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REVIEW ARTICLE

Attention and executive deficits in Alzheimer's disease
A critical review

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Summary
In this review we summarize the progress that has been made in the research on attentional and executive deficits in Alzheimer's disease. Like memory, attention is now recognized as consisting of subtypes that differ in their function and anatomical basis. We base our review upon a classification of three subtypes of attention: selective, sustained and divided. This model derives from lesion studies, animal electrophysiological recordings and functional imaging. We examine how these sub-components of attention can be reconciled with neuropsychological models of attentional control, particularly the Supervisory Attentional System and the Central Executive System of Shallice and Baddeley, respectively. We also discuss the relationship of attention to the concept of executive function. Current evidence suggests that after an initial amnesic stage in Alzheimer's disease, attention is the first non-memory domain to be affected, before deficits in language and visuospatial functions. This is consistent with the possibility that difficulties with activities of daily living, which occur in even mildly demented patients, may be related to attentional deficits. It appears that divided attention and aspects of selective attention, such as set-shifting and response selection, are particularly vulnerable while sustained attention is relatively preserved in the early stages. The phenomenon of cognitive slowing in Alzheimer's disease and normal ageing emphasizes the need to discriminate quantitative changes in attention dysfunction from qualitative changes which may be specifically related to the disease process. The neuropathological basis of these attentional deficits remains unsettled, with two competing hypotheses: spread of pathology from the medial temporal to basal forebrain structures versus corticocortical tract disconnection. Finally we discuss the difficulties of comparing evidence across studies and look at the implications for the design of future studies and future directions that may be fruitful in the research on attention in Alzheimer's disease.

Keywords: Alzheimer's disease; attention; executive function

Abbreviations: CDR = Clinical Dementia Rating Scale; CES = Central Executive System; CMRglc = cerebral metabolic rate for glucose; DRS = Dementia Rating Scale; ERP = event-related potential; MMSE = Mini-Mental State Examination; rCBF = regional cerebral blood flow; RT = reaction time; SOA = stimulus onset asynchrony; SPECT = single photon emission computed tomography; WCST = Wisconsin Card Sorting Test

Introduction
For many years Alzheimer's disease was considered as a dementia characterized by global cognitive impairment, and indeed little distinction was made between types of dementia. Early studies often referred to 'senile dementia' and probably included patients with various aetiologies, including multi-infarct dementia, cortical Lewy body disease and fronto-temporal dementia as well as Alzheimer's disease. Since the cognitive profile of Alzheimer's disease has been examined in more detail, it has come to be accepted that the initial deficit manifests as an amnesic syndrome which may progress very gradually for several years before impairment in other cognitive domains, such as language, semantic memory and visuospatial function, becomes apparent (McKhann *et al.*, 1984; Grady *et al.*, 1988; Welsh *et al.*, 1992; Hodges and

Patterson, 1995). Investigation of the profile of the initial memory loss in Alzheimer's disease has been based on the recognition that memory is not a unified concept (Tulving, 1972), and it is now accepted that different subtypes of memory may be differentially impaired in different disease states.

Although the role of attention has often been seen in the past as a general and non-specific factor affecting performance, converging lines of evidence from neuroscience suggest that the attention system, like memory, can be divided into separate subsystems performing separate but interrelated functions which interact with other domain-specific systems. From evidence of the anatomical and functional separability of these systems it has been suggested that attention is carried out by a network of anatomical areas; attention is therefore neither the property of a single centre nor a function of the brain as a whole (Posner and Petersen, 1990).

Clinical observation of Alzheimer's disease patients reveals that they often have great difficulty in performing everyday tasks at a relatively early stage in the disease when formal testing of non-memory functions, such as language, praxis and visuospatial abilities, show little or no deficit. They are often described by carers as being unable to concentrate, being easily distractible, or getting into a muddle when confronted by tasks that were previously easily performed. These observations have led to speculation that Alzheimer's disease patients may have attentional deficits that underlie these difficulties with everyday activities and that these deficits may be an early feature of the disease. The progress in neuroscience in fractionating attentional processes into separate functions (such as orienting, shifting attention, response selection, divided attention, vigilance, etc.) has enabled researchers to investigate attention in Alzheimer's disease in a more systematic fashion by attempting to separate a cognitive operation into its component parts.

The following questions arise. Is the current characterization of the neuropsychological profile of early Alzheimer's disease as a pure amnesia an accurate one or is the amnesia invariably accompanied by impairment of attention at the earliest stages? If not, then what is the relation of attentional deficits to other cognitive modules such as semantic memory, language and visuospatial functions? Are all types of attention affected in Alzheimer's disease or are some preserved until later in the disease whilst others are profoundly disrupted early on? What do the particular deficits in attention tell us about the neural systems that are affected by the disease process? We shall try to answer these questions by reviewing the growing literature on attention in Alzheimer's disease.

A synthesis of animal studies, human neuropsychology, neuropathology and neuroimaging has led to the identification of the neural substrates for subtypes of memory, particularly in identifying the hippocampal complex as a crucial area in the encoding of new memories (Squire, 1992). The pathology of Alzheimer's disease is known to affect the medial temporal structures, including the hippocampus, in the earliest stages of the disease (Braak and Braak, 1991), and this is in agreement with the initial cognitive deficits seen in the formation of new episodic memories. We shall also consider theories of how the disease process, which then spreads to involve the basal forebrain and the neocortex proper, can be reconciled with the pattern of attentional impairment seen in Alzheimer's disease.

Neurological models of attention such as that proposed by Posner and Petersen (1990) have differentiated separate subcomponents of attention, such as sustained attention and selective attention, which can be defined functionally and, to some extent, anatomically. More psychological models of attention have been proposed by Norman and Shallice (1986), Hasher and Zacks (1979), Shiffrin and Schneider (1977) and Baddeley (1986), who explore the neuropsychological processes involved in attentional control (for review, see Spinnler, 1991). Since there is no wholly satisfactory model of attention, we have combined the above approaches in order to structure the review and have divided attention into the broad categories of (i) selective attention and shifting, (ii) sustained attention and (iii) divided attention (Table 1).

