegal, 1996). Although explanations can be provided for the significant

association between extroversion and aggression, in essence this result of Kolanowski et al. (1997) is contradictory to the findings of the present study.

7.4.1.2 Disease concomitants

In the present study, the profile of Alzheimer's patients tended toward a moderately affected group, whereas Kolanowski et al. (1997) used a severely impaired group. One can assume that the disease process impact more on the severely affected group than on the moderate group, and disrupts more acutely the complex relationships between predisposition and behaviour. Lopez et al. (2003) identify aggressive behaviours as one of the noncognitive symptoms that manifests as a function of disease severity. This provides support for the notion that occurrence does not necessarily follow a linear pattern for all noncognitive symptoms. Furthermore, later in the disease process, low reactives may be more in need of enhancing stimulation because of the decreasing stimulation load (cognitive processing failure), and persons with this predisposition may react more adversely to the discrepancy between optimal and current levels of functioning. Notwithstanding the contradictory results, it is important to consider that perhaps the relationship between predisposition and symptom occurrence may change because of the disease process and longitudinal studies are needed to address the probability of these changes. Therefore, the equivocal results may reflect the methodological deficiencies in sample categorization that do not include the possibility that reactivity, as a trait is changeable and malleable in disease states (Eliasz & Reykowski, 1986).

Welleford et al. (1995), in addition to the exacerbation or exaggerated symptom profile, also found that Alzheimer's patients may manifest with a stereotypic profile where they display similar increases and decreases in certain traits while maintaining individual

variability. There has been some concordance among researchers regarding the latter profile (Bozolla et al., 1992; Kolanowski et al., 1997; Welleford et al. 1995). Studies of Alzheimer's patients indicate that traits such as neuroticism tend to increase and extraversion, openness agreeableness, and conscientiousness tend to decrease relative to premorbid levels, and this appears to reflect a uniform and stereotypic change. If one considers these changes to be a natural manifestation of the disease and its unique neuropathological profile, then one must consider how biological disposition may interact with this stereotypic profile.

Strelau and Zawadzki's (1995) study may provide some insight into the interaction between the disease profile and disposition. Using Factor analysis, they located the Regulative Theory of Temperament traits among other temperament dimensions, and found that sensory sensitivity and openness share a significant positive relationship (.35). Utilising the findings of Bozolla et al. (1992), Kolanowski et al. (1997) and Welleford et al. (1995) on stereotypic changes, one can deduce that if a stereotypic temperament profile is superimposed onto individual differences in temperament then different noncognitive manifestations may arise for different individuals.

A reduction in openness, as stipulated in the stereotypic profile, may influence an introverted temperament. For example, decreased levels of openness (biological disease changes) impact on high sensory sensitivity (an inherent disposition), because people with high sensory sensitivity are categorised as high reactives and introverts, thus with changes in openness they are more introverted augmenters. Welleford et al. (1995) found that the fantasy facet of openness increased and the facets of ideas and aesthetics decreased. Thus, the reactions of patients with high sensory sensitivity and lower openness may arise from the loss of cognitive and functional abilities (low cogstat score) that are needed to

negotiate the environment. These patients may require more structure and consistent routine and any ambiguity may be perceived as a novel situation to which they will react adversely. Furthermore, resilience is also associated with openness and if the typical profile is a decrease in openness, then persons who have limited structure in their environment and a decrease in resilience to stress are more likely to respond negatively (Garmezy & Rutter, 1983).

7.4.2 The premorbid antecedents of behavioural dysregulation

Features of behavioural dysregulation may arise from a patient's attempt at behavioural adaptation in the event of his or her neurological condition co-habitating with the inherent temperament disposition.

