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 it 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 (Ψ) 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 ($B^{\underline{d}}$) and secondly, it is vulnerable to disease and age-related neuronal losses (B_p). The equation reflecting the above processes can be stated as:

$$\frac{\Psi \approx b}{B^{\underline{d}}, B_p}$$

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 $B^{\underline{d}}$ 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 ($B^{\underline{q}}$) 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 Lucus (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. Näsman 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; Näsman, 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 noncogntive 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

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[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 & McNaugton, 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 localisationalists 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 were 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, Wisconson 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 & Grosssberg, 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 Claasen (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

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[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, Fregioli 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 Fregioli 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 prosogagnosia. 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, Hoogendijk, 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, supranucleur 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.
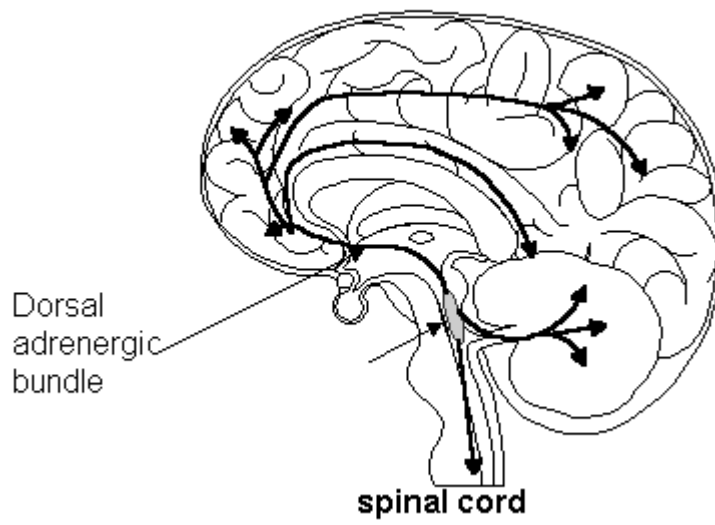
3.2.2.1.4 Underlying substrates

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 pharmacotheraphy (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 nuclues, 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

Dorsal
adrenergic
bundle

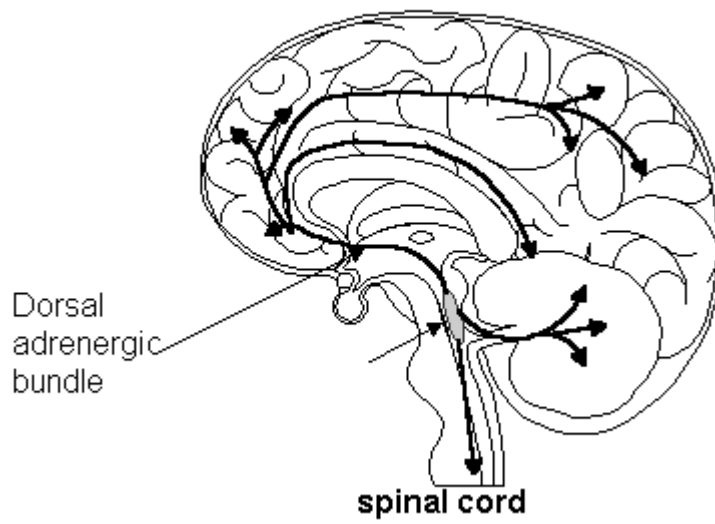spinal cord

Locus coeruleus projections

Dorsal
adrenergic
bundle

spinal cord

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

Dopaminergic projections

ventral
tegmentum

mesocortical pathway
projects to the frontal cortex

mesolimbic pathway projects
to the limbic striatum
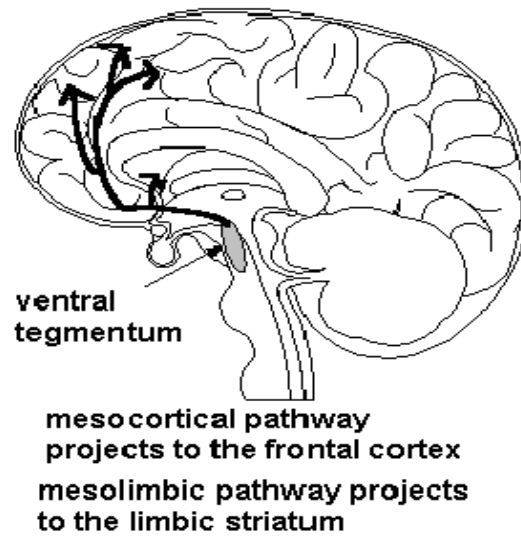
Figure 3.2-2 Dopamine pathways (Schatz & Chute, 2000)

Serotonin projections

Raphe Projects throughout the
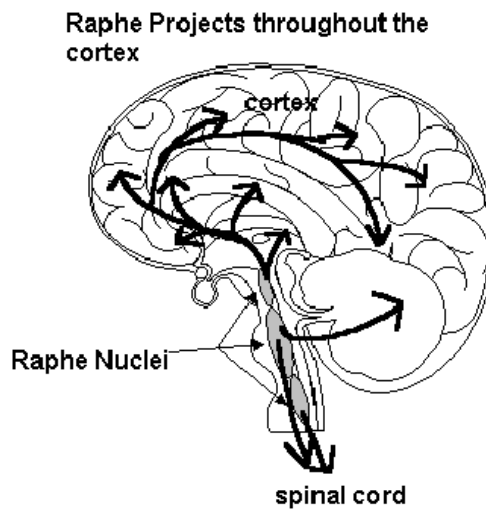cortex

cortex

Raphe Nuclei

spinal cord

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).

3.2.2.2.2 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, $\underline{p}$=0.001) and hippocampal volume (r=0.49, df=34, $\underline{p}$=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

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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 liability 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, disihibition, 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 amydala. 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.

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[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 that 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, Näsman 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 suprachiamatic 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 then 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, Ebbit, 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 that 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, it 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).

Hoogendijk 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.