One cognitive area which overlaps with attention is so called 'executive function'. Executive functions refer to the mental activity that is involved in the planning, initiation and regulation of behaviour (Lezak, 1983). There is also a growing body of evidence that deficits in executive functioning form an important part of the neuropsychological dysfunction in Alzheimer's disease and may relate particularly to some of the problems patients experience in activities of daily living (Patterson *et al.*, 1996). Many neuropsychological tests that purport to test executive functioning are also interchangeably used as tests of attention. We attempt, therefore, to examine the relationship between these two aspects of cognition, particularly with reference to their separability or codependence.

Methods of evaluating attention

The four main investigative tools used by neuropsychologists in attentional research have been: (i) conventional neuropsychological tests, (ii) computer-based information processing tasks, (iii) functional imaging [PET, single photon emission computed tomography (SPECT) and functional MRI] and (iv) cognitive event-related potentials. Each of these methods has its particular advantages and disadvantages (Table 2), and a synthesis of contributions from all four will be required in order for us to move towards a more complete picture of attention.

Conventional neuropsychological tests remain popular because of their ease of administration and the existence of well-established normative data. These widely used tests are available in standardized versions and so performance can be compared across studies as well as with the performance of other cognitive domains such as semantic memory and visuospatial functions. Drawbacks include poor temporal resolution and lack of specificity; although they require

Table 1 *Characteristics and possible neural substrates of subtypes of attention*

Attentional subtype	Defining characteristics	Possible neural substrates
Selective attention	Focusing on single relevant stimulus or process at one time while ignoring irrelevant or distracting stimuli	Posterior parietal systems for orienting and shifting modulated by anterior midline and basal ganglia system for response selection
Sustained attention	Maintenance of abilities to focus attention over extended periods of time	Right-sided frontoparietal system
Divided attention	Sharing of attention by focusing on more than one relevant stimulus or process at one time	Dorsolateral prefrontal cortex and anterior cingulate gyrus

Table 2 *Relative advantages and disadvantages of methods of investigating attention in Alzheimer's disease*

Investigative method	Advantages	Disadvantages
Conventional neuropsychological tests	Ease of administration Standardized versions Links to brain regions	Lack of specificity Poor temporal resolution
Information processing tasks	Good temporal resolution Reproducible Some specificity for component parts of cognitive process	Few standardized versions
Functional imaging	Good spatial resolution	Poor temporal resolution Vulnerable to subtleties of experimental paradigm Do not transfer well to brain-damaged subjects
ERP	Good temporal resolution Differentiate sensory/cognitive/response processing	Poor spatial resolution Little application to date

attentional capacities they often rely heavily on working memory, episodic memory and low-level visuospatial abilities without teasing apart the underlying components of attention. Another problem relates to the fact that traditional pen and paper neuropsychological tests antedate current theoretical models of attention, so that there is a poor match between tests and subtypes of attention. The best use of these tests probably lies in their ability to detect and quantify, rather than qualify, attentional impairment by using a test battery approach to examine the relationships of attentional factors in comparison with other cognitive domains and their relationship to disease severity.

The technological advances of the last 10–20 years have allowed researchers to make more use of computerized tests which are reproducible and accurately timed. Such information processing tasks have much better temporal resolution (~40 ms) than traditional pen and paper neuropsychological tests and can, by careful design, narrow down the component operations of attentional function. As these tests are usually devised by individual researchers, few standardized versions are commercially available, leading to difficulty in comparing results across studies and in linking tasks to anatomical areas. One exception to this is the CANTAB (Cambridge Neuropsychological Test Automated Battery), which has been widely applied and for which there is now extensive normative data (Robbins *et al.*, 1994).

Functional imaging techniques such as PET and SPECT have been used under resting conditions to measure abnormal patterns of regional cerebral blood flow (rCBF) and cerebral metabolic rate for glucose (CMRglc) in patients with particular neuropsychological profiles, and to attempt to correlate the two (Grady *et al.*, 1988; Parasuraman *et al.*, 1992). Far fewer studies have examined rCBF or CMRglc while Alzheimer's disease patients have performed cognitive tasks. Such activation studies with PET permit the visualization of neural activity engaged in cognitive operations with good spatial resolution of the order of 1 cm, but fairly poor temporal resolution (40–100 s) when compared

with information processing tasks and event-related potentials (ERPs). While measurement of the metabolic state at rest may estimate the extent of the morphological damage, activation studies indicate the brain's reserve capacity to respond to functional tasks. The pattern of cerebral activation induced by a cognitive task is highly dependent on the subtleties of the experimental paradigm, and it is often the case that classical neuropsychological tests do not necessarily make good PET paradigms. The finding of activation seen in cortical areas of Alzheimer's disease subjects which are not activated by controls performing the same task is of great interest but requires careful interpretation as to whether there is truly a reallocation of cortical areas to perform a task or whether this represents compensation for neuropathological changes which have occurred in the brain region activated in controls (Becker *et al.*, 1996).

Cognitive ERPs are scalp-recorded electrophysiological responses that are related to an internal cognitive event. The early components up to 100 ms are considered to reflect 'exogenous' brain activity related to responses to physical stimulus properties, and abnormalities in this range reflect the integrity of sensory processing. Later components, such as N140, N150, P300 and N400, are presumed to reflect brain processes involved in more complex 'cognitive' operations, several of the components between 100 and 300 ms being related to attentional processes (Celesia and Brigell, 1992; Viggiano, 1996). The main theoretical advantage of ERPs lie in their excellent temporal resolution and their ability to differentiate between sensory and cognitive processing. Spatial resolution, however, remains poor when compared with functional imaging. As the timing of ERPs does not include the output stages of cognitive processes that are incorporated into reaction times (RTs), these two measures may be used in conjunction in the same test paradigm to examine whether deficits are at the cognitive processing stages or reflect difficulties in response selection and execution. The early promise of ERPs as an investigative tool has yet to be realized, and few studies have been conducted in degenerative brain diseases.