7.4.2.1 Low threshold

Person's with a low sensory threshold and unstable predisposition (high emotional reactivity) are more likely to act out quickly and intensely and their attempts at adaptation in the light of cognitive breakdown may manifest as dysregulated behaviour. Gray (1991) suggests that the efficiency of learning is associated with certain temperament dimensions and reinforcements, and lower cognitive status may have a more profound impact on high reactives than on low reactives. Due to the compromised efficiency of the cognitive system, the interactions between caregiver and Alzheimer's disease patients is more likely to be interpreted as threatening and high in punishment value, and since high reactives are more sensitive to punishment stimuli they are more likely on a behavioural level to react in maladaptive ways.

On the level of behaviour, for example, an anxious individual (high reactive with high sensitivity) tends to be sensitive to punishment because of the dominance of the behavioural inhibition system. On the other hand, the impulsive individual (low reactive) is more sensitive to reward because of the workings of the behavioural activation system. In the context of Alzheimer's disease therefore, the high reactives are more likely to perceive caregiver reproaches as punishment and thus, respond in an inappropriate manner. With the accompanying neurological profile, the person is unlikely to purvey any semblance of an adaptive response and the reaction is likely to be intense even in situations that would normally be deemed as one with a low evocative potential.

The energy systems model expands on the general regulatory principles of Strelau (1987b), and uses the capacities of four energy systems and their set points of efficiency as a model of extrapolation relating to predisposition and behaviour (Gale, 1987). Individuals with high levels of emotional reactivity tended to show greater behavioural dysregulation and irritable and aggressive behaviours. If one equates high neuroticism with high emotional reactivity, high reactives would have an inefficient energy store characterised by a "leaky" system with a high set point. Energy is drained in a disorganised and chaotic manner, creating a scenario where the control system has to work at a maximum rate to counter the anomalous energy expenditure.

The system's attempt at restoring homeostasis involves focusing on the acquisition system and input to this system. Neurotic individuals have problems in both the storage systems and acquisition systems. This attempt at avoiding inimical stimuli attenuates the opportunities to learn and hence conserve energy. Individuals with porous energy stores cannot, in terms of attention sustain continuous focus. The symptoms of dysregulated behaviour can be a reflection of the disorganised energy store. Furthermore, individuals in

the mild to moderate stages of dementia experience significant levels of anxiety at their condition and this may enhance the occurrence of symptoms because the psychological "experience of anxiety may include amalgams of correlates of both energy loss, and the effort required to sustain the energy level of the system" (Gale, 1987, p.300). Dementing individuals with impaired cognitive abilities face the consequences of disrupted input-output mechanisms with inefficient storage processes as well as diminished compensatory strategies to control further energy loss evoked by discrepant output activities.

7.4.2.2 Disease concomitants

In Alzheimer's disease, one has to ask whether there will be a direct influence of temperament predispositions that may be impervious to external influences, or whether the predispositions may be ameliorated by caretaker intervention. This interaction between disease, temperament, and caregiver responses is documented by Ware et al. (1990). Collating the circumstances in which dysregulatory behaviour occurs lends itself to the expedient classification of these behaviours. Most of the occurrences tend to be triggered during times of intimate care (bathing, dressing) where the Alzheimer's patient has to respond to instruction. Ware et al. (1990) conclude that although noncognitive behaviours differ from normal behaviour, the changes experienced still follow ordinary rules of behaviour. Events can serve as antecedents or triggers and responses can reinforce them. As with any other behaviour, changing the pattern of antecedents and consequences will affect the rate of any particular behaviour (Zarit, 1996). In some cases, the inappropriate behaviour may be explained by moderating variables that provide the contextual link between predisposition and behaviour. For example, if an Alzheimer's patient with a certain predisposition is not comfortable in novel situations (perhaps social interactions with strangers) and caregivers impel the person to engage in these, then the

reaction for a person who had a inherent aversion for novelty would likely be more pronounced than one who's predisposition is based more on an approach than withdrawal tendency.

Calkins and Fox (1994) support the idea that emotion and behaviour that is displayed is a function of both the event and the process of socialisation. Although individuality of temperament plays a role in behaviour and physiological responsivity there is also a clear process of caregiver feedback, which allows for the modulation of emotional responses. They propose a model that describes how caretaking premorbidly influences the display of particular reactive tendencies. They begin with the premise that emotional reactivity influences premorbid caretaking style, which in turn affects a patient's ability to cope with emotion-eliciting events.