Selective attention and attentional shifting in Alzheimer's disease

Selective attention refers to the ability to screen out irrelevant stimuli. Although many studies and reviews of attention in Alzheimer's disease refer to 'selective attention', the term in itself is rather an arbitrary grouping for many component processes or behaviours that can range from the earliest attentional modulation of visual stimuli in the prestriate cortex to the control of the orienting and shifting of spatial attention and to the detection, filtering, inhibition and selection of appropriate targets from distractors. The early attentional modulation to the colour, form and motion of visual stimuli in separate prestriate areas, but not the striate cortex, has been shown by PET functional imaging (Corbetta *et al.*, 1991), and is supported by electrophysiological evidence that has demonstrated early (100 ms) amplification of neural activity in cells that are oriented to respond to selected stimuli with corresponding inhibition of activity in nearby cells that are oriented to unselected locations (Posner and Driver, 1992). Similar enhancement and inhibition of activity in relevant and neighbouring irrelevant areas have also been demonstrated in responses to tactile stimuli *in vivo* by PET imaging (Drevets *et al.*, 1995). How modulations such as those observed in the prestriate cortex are influenced by neural networks resolving competition between stimuli is a growing, stimulating, yet controversial area in neuroscience.

To examine how these neural networks may be involved in selective attention, we shall first examine evidence relating to the standard Posner model, which breaks down attention functions into component processes that are linked with specific brain areas. We shall then go on to other models of visual search in which the particular features of the target, apart from location, influence the mechanisms underlying search.

The Posner model describes a network of anterior and posterior attentional systems involved in spatial attention. Although it does not encompass object-based selection procedures, it has been widely used in Alzheimer's disease and is therefore a useful starting point from which to discuss deficits related to Alzheimer's disease. According to this model a posterior attentional network controls three separate component processes of spatial attention: (i) disengaging attention from a spatial location controlled by the posterior parietal lobe; (ii) shifting attention to a target at a new spatial location dependent on the superior colliculus; and (iii) engagement of attention on a new target dependent on the thalamus (Posner and Petersen, 1990).

Spatial cueing tasks have often been used to investigate the disengagement of attention. In such a task (Posner, 1980) a target stimulus to be detected or identified appears either to the left or the right of a central fixation point. The stimulus is preceded by a cue which may be valid (on the same side as the target), invalid (contralateral to the target) or neutral (central). The RT measurement of the disengagement of attention from an invalid cue to a target can be calculated as RT costs (RT to target after an invalid cue minus RT to target after a neutral cue) or as RT costs plus benefits (RT to target after an invalid cue minus RT to target after a valid cue). The role of the posterior parietal lobes in the disengaging of attention is suggested by studies of primates and humans with parietal lesions, which have shown slower responses when attention is disengaged from an invalid cue ipsilateral to the lesion to a contralateral target than when the cue is valid or when the target is ipsilateral to the lesion (Posner and Cohen, 1984; Lawler and Cowey, 1987; Petersen *et al.*, 1989).

Parasuraman *et al.* (1992) used a spatial cueing task, based on the Posner paradigm described above, to demonstrate that Alzheimer's disease subjects could use a valid cue to shift visuospatial attention to an expected location as effectively as controls, i.e. attentional focusing, or engaging of attention,

by spatial location appeared to be intact. Responses to invalid cues, however, showed higher costs and costs plus benefits, a finding also reported by Oken *et al*. (1994) using a similar paradigm. Studies using target detection rather than discrimination have failed to show this deficit in disengagement (Caffara *et al*., 1997; Faust and Balota, 1997), suggesting that a specific impairment in disengaging attention in mild to moderate Alzheimer's disease is dependent on the nature or degree of the engagement required.

In the Posner model of visual orienting, the actual shift of visual attention from one location to another is associated with the superior colliculus. It is important that both this shift of attention from location to location, and the shifting of attention between or within objects, should be distinguished from the set-shifting of attention referred to in studies where subjects have to shift or switch a pattern of response, or mental set. The possible neural correlates of this higher-order set-shifting, typically seen in tasks such as the Wisconsin Card Sorting Test (WCST), is dealt with in more detail in the section headed Executive functioning in Alzheimer's disease (see below). Studies using inhibition of return paradigms on subjects with superior colliculus lesions, including subjects with progressive supranuclear palsy, known to affect the midbrain and superior colliculus, have suggested a role for this brain area in the shifting of visual attention (Posner *et al.*, 1982, 1985; Sprague, 1991). In this paradigm the shift of attention is studied using an adaptation of the standard Posner paradigm in which a second cue appears between the first cue and the target. Normal subjects are then slower to respond to targets at the originally cued site than to targets appearing at a novel location. This phenomenon, termed inhibition of return, is thought to be an adaptation which prevents the repeated searching of already searched locations. Subjects with lesions of the superior colliculus show no inhibition of return (Posner *et al.*, 1985), but Faust and Balota (1997) have shown that both Alzheimer's disease subjects and elderly controls perform normally on such tasks, suggesting normal inhibition of return.

The evidence supporting the role of the thalamus in the engagement or filtering of spatial attention would seem to be inconclusive. Unilateral lesions and deactivation of the pulvinar nucleus produce slowed reaction times to targets in the contralateral field, especially if paired with a distractor in the ipsilateral field (Petersen *et al.*, 1987; Rafal and Posner, 1987; Robinson and Petersen, 1992). It has been postulated that the thalamus acts as a gating mechanism to filter out unwanted target locations, following a PET study demonstrating increased activation in the pulvinar contralateral to a visual field containing a single target amongst multiple distractors when the opposite visual field contained only a single target (La Berge and Buchsbaum, 1990). It is unclear at present whether the thalamus acts as a spatial filtering gate for inputs between the parietal and extrastriate cortex or is acting to modulate or relay the attentional bias given to targets and distractors in opposite visual fields. Although some studies of Alzheimer's disease subjects have demonstrated intact engagement of attention (Parasuraman *et al.*, 1992; Oken *et al.*, 1994; Faust and Balota, 1997) using variations on the Posner paradigm, there is little to support the linking of these functions to thalamic integrity.

The findings of the investigation of the orienting of visual attention with the Posner paradigm, described above, do not account for the more everyday occurrence when a visual target must be selected on the basis of feature or location, or a combination of both, from multiple distractors in the same field of view. Early visual search experiments revealed that the time taken to detect a target with a unique feature, such as a red shape in an array of blue distractors, producing the phenomenon of 'pop-out', is independent of the number of non-targets, and was thought to proceed in parallel. If the target identification is based upon a conjunction of features, known as conjunction search, such as a red circle amongst blue circles and red squares, then the time taken increases linearly with the number of distractors. This led researchers to distinguish between parallel search and serial models of visual search (Treisman and Gelade, 1980), where an 'attentional spotlight' was moved in a serial and rapid fashion from item to item until a target was found. After many reports of conjunction search being unaffected by the number of distractors, several modifications of the serial search hypothesis have been proposed to explain pop-out effects with targets defined by a conjunction of multiple features (Wolfe *et al.*, 1989; Treisman and Sato, 1990). Given that there is some evidence for early involvement of the parietal cortex in Alzheimer's disease (Haxby *et al.*, 1986; Grady *et al.*, 1988; Kumar *et al.*, 1991), it might be expected that Alzheimer's disease subjects would show disproportionately greater deficits on conjunction search than feature search, especially after Corbetta *et al*. (1995) demonstrated activation of the right superior parietal cortex during conjunction but not feature search. The evidence to date would suggest that single-feature search appears to be intact in Alzheimer's disease (Nebes and Brady, 1989; Greenwood *et al.*, 1997), conjunction search producing a similar increase in RTs with number of distractors, as is seen in healthy young and old adults (Greenwood *et al.*, 1997).

The mechanism by which attention moves over the visual field has been a subject of continued controversy; recent experimental data confound existing models and new or hybrid models are under investigation (Grossberg *et al.*, 1994; Desimone and Duncan, 1995; La Berge *et al.*, 1997).

Evidence from a combined space and object search paradigm (Egly *et al.*, 1994) suggests that left parietal lobe lesions may cause problems in disengaging from and shifting attention between objects, in contrast to the spatial shifting deficits found with right parietal lobe damage. Support for hemispheric dissociation of object- and spatial-based attention has come from a study of Alzheimer's disease subjects [average Mini-Mental State Examination (MMSE) score = 20.6; Dementia Rating Scale (DRS) = 111] who were tested on a version of the Egly paradigm and demonstrated increased

RT costs plus benefits for both the shifting of attention between spatial locations and between objects. A subgroup of these subjects underwent SPECT scanning, which showed significant relationships between left spatial reaction time costs and right superior parietal hypoperfusion and between right object reaction time costs and left inferior parietal lobe hypoperfusion (Buck *et al.*, 1997). Patients with bilateral parietal lesions, caused by stroke or degenerative disease such as Alzheimer's disease, may show simultanagnosia as part of a triad of visual symptoms known as Balint's syndrome. Alzheimer's disease subjects with simultanagnosia, which has both object-based and spatially based attentional deficits, have difficulty in identifying more than one object simultaneously, are often visually stuck on local features, and are unable to synthesize a coherent whole from segments of a visual scene (Rizzo and Hurtig, 1987; Hof *et al.*, 1990; Coslett and Saffran, 1991; Coslett *et al.*, 1995). Alzheimer's disease is also known to cause problems with tests involving the identification of overlapping line drawings, such as Gottschaldt's Hidden Figures Test (Capitani *et al.*, 1988). In an elegant study, Filoteo *et al.* (1992) used global-local stimuli to investigate the shifting of attention across levels of perceptual organization within the same stimulus. Here the shifting of attention is not from location to location but from one aspect of a stimulus to another aspect of the same stimulus. Thus, one stimulus would consist of a large number 1 composed of smaller 4s and the next stimulus may consist of small 2s made into the shape of a large number 3, etc. They found that Alzheimer's disease subjects (mean DRS score = 116) had particular difficulty when they had to shift the focus of attention between global-local levels (e.g. attending to the value of the small numbers within a figure on one stimulus and attending to the value of the large number of the figure on the next stimulus).

On a less experimental basis, timed tasks of selective cancellation of digits, letters or patterns have often been used as clinical tasks of selective attention. In a typical paradigm, subjects are asked to cross out all the 2s, or all the 2s and 4s, on a sheet of randomly ordered single digits. Their advantages lie in ease of administration, the relatively low demand placed on other cognitive abilities, and the requirement of the subject to monitor speed/accuracy trade-off due to the time constraint usually used in these tasks. Della Sala *et al.* (1992) have developed a timed digit cancellation test which discriminates between controls and Alzheimer's disease patients. Their error analysis led them to postulate that the deficit in the Alzheimer's disease subjects was one of defective or 'passive' scanning in which subjects were 'looking but not seeing', and of slowness in making a discriminating decision. Unfortunately there was no analysis of performance in relation to dementia severity. Their data suggest that the sensitivity of the test may be insufficient to discriminate those with mild dementia, since 24% of their patients showed little or no impairment. Error analysis on another cancellation test of symbols suggested that the quantity of distractors in an array was of more critical importance than their variety (Foldi *et al.*, 1992). Rather unusually, this task was performed with no time limit and so the results take no account of speed–accuracy trade-off.

It has been suggested that anatomically distinct areas, probably comprising an anterior attentional network involving the basal ganglia and anterior cingulate gyrus, aid in the detection and discrimination of multiple targets; by the selection of appropriate responses these regions are able to modulate the more posterior parietal lobe systems which orient to, disengage from and shift to stimuli (Pardo *et al.*, 1990; Posner and Driver, 1992).