Wachs and King (1995) identify two factors that may moderate the association between predisposition and behaviour and label this reactive and active covariance. The former states that a person with specific behavioural patterns would educe specific types of behaviours from caregivers. In the case of active covariance, persons with a specific predisposition would select specific situations and environmental contexts. Active covariance refers to the tendency of individuals to approach, explore, and express positive effect under conditions of novelty. The opposite tendency would include persons who are more reticent in such circumstances and in extreme cases may display extremely negative affect and withdrawal when confronted with novel situations.

The subcortical asymmetries in amygdala functioning have been demonstrated by Calkins and Fox, (1992), who show that during approach behaviours there seems to be greater left frontal activation, whereas with withdrawal behaviours there is a right frontal activation. In

Alzheimer's disease, researchers have demonstrated impairment in fear conditioning and emotional responsivity that is linked to the functioning of the amygdala (Hamann et al., 2002; Mori et al., 1999). The importance of these results lies in its association with pathological features especially anxiety related symptoms and uninhibitory behaviour. Negative reactivity, for example, as reflected in accentuated motor activity (behavioural dysregulation), is often accompanied by irritability, fearfulness and behavioural inhibition (right frontal activation). Thus, asymmetrical frontal activation may be a neural substrate of the predisposition to display behavioural dysregulation in the face of novelty among Alzheimer's patients. The expression of temperament dispositions among Alzheimer's patients may involve both an expressive component and a regulatory component, which incorporates the effects of the environment.

7.4.3 The premorbid antecedents of depressive symptoms

It would appear that persons who are classified as high reactives should be more susceptible to depressive symptoms because high emotional reactivity is associated with negative emotion and high sensory sensitivity renders a person less capable of behavioural regulation and enhances their susceptibility to anticipatory stress. Interestingly, there is a contradictory relationship between sensory sensitivity and depression when one interprets the two significant variates. In the first variate sensory sensitivity and depression share a negative correlation and in the second variate they share a positive association. The negative relationship between sensory sensitivity and depression is probably more a function of decreased insight and high sensory sensitivity than emotional reactivity. In this case, disease effects could alter the reactivity thresholds and cause more systemic cortical changes.

If a person is more susceptible to environmental stimuli (high arousal/low threshold) as well as inept at intrinsic self-regulation (high reactives), then a more advanced disease state (low cogstat) may interrupt more sensitive positive and negative feedback systems and produce a devolution of the person's metacognitive ability to monitor subjective feelings. In other words, in the absence of disease induced cognitive deficits, a high reactive may be likely to display depressive symptoms, whereas in the context of this brain disease the cognitive devolution may desensitize the high reactive to anticipatory stress and the ability to monitor his/her coping repertoire (see Klonowicz, 1987). Even in the presence of altered capacity to deal with stimuli, the anosognosic orientation would negate the manifestation of depressive features. On a neurobiological level one can hypothesise that the more advanced the cognitive impairment the more acetylcholine depletion is evident. Cummings and Black (1998) show that lower levels of acetylcholine may protect Alzheimer's patients against depression irrespective of a predisposition for occurrence.

The relationship between symptoms and cognitive status helps to identify symptoms that are stage specific and characteristic of the disease process (Teri et al., 1998). These symptoms can therefore, be anticipated because of the information that is available on the stages of the disease and the atrophy accompanying these stages, and the alleviation of such symptoms are more amenable to pharmacological intervention. On the other hand, the genesis of symptoms that have no relationship with cognitive status are more likely to occur at variable stages and to be more idiosyncratic. These symptoms may prove more problematic for caregivers and their anticipated behavioural pattern may be predicted more by correlates such as premorbid temperament. The management of these symptoms are more amenable to psychological interventions dealing with adaptive behavioural patterns and caregiver reactivity.