Recent PET studies using the Stroop paradigm have suggested that the anterior cingulate gyrus is consistently activated and hence may be implicated as a critical substrate for the processes of response selection and response inhibition (Pardo *et al.*, 1990; Bench *et al.*, 1993). Many versions of the Stroop test have been used, but the classical paradigm is a measure of the ability to resolve the conflict between two competing response tendencies when the subject is required to replace the more automatic response of reading with the more effortful response of colour-naming. The cognitive process of response inhibition which is seen in the Stroop paradigm is an example of the role which may be played by the so-called 'supervisory attentional system' proposed by Norman and Shallice (1986) as a neuropsychological model of attention. In this hierarchical model the first or lower level allows the running of well-rehearsed 'automatic' programmes of thought or action. These can be modulated or supervised by the higher-level device, which can, by effortful intervention, change or stop ongoing, more automatic, activities allowing greater cognitive flexibility and the ability to perform novel activities (Norman and Shallice, 1986).

The Stroop test (MacLeod, 1991) would appear to be particularly sensitive to even minimally demented Alzheimer's disease patients (Grady *et al.*, 1988; Fisher *et al.*, 1990; Haxby *et al.*, 1990; Spieler *et al.*, 1996). Given the apparent sensitivity of this task in Alzheimer's disease subjects, it is unclear whether the difficulty that Alzheimer's disease subjects have with this paradigm reflects the complexity and inherent difficulty of the task or a specific defect in either response selection or response inhibition.

To reach any conclusions regarding the staging of selective attention deficits in Alzheimer's disease requires comparison across different studies using different tasks. Unfortunately, many studies fail to subdivide Alzheimer's disease subjects into groups of different disease severity or to use standard severity rating scales.

In summary, current evidence points to an early defect in selective attention in Alzheimer's disease, sparing the focusing of attention but predominantly affecting the ability of patients to disengage and shift their attention from one stimulus to another whether this shift is by stimulus location or by feature within the same stimulus. The differential performance of Alzheimer's disease subjects relative to controls on detection and discrimination paradigms may reflect impaired modulation by top-down processes necessary

for inhibition of competing and conflicting responses. It would seem that facilitatory selective functions are preserved but Alzheimer's disease subjects are more prone to the effects of interference from distractors due to impaired inhibitory mechanisms. The issues of whether the deficit in selective attention is universally present in the early stages of Alzheimer's disease and the temporal relationship between amnesic and attentional deficits remain to be clarified.

Sustained attention and vigilance in Alzheimer's disease

Sustained attention or vigilance may be defined as the ability to focus attention on a task over unbroken periods of time (Wilkins *et al.*, 1987; Parasuraman and Haxby, 1993) and is most frequently measured by the speed and accuracy of detecting infrequent and unpredictable targets among more frequent non-targets. Arousal is the state needed to remain vigilant, and measures of this, such as skin conductance, change according to whether a subject is performing a task or not. Alertness refers to the degree of receptivity to external stimuli. Fluctuations in alertness are usually classified as either phasic or tonic (Posner, 1978), phasic changes occurring rapidly and typically being under voluntary control, while tonic changes occur much more slowly, most often involuntarily, and are associated with long periods performing a repetitive task (e.g. a vigilance task). Even in normal subjects, sensitivity, which refers to the subject's ability to distinguish between targets and non-targets, declines over time, and this can be manipulated in tests by degrading the stimuli (Parasuraman, 1985).

Recent functional imaging studies using PET scanning or functional MRI have suggested a predominantly right-sided frontoparietal network for sustained attention, functionally and anatomically separate from that involved in selective attention, and activation of the prefrontal cortex has been demonstrated in vigilance tasks using visual, somatosensory and auditory tasks (Cohen *et al.*, 1988; Pardo *et al.*, 1991; Coull *et al.*, 1996; Lewin *et al.*, 1996).

Clinical observation of Alzheimer's disease patients in everyday situations suggests that there are problems in maintaining attention whilst performing tasks fairly early in the course of the disease, and one may expect deficits on measures of sustained attention. The majority of studies have used variations of the Continuous Performance Test (Rosvold *et al.*, 1956), in which the targets are letters appearing infrequently and randomly in a series of non-target letters. Most, but not all, of the earlier studies in Alzheimer's disease, although difficult to compare, tended to show unimpaired sustained attention in the subjects with milder Alzheimer's disease. Problems with sustained attention tasks that researchers have had to overcome include ceiling effects in normal control populations, confounding effects of the memory components of tests, short duration of testing, and measurement of vigilance change over time on the test (Alexander, 1973; Sahakian *et al.*, 1989; Lines *et al.*, 1991; Jones *et al.*, 1992).

Longer duration studies by Nebes and Brady (1993) and Brazzelli *et al.* (1994), which included analysis of the vigilance decrement over time, have shown somewhat conflicting results. The Nebes and Brady cohort of Alzheimer's disease patients (average MMSE score = 20.5, DRS score = 118) performed an 18-min self-paced task in which the subjects had to make a response to every stimulus. Both the Alzheimer's disease patients and the controls took longer to respond towards the end of the test, and although Alzheimer's disease patients were slower than controls in all sections of the test, this difference did not increase over time on the task. The patients examined by Brazzelli on a 45-min high event-rate 'Jump Clock Test' showed a similar trend for reaction time, but there was evidence that Alzheimer's disease patients had more difficulty in accurately discriminating targets from non-targets (sensitivity decrement) as time on the task increased.

In summary, compared with the wealth of data on selective attention and attention-switching, sustained attention has been investigated relatively little. The limited evidence to date suggests that, at least in the milder stages of disease, sustained attention remains intact in terms of the same degree of decline in RT performance seen in normal controls, but Alzheimer's disease subjects possibly experience greater difficulty with target discrimination. The differing results of studies of sustained attention indicate that careful consideration should be given to task duration and the nature of response measures such as accuracy and RT. Although there are exceptions (Jones *et al.*, 1992), a feature that again is often lacking in these studies is a comparison of subgroups of Alzheimer's disease subjects with differing degrees of dementia severity in order to assess when deficits in sustained attention occur in relation to memory, non-memory domains and other aspects of attentional functioning.

Executive functioning in Alzheimer's disease

Despite the growing interest and literature on executive functions, a consensus on its meaning remains elusive. For the purposes of this review we refer to executive functions as those higher-order cognitive capabilities that are called upon in order to formulate new plans of action and to select, schedule and monitor appropriate sequences of action. It thus includes many stages by which goal-directed behaviour is manifested. First, the subject must appreciate the meaning of that goal and form an intention to fulfil it. The problems inherent in the task must be assessed and plans made to overcome these. The plan must then be initiated, with continual monitoring of the progress made towards this goal, and if necessary the subject must show sufficient flexibility to change strategy and correct mistakes if the goal is not being achieved. The subject must finally be able to distinguish when the goal has been reached and to judge the effect of

his actions relative to the original goal before finally terminating the activity.

Disorders of executive functioning and attention have been linked to frontal lobe damage for well over 100 years. Patients such as Phineas Gage, who survived after an iron bar was propelled through his frontal lobes in a mining accident (Harlow, 1868), showed behavioural disturbances now accepted as being typical of a dysexecutive syndrome. Unsurprisingly, but unfortunately, the concepts of executive functions and frontal lobe functions have become so inextricably linked that the terms are often used interchangeably to the extent that tasks such as the WCST (Milner, 1963; Nelson, 1976) were known as 'frontal lobe tests' for many years. More recent evidence showing that many more brain areas are involved in performing this task suggests that this claim no longer holds strictly true (Anderson *et al.*, 1991; Reitan and Wolfson, 1994; Berman *et al.*, 1995) and demonstrates the importance of making a distinction between the anatomically descriptive term 'frontal lobe function' and the more preferable functional term 'executive function' when describing performance on tests. The mass of lesion studies which link deficits in executive function to damage in the frontal lobes (Milner, 1963; Luria, 1966; Nelson, 1976; Stuss and Benson, 1984; Neary *et al.*, 1988; Stuss *et al.*, 1994), also supported by functional imaging (Berman *et al.*, 1995; Baker *et al.*, 1996; Konishi *et al.*, 1998), means that a discussion of one necessarily entails a discussion of the other.

Everyday tasks that intuitively appear to rely upon executive functions (such as choosing the appropriate clothes to wear, planning and cooking a meal, travelling to a new location, or a shopping trip) are known to cause problems for demented patients even at a relatively early stage of the disease. But only recently has evidence begun to emerge that executive deficits are actually present in early Alzheimer's disease.

Although in theoretical terms it may be invalid, in practical terms it is worthwhile at this stage to attempt to distinguish those tests which are primarily tests of attention, those that are primarily tests of executive function, and those that require both attention and executive function. Tests of attention differ from tests of executive function in that the goal is specified and exact instructions are given, including information on when to begin, how to proceed and when to finish. The most general property of tests of executive function is that they require problem-solving. Aspects of problem-solving such as planning, monitoring and adapting strategies clearly require a degree of attention, but other components, such as judgement, depend upon facilities inherent in executive functioning alone. While the identification of subcomponents of executive function and the development of tests that address these subcomponents specifically is in its infancy it is possible to identify some widely used tests that tap certain aspects to a greater degree (Patterson *et al.*, 1996). The Porteus Maze Test requires foresight and planning, the Cognitive Estimation Test (Shallice and Evans, 1978) places demands on reasoning and self-monitoring, the Tower of London task tests planning abilities and visuospatial working memory (Shallice, 1982), the Trail-Making Test (Reitan, 1958) requires attentional tracking in part A and concurrent manipulation of information in part B, and the WCST emphasizes the need for a form of concurrent manipulation in the attention-demanding sense of set-shifting as well as the executive function of problem-solving. By contrast, conventional neuropsychological tasks such as tone-counting, letter-cancellation, continuous performance tests and the Stroop test place relatively little demand on executive function and can probably be considered tests of attention despite the fact that, when compared with more theoretically devised information-processing tasks, they have questionable ability to parse the component operations of attention. One type of task that has been variously allocated to either attentional or executive functioning is the dual-task paradigm. This will be discussed in more detail below.

Grady *et al.* (1988) performed one of the few longitudinal studies in Alzheimer's disease and used tests such as the Porteus Maze Test, Trail-Making Test, part B and Ravens Progressive Matrices, which were referred to as 'tests of attention and abstract reasoning' but which tap many aspects of executive functioning. Deficits in these tests were manifested after episodic memory impairment but before visuospatial and language dysfunction. The same pattern was seen by Reid *et al.* (1996), Lafleche and Albert (1995) and Binetti *et al.* (1996) in cross-sectional studies. Lafleche and Albert attempted to divide their tests of executive function into three broad areas that they termed 'concurrent manipulation of information', 'cue-directed attention' and 'concept evaluation'. Their results suggested that it was on the tasks of concurrent manipulation of information that the early Alzheimer's disease patients showed the greatest deficit, and that although they were slower than controls on the single cue-directed attentional task this difference did not reach significance.

Thus, it would seem from these studies that deficits in executive functioning generally occur as the disease progresses from the initial amnesic stage, and that these deficits occur before impairment in language and visuospatial tasks and mainly involve operations that require the concurrent manipulation of information. There has been increasing recognition of the heterogeneity of the cognitive profile in Alzheimer's disease, and cases presenting with predominant visual symptoms (Hof *et al.*, 1990; Levine *et al.*, 1993; Victoroff *et al.*, 1994), a biparietal syndrome (Ross *et al.*, 1996) or progressive language impairment (Green *et al.*, 1990; Greene *et al.*, 1996) have been found to have confirmed Alzheimer's disease pathology. Subjects have also been found with predominant executive deficits combined with relatively preserved episodic memory functions (Becker, 1988; Baddeley *et al.*, 1991*b*; Becker *et al.*, 1992), but as yet the pathological verification needed to differentiate these subjects from those with frontal lobe dementia is missing.