Ross et al. (1998) argue against this reactive categorization of depressive symptoms in Alzheimer's disease, and contend that depressive symptoms are not necessarily a function of relatively intact cognition but are rather associated with the specific topography of Alzheimer's lesions. This proposition implies that depression is not confined to the early stages of the disease, but can occur at all stages. In the latter case, one assumes that the disease process and biological based temperament parameters interact at a neural level, and in the former case patients premorbid disposition influence their stress responses and resilience strategies on a psychological level.

7.4.3.1 Low thresholds

Based on the principles of arousability and reactivity, one can hypothesise that high arousability would likely lead to neurobehavioural problems rather than neuropsychiatric disturbances i.e., depression and psychosis (Strelau, 1994). Our findings, however, are contradictory to Chatterjee et al. (1992) who suggest that in Alzheimer's disease the more neurotic patients become (higher emotional reactivity), the more likely they are to manifest with depressive symptoms. Chatterjee et al. (1992) themselves note that one of the flaws in their design was the use of the same caregiver to rate premorbid and current behaviour and this may have allowed retrospective bias to colour the recollections of caregivers. In this instance, caregivers of a depressed patient may have recalled the more neurotic inclinations of the patient. Alternatively, high emotional reactivity (neuroticism) may contribute to depression but deteriorating cognitive status may temper this relationship.

7.4.3.2 The activity trait and depressive symptoms

The activity and sensory sensitivity traits are action-oriented energetic traits that have their physiology and biochemistry related to cortico-reticular structures, as opposed to the emotional traits, which have their underlying physiology linked to the limbic and autonomic systems (Strelau & Zawadzki, 1993). Activity is reported to share a positive association with extraversion, openness and strength of excitation and an inverse correlation with neuroticism. According to Strelau and Zawadzki (1993, 1995), a high level of activity serves as organiser of stimulation and a low level allows one to maintain or attain low levels of stimulation. Thus, this trait serves in a regulatory capacity to temperament disposition. Activity is mainly expressed in social situations/interactions and as a source of stimulation refers to all kinds of behaviour and events including behaviour in risky situations (sensation seeking).

By means of activity, the individual regulates the stimulation value of behaviour or situations in such a way as to satisfy his/her need for stimulation and it is co-determined by the level of reactivity. The need to maintain or attain an optimum level of arousal is a standard for the regulation of stimulation. The stimulation value of activity includes a component whereby activity itself is a source of stimulation and the more complex and different the activity, the higher the stimulation being generated (Strelau & Zawadzki, 1995). One of the most efficient generators of stimulation is the emotional content of activity. Activity is not only the direct source of stimulation but by means of activity, the individual may also modify the stimulation value of the environment. Activities aimed at avoiding or approaching stimuli from the environment illustrates this ability to self-regulate stimulative intensities. Thus, on a behavioural level it serves as an organiser of stimulation and an indirect source of stimulation.

The results of the present study showed that there was an inverse relationship between activity and depression. Perhaps, individuals who display inhibitory behaviour are less likely to generate both internal and external stimulation of any considerable intensity, and in the light of the disease processes, would likely be inept at organizing stimulation and limiting sources of stimuli and responses to these sources. On a neurochemical level, Zuckerman (1987b) and Zuckerman et al. (1984) found a negative relationship between norepinephrine and sensation seeking and hence the activity trait identified by Strelau and Zawadzki (1995).

The neurotransmitter norepinephrine, according to Netter (1991), plays a role in mediating responses to stimuli of punishment and novelty. Zuckerman et al. (1984) also associate this neurotransmitter with responses to reward signals and regulation of fear responses in novel and unfamiliar situations. Therefore, the behavioural role of the norepinephrine system appears to be nonspecific and functions in a mediatory role to all emotive systems. Due to the assumption of an inverse relationship between activity and norepinephrine levels, the deduction that high levels of this neurotransmitter appears to bias attention to the external sources of stimuli and high levels of norepinephrine release is related to the inhibition and disorganisation characterised by anxiety (fear) responses. Although the activation of the norepinephrine system is normal in anxious individuals during sedate states, Zuckerman et al. (1984) found that this system responds intensely when individuals encounter unavoidable stressful situations and activities.