While this test battery approach on groups of subjects with Alzheimer's disease is useful in the identification and

quantification of executive dysfunction, a more theoretically based use of neuropsychological tests is necessary in order to isolate specific components of executive function and to relate these to specific areas within the frontal lobes.

Many neuropsychological theories and models of executive functions and their relationship to the prefrontal lobes have been proposed. Stuss and Benson (1986), using evidence from neurobehavioural studies, have proposed a division of functions into a group that includes the sequencing of behaviours and formation of mental sets associated with the dorsolateral prefrontal cortex, and another group of functions that is concerned with drive, motivation and will associated with the ventromedial prefrontal cortex. Electrophysiological studies have led some to suggest working memory as the predominant function of the prefrontal cortex (Goldman-Rakic, 1987), and some researchers have expanded models of working memory function to encompass executive capabilities (Baddeley and Della Sala, 1996). Attempts to map executive functions onto lesioned sites in the prefrontal lobes have tended to show an absence of any pattern in the tasks impaired by frontal damage. Similarly, factor analysis techniques, to look for clusters of tasks that load on a common operation, have often failed to show clear dissociations. Such difficulties may arise from the nature of executive tasks used; executive functions cannot be measured on their own and a variety of tasks necessarily employ non-executive cognitive operations, known to be linked to brain areas outside the prefrontal lobes, to complete them. Another illustration of the problems inherent in executive task design and administration is the contrast between the often unimpaired performance of frontally lesioned subjects on clinical and experimental tasks and their gross abnormalities in behaviour and decision-making in everyday situations (Eslinger and Damasio, 1985; Shallice and Burgess, 1991). Subjects with ventromedial frontal lesions can often select the appropriate response to a social dilemma when tested on forced-choice verbal problems in the laboratory, showing unimpaired social knowledge and access to this knowledge on a theoretical basis (Saver and Damasio, 1991). It is suggested that the failure of such subjects to select appropriate behaviours in a real-life situation is due to a defect in the activation of 'somatic markers'. According to the theory of Damasio *et al.* (1991), these somatic markers are activations of the autonomic nervous system tagged to specific evocative or emotionally based stimuli, measurable by skin conductance responses, which, mediated via the ventromedial cortex, are integrated with stored knowledge of social responses and conduct. Tranel *et al.* (1994) found that patients with ventromedial damage and disturbances in social conduct had impaired skin conductance responses to pictures with a high social/emotional content. It is hypothesized that the severe neurofibrillary tangle pathology found in the orbitofrontal subdivision of the ventromedial frontal cortex may contribute to the behavioural and emotional disturbance seen in Alzheimer's disease (Chu *et al.*, 1997).

The 'supervisory attention system' model for executive function proposed by Norman and Shallice (Norman and Shallice, 1986; Shallice, 1988) promoted two basic control mechanisms that determine how activities are executed. On the first, lower level, the so-called 'contention scheduling system' includes overlearned and automatic behaviours such as stopping at red lights, drinking a cup of coffee, brushing one's teeth, etc. The second, higher level, termed the 'supervisory attention system', deals with the modulation of the activities of the first level in a flexible or adaptive way, enabling these schemata to be run as new activities or stopping ongoing activity by a selection process that adds either activation or inhibition. It has been argued that, while automatic processes are available in the early stages of Alzheimer's disease, the increased allocation of attention and increased concentration usually reserved for novel tasks may be needed to perform even familiar activities (Spinnler, 1991). When such tasks increase in complexity or are run concurrently, the processing resources needed exceed those available either because of depletion or inefficient deployment. It has been shown that brain regions different from those activated by controls may be recruited by Alzheimer's disease subjects in the performance of cognitive tasks (Becker *et al.*, 1996), and these alternative brain regions have also been associated with increased task effort (Furey *et al.*, 1997). Shallice and Burgess (1996) have argued that the supervisory system can be fractionated into different subsystems which operate together to give a globally integrated function. Moreover, they suggest that these separate components of the supervisory system can be dissociated on the basis of patterns of correlation between the performance of lesioned and non-lesioned subjects on different parts of two executive tasks: the Hayling sentence completion task and the Brixton spatial anticipation test (Burgess and Shallice, 1996). Functional imaging studies using the Hayling task have failed to show any difference in the frontal areas activated by the parts of the task which were argued to dissociate (Nathaniel-James *et al.*, 1997). These tasks have yet to be used with Alzheimer's disease subjects, and although these arguments provide an interesting framework for future investigation they remain as theoretical constructs.

Some progress is being made in isolating specific aspects of executive function using computerized tasks of self-ordered working memory, planning and attentional set-shifting using large numbers of healthy controls and groups of frontally lesioned subjects (Robbins *et al.*, 1994; Robbins, 1996). The evidence for dissociations in specific components of the tasks again comes from correlational data, with functional imaging providing some evidence for these processes employing different neuroanatomical areas. PET activation studies using a version of the Tower of London task have shown activation in the lateral prefrontal cortex (Baker *et al.*, 1996), as has an analogue of the self-ordered memory task used by Robbins and colleagues (Owen *et al.*, 1996). These studies have also provided evidence for more specific localization with working memory components of tasks linked to the ventrolateral prefrontal cortex and the manipulation of information

associated with the dorsolateral prefrontal cortex, and increased activation of the rostrolateral prefrontal cortex was seen with increased planning demands on the difficult problems of the Tower of London test. A comparative study showed that 13 Alzheimer's disease subjects (average MMSE score = 20.3) were significantly worse than controls but better than a group of Huntington's disease subjects on this same computerized Tower of London test (Lange *et al.*, 1995).