Person's with a low activity trait are considered as hyper-responsive and would thus, normally avoid novel situations because of the high stimulatory potential in these situations. In essence, this interpretation is similar to the arousal construct underlying introversion, where introverts seek lower levels of stimulation in order to maintain an

essentially low level of arousal without exceeding the threshold. Furthermore, because neurotransmitter effects do not occur in isolation it is important to consider the effect of increased norepinephrine levels on dopamine discharges in the cortex. Basic neurochemistry suggests that high levels of norepinephrine could result in lower levels of dopamine because norepinephrine is in essence synthesized from dopamine (Kalat, 2001).

The role of dopamine involves the stimulation or activation of behaviour and together with the norepinephrine system enhances the organisms ability to “adapt to physiological and psychological stress, tolerate strong stimulation, and enhance the capacity to respond adaptively to weak stimulation” (Zuckerman et al., 1984, p.414). An imbalance in this system often translates on a behavioural level to a motivational deficit, which is characteristic of depressive features. Considering the disruptive nature of the disease on a neurochemical level, one can see that persons who are premorbidly inhibited would be likely to respond with negative affect because of the maladaptive responses (both psychological and physiological) to the stressful disease situation brought on by the synaptic changes accompanying the disease. Moreover, dopamine is linked to the rewards systems in the brain and to positive emotions. Consequently, low dopamine activation translates into low stimulation of the reward centers of the brain and thus, less positive affect.

Disruption in dopamine levels can either aggravate levels of spontaneous activity, or enhance the rigidity and diminish the plasticity of adaptive behaviour. In the vignettes of the Alzheimer’s patients outlined in Chapter 5, one can clearly see the perseverative and rigid thought patterns that permeate their present experiences. Netter (1991) elaborates on the aspect of rigidity but employs the notion of reflexivity to indicate aspects of cognitive

flexibility. He suggests that low dopamine levels may reduce the capability of individuals to alter their strategies for adapting to changing stimuli. He concludes that the dimensions of flexibility and adaptability may have robust associations with the functioning of the dopamine system. Similarly, the acetylcholine system influences cognitive functions and the use of adaptive strategies for negotiating environmental stressors.

In an intact cortex, serotonin usually mediates responses to fearful and aversive situations. An Alzheimer's patient with a particular premorbid profile (low activity and high perseverative disposition) perceives neutral stimuli as novel, and they are likely to react adversely to this. In situations of stress, serotonin mediates fear responses and sensitivity to punishment signals. As an identifier of aversive stimuli, during stress situations, serotonin reduces activity and preserves energy through behaviours resembling apathetic immobility mixed with fearfulness and hyper-vigilance with a negative accompanying tonus (Zuckerman et al., 1984).

Support for the neurochemical correlate of activity is enhanced by the results, which show that this occurs in the absence of gross cognitive deficit, which signifies minimal structural damage to the cortex. The existence of depressive features in the absence of severe cognitive deterioration implies that the complicated emotions and abstract thought processes, which are required to experience some of these symptoms, are dysfunctional in the later stages because of greater brain atrophy (Burns et al., 1990c). Therefore, the results of this study, which found that depressive features in Alzheimer's disease has a negative relationship with rate of cognitive decline supports the contention that depressive symptoms may be a reactive manifestation that includes coping processes, which underscore attempts at energetic and temporal regulation of behavioural and emotional responses and therefore, aspects of temperament.

7.4.3.3 The perseverative trait and depressive symptoms

The perseverance trait is regarded as a temporal characteristic and is linked to emotion (Strelau & Zawadzki, 1995). As a temporal trait, the underlying neurophysiological mechanisms include the speed of elicitation, termination, and mechanism of neuronal interactions. The perseverance trait has two components namely recurrence and persistence. The former refers to repetitive behaviour after termination of stimulation and the latter to the maintenance of these behaviours. Perseverance is regarded as a secondary function of the nerve cells in the cortex. Secondary effects occur as long lasting states after the original content has withdrawn from the center of consciousness. Stimulation generating emotions are effective in developing secondary effects thus, there exists a strong link between perseveration and emotional components. Individuals with a dominance of secondary functions (perseverative temperament) can be described as being for a long time under the influence of formerly acting stimuli, persistent in emotions, and ‘stuck’ on old recollections. Perseveration also alludes to lability, degree of cognitive inertia, and rigidity of habits. The components of perseveration include ideational, behavioural, and emotional perseveration.

A person with a perseverative temperament cannot easily unhook from emotional states and this implies a rigidity of habits and an inflexible disposition. In the absence of gross cognitive impairment, perseverative dispositions may accentuate the depressive features that are manifested and together with low activity trait and high sensory sensitivity, a person experiencing changes in the synaptic functions may still maintain the use of old learning and coping strategies and enhance the anticipatory stress that a changing environment is delivering. The results also show that high perseverative tendency can result in behavioural dysregulation as well. This would likely be the mediatory effects of

dopamine, which if disrupted can cause a rigidity in activity behaviour, which is evident when Alzheimer's patients tend to repeat certain motor behaviours and appear to have problems with initiation, volition and termination of repetitive motor behaviour.

7.4.4 Summary

Whatever the probable explanations (psychological or neurobiological) the study highlights the complex relationship between premorbid disposition and noncognitive pathology in Alzheimer's disease and the interaction between the neurobiological correlates of the disease and the behavioural/psychological manifestations that arise from the interaction of predisposition, disease, and symptoms.

7.5 Conclusion

The increase in the volume of studies related to noncognitive features attests to their wider recognition as an important concomitant of Alzheimer's disease and a contributing factor to the psychological distress and burnout among caregivers and nurses (Heyns, Venter, Esterhuyse, Bam, & Odendaal, 2003; Welleford et al., 1995). There is still debate, however, as to whether it is a core symptom of the disease or a secondary correlate of cognitive impairment. Notwithstanding the current debates on the cognitive-noncognitive relationship in Alzheimer's disease, research has shown that noncognitive sequelae are the primary motivators underlying the institutionalization of patients because of their adverse consequences on the psychological morbidity of caregivers. A derivative of the challenging consequences of the noncognitive manifestations is a wealth of new research on the correlates of these manifestations.

Utilising a national sample of Alzheimer's patients, this study attempted to elucidate the role of premorbid temperament in the genesis of noncognitive disturbances. The subjects were 63 community-dwelling patients with probable Alzheimer's disease. They were required to reside in the community with a reliable primary caregiver who agreed to act as informant, to have no history of neurological or psychological diseases or disorders, and be younger than 80, and not on any regimented experimental drug trials. The results of this study indicate that the relationship between premorbid temperament and noncognitive symptoms is multidimensional. For example, cognitively impaired Alzheimer's disease patients with a proclivity for aggressive behaviours and inappropriate behaviours but lower depressive profiles, were premorbidly emotionally reactive and sensitive to sensory stimuli, whereas Alzheimer's patients who tend to manifest with depressive and dysregulatory behaviour displayed a premorbid perseverative temperament with low neuronal sensory thresholds and a tendency to maintain low stimulative levels (low activity). Moreover, specific neuropsychiatric features such as depression has premorbid correlates, but patient characteristics such as cognitive status mediate the influence of the correlates. These findings underscore the necessity for future research that deals with the specific mechanisms of noncognitive manifestations. In this manner, one can anticipate behavioural patterns and caregiver reactivity thereby enhancing the adaptive potential of the caregiver-patient relationship during the disease course.

The relationship between premorbid temperament and noncognitive symptoms is complex at a biological and psychological (functional) level. A reflective look at the results yield insight into our constructions of meaning attached to aging and the neurologically impaired aged population. When we consider this group of people our understanding of both biological and behavioural processes is likely to be couched in terms denoting a loss of complexity. Although on a molecular biological level the latter holds true on a

psychological level one is wont to concur with Vaillancourt and Newell's (2002) idea that the relationship between aging and complexity can reflect a bi-directional alteration in complexity that is determined by the nature of the change requirements.

In a psychological sense, hallucinations and wandering behaviour can reflect an increase in behavioural complexity that is underscored by an adaptive need to communicate or compensate for a lack of environmental stimulation. Apathetic behaviour on the other hand, could reflect a decrease in complexity brought about by connectivity and coupling anomalies indicative of the disease processes. A question that arises from this idea of complexity is whether symptoms that are related to premorbid temperament have a specific directional profile (conceptualized as more or less complex) compared to symptoms that are not related to premorbid disposition. In other words, are their specific clusters of symptoms that are direct concomitants of the disease process and specific clusters that are predicted through the disease course by premorbid disposition? Studies combining electrophysiological and psychological angles would likely yield some insight into these questions.

The importance of addressing these questions is linked to the idea that interventions for challenging behaviour should not necessarily lean towards the elimination of symptoms especially if some symptoms reflect an increase in complexity and an attempt at adaptation in the light of a debilitating brain disease. Perhaps a nursing home resident who manifests with frequent hallucinations is attempting to stave off feelings of fragmentation and maintain a semblance of continuity, which enhances their sense of belonging or familiarity (Lazarus et al., 1996). The results reported by Kolanowski et al. (1997), which show that Alzheimer's patients continue to utilize patterns of adaptation that served them premorbidly, support the contention that interventions need to incorporate the

idea that noncognitive symptoms are not a homogeneous cluster that require alleviation via pharmacological intervention.

In sum the results of this study:

1. Provides empirical evidence for the prevalence of neuropsychiatric and neurobehavioural symptoms in a group of Alzheimer's patients and indicates that symptoms are heterogeneous in terms of prevalence and association with patient characteristics.
2. Supports a multidimensional relationship between premorbid temperament and noncognitive symptoms.
3. Suggests that the relationship between premorbid temperament and noncognitive symptoms could more likely reflect a premorbid diathesis for these symptoms than a retrospective bias imposed by caregiver informants.
4. Supports a relationship between specific premorbid symptoms and patient characteristics such as cognitive status thus, implying that temperament influences may be causal in the early stages of the disease but their effects may be mitigated by the neurological potency of the disease in the later stages.

7.6 Limitations

The following limitations pertain to the study:

- Although the researcher set out to capture a large sample, after stringent exclusion criteria a relatively small sample formed part of the target group that was involved in this study.

- The target group was confined to caregivers of Alzheimer's patients and not to patients with other dementias and neurological conditions (Parkinson's).
- Due to the nature of the study, a convenience sample was used instead of a random sample and the community-dwelling nature of the sample limits the generalisation of results to patients at care-facilities.
- The sample is comprised mainly of english and afrikaans speaking individuals, and is therefore, not representative of all groups with Alzheimer's disease.
- Interaction between caregiver characteristics (temperament, gender, status), patient characteristics, and noncognitive manifestations was not addressed in this study. The inclusion of this dynamic context allows for the avoidance of the reductionistic fallacy that all challenging noncognitive symptoms arise from underlying pathology.
- This study quantified the occurrence of noncognitive symptoms, but did not contextualise these changes as meaningful to caregivers. The reactivity of caregivers to specific symptoms is an important factor when considering therapeutic interventions. The researcher has initiated a follow-up study that addresses the impact of the temperament-symptom relationship on caregivers and their experiential punctuation of the changes they encounter and endure during the disease process.
- Due to the nature of the study neurological data was not included as a diagnostic aid, and informants provided the relevant information.

7.7 Recommendations

The following recommendations are pertinent to future studies:

- Neuropsychiatric and neurobehavioural symptoms are not a homogenous cluster. In this light, research dealing with specific noncognitive manifestations may contribute more substantially to the correlates, both psychological and neurobiological, of specific manifestations.
- Future studies should include a longitudinal assessment because of the curvilinear nature of noncognitive manifestations. This would render valuable data on the stability of premorbid contributions to the occurrence of noncognitive symptoms and the specific disease mechanisms that underlie emergent pathologic behaviour.
- In terms of instrumentation, a more comprehensive battery for cognitive assessment should be used so that a more specific information can be attained and used to understand the aetiology of noncognitive manifestations.
- To enhance the robustness of the relationship between premorbid temperament and noncognitive occurrences in Alzheimer's disease, comparisons to normal age-matched controls need to be made. In this way, one can determine if the relationship is unique to Alzheimer's dementia or common in the process of normal aging.
- Studies on the salutogenic properties of temperament should complement studies on predisposition to pathology. This would create valuable insights into the topography of temperament traits and their role as antagonists or agonists for pathologic behaviour.
- Interactions between caregivers and patients form a key component of the relationship, considering the progressive nature of the disease. Furthermore,

temperament influences the way in which caregivers interact and these nuances are relayed into the post-disease relationship. The interaction between the disease factors, caregiver responses, and patient reactions should be considered in future studies.

- By including the latter, researchers would be able to develop tangible programmes for caregivers regarding the management of both the challenging behaviours of their wards and their own levels of stress, which are endemic to this caregiving process.
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"A student asked his guru what does the proverbial turtle rest on. The master replied that it was another giant turtle...the student pressed on: and what does that turtle rest on? The guru answered as before.

The student persisted with the same question and the guru, growing more testy with each query, responded with the same answer. When they reached the seventh turtle, the guru stopped the regress by proclaiming: and there it ends because seven is a magic number."

(Zuckerman, 1995, p. 219).

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APPENDIX A

Biographical Details

Evaluation Detail(time of contact)_____

Evaluation Date:_____

*Centre/Area code:_____

Patient No:_____.

Title of Protocol: **Neuropsychological symptoms and premorbid temperament traits in Alzheimer's**

dementia

Alzheimer's Subjects Name: _____

Age:_____

Gender: _____

Language/Race: _____

Years of education:_____

Occupation:_____

Medication Details: Type _____

Duration:_____

Has any member of your spouse's/parent/ward's family members been previously diagnosed with Alzheimer's disease? If Yes: relation to spouse's/parent/ward's.

Informants Name: _____

Relationship to Alzheimer's subject: _____

Data Checklist

INSTRUMENT	Rotation (1 st or 2 nd administration)	COMPLETION	USERBILITY
BDRS			
BRS			
TI-primary informant			
TI-secondary informant			

*e.g. area, group ID

APPENDIX B

ID (caregiver): _____

ID (patient): _____

Screening Schedule

<input type="checkbox"/>	<input checked="" type="checkbox"/>
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1. Do you live with the family member/ward who has Alzheimer's disease?

If NO, how many contact days per week do you have with the person?

2. How old is the family member? _____.

3. Has the person had any major medical/neurological/psychiatric conditions *before* the dementia?

<input checked="" type="checkbox"/>	<input type="checkbox"/>
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If Y describe: _____.

4. When did you first observe the symptoms/changes? _____(years)

5. What diagnosis was your spouse/parent/ward given? _____

6. When was this diagnosis given? _____(Year)

7. By whom: Neurologist /Psychiatrist/Neuropsychologist/GP/other

<input checked="" type="checkbox"/>	<input type="checkbox"/>
-------------------------------------	--------------------------

8. Was there a second opinion or evaluation?

If Y what was the second diagnosis: _____

By whom: Neurologist /Psychiatrist/Neuropsychologist/GP/other

How long after the first diagnosis/evaluation? -----

❖ Will you be willing to participate in this study

<input checked="" type="checkbox"/>	<input type="checkbox"/>
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