Another possibly dissociable aspect of executive function is the ability to shift cognitive set. This is a process different from the shifting of attention between spatial locations and objects as described in the section headed Selective attention and attentional shifting in Alzheimer's disease (see above), and is likely to rely upon different neural networks. The classic test of cognitive set-shifting is the WCST, where, in an extradimensional shift, a pattern of response has to be changed by the shifting of attention from one perceptual dimension of a stimulus (e.g. shape) to another (e.g. colour). In a PET study of the cortical activation produced by normal subjects performing the WCST, the major areas of activation were the frontal and inferior parietal cortices. After training and practice on the test, activation in the dorsolateral prefrontal cortex remained significant, suggesting that working memory may be largely responsible for the physiological response in the dorsolateral prefrontal cortex during the WCST (Berman *et al.*, 1995). Konishi *et al*. (1998) used time-sequenced functional MRI to show that prefrontal cortex involvement occurred at the time of shifting of cognitive set.

Sahakian *et al.* (1990) used a set-shifting task from the CANTAB battery (Robbins *et al.*, 1994) to explore the ability of Alzheimer's disease subjects to make attentional shifts from target to target within the same stimulus dimension (intradimensional shifts), from the ability to make shifts to a currently non-attended dimension (extradimensional shifts), the stimulus dimensions being shape and colour. All patients were impaired on tests of recognition memory and learning, but a subgroup of more mildly demented patients (MMSE score = 22.8, CDR = 1.0 versus MMGE score = 15.7, CDR = 1.5 for the second subgroup) were unimpaired relative to controls in the set-shifting task and as accurate as, although slower than, controls in the separate visual search task. The same paradigm was used by Sahgal *et al.* (1992) with a group of mildly demented Alzheimer's disease subjects (average MMSE score = 19.6, CDR = 1.1) in an attempt to find qualitative differences in attentional function between subjects with Alzheimer's disease and cortical Lewy body disease. The subjects, whose dementia severity lay between those of the two groups tested by Sahakian *et al.* (1990), were impaired on this task of attentional set-shifting.

There is no doubt that Alzheimer's disease subjects are impaired on many tests of executive function and that these deficits tend to occur early in the disease. It is at present unclear whether all executive functions are equally affected or if there are dissociations between performance on specific aspects of executive function.

In Baddeley's (1986) model of working memory it is the 'central executive system' (CES) that co-ordinates attention and information flow to and from verbal and spatial short-term memory slave systems, termed the 'articulatory loop system' and the 'visuospatial sketchpad', respectively. The articulatory loop system deals with auditory–verbal information and contains a buffer and a rehearsal loop which recycles verbal material, as in repeating a string of digits or a short list of words. The visuospatial sketchpad performs similar functions with visuospatial information and can be examined by tests that involve a specific sequence of tapping movements on a series of purposefully arranged blocks. Although the functioning of the articulatory loop system and the visuospatial sketchpad is known to be impaired in moderate to severe stage Alzheimer's disease patients, it is in the operations of the central executive system (CES) that the most profound and earliest dysfunction is thought to occur. According to this hypothesis the capacity of the CES is limited, and when tasks become more complex this capacity is exceeded and performance starts to break down. This concept has grown out of the results of a series of dual-task experiments, sometimes referred to as tasks of divided attention, which are discussed in more detail in the section below (Baddeley and Hitch, 1974; Baddeley *et al.*, 1986, 1991*a*).

Divided attention and dual tasks in Alzheimer's disease

Divided attention tasks take two main forms. In one type more than one feature of a stimulus, or multiple stimuli, must be attended to. Experiments in normal subjects show that when several stimuli must be identified at once, costs in performance are reflected in decreased accuracy or by increased RT (Posner, 1978). The second, more common, dual-task paradigm requires the subject to perform two tasks separately before performing both tasks simultaneously. Normal subjects show a deterioration in performance on task A or B when they are performed together compared with when they are performed on their own. This deterioration in performance is known as the dual-task decrement.

A typical example would be the combination of tracking and digit span repetition used by Baddeley *et al.* (1986). In one version, task A, the primary tracking task is to use a light-sensitive pen to follow a white square as it moves randomly about a screen. Performance is measured as the proportion of testing time that the light is kept in the square, and the speed of movement of the square is adjusted to an individual subject's performance. Task B is to repeat strings of digits at each subject's own digit span. Both tasks are attempted on their own for 2 min before being performed together for a further 2 min. Although calculations of the dual-task decrement have differed in their methods (Baddeley *et al.*, 1991*a*, 1997; Greene *et al.*, 1995), the majority of such studies have shown that Alzheimer's disease patients

perform as well as controls when the two tasks are attempted separately but show a disproportionate decline in performance when the tasks are performed concurrently. A longitudinal follow-up study with variations in difficulty in the single task showed a far greater rate of decline in dual-task than single-task performance and no interaction between task difficulty and deterioration. This has been interpreted by the authors as suggesting that the deterioration in performance is a function of whether a single or dual task was being performed and was not dependent on task difficulty alone (Baddeley *et al.*, 1991*a*). This deficit in performing two tasks simultaneously has usually been ascribed to specific dysfunction in Alzheimer's disease of the 'central executive system' (Baddeley *et al.*, 1991*a*; Grober and Sliwinski, 1991; Morris, 1994) but may also be seen as a deficit in the ability to divide or share attention when the demand is for attention to be in more than one place at a specific time.

The stage at which patients with Alzheimer's disease show impairment on dual-task paradigms remains controversial. Although it is clear that the vast majority, if not all, patients in the moderate stages (i.e. MMSE score < 17) show marked impairment, Greene *et al.* (1995) found that patients in the very early amnesic stages (designated minimal dementia) performed normally on two different dual-performance tests. It would seem that when devising dual-task experiments care must be taken to manipulate the difficulty of the single tasks so that they are sufficiently demanding of attention to stretch Alzheimer's disease patients to the limits of the central executive capacity without producing single-task differences with respect to controls. Ideally, the two tasks employed should use different modalities that do not compete for the specific resources of one modality. For example, a dual-task decrement on two verbal tasks may indicate only that there is inefficiency in linguistic processing rather than CES dysfunction. One area of interest for further study is to examine the pattern of dual-task decrements arising from tasks within and across modalities apart from the visual, verbal and auditory tests commonly used. Tests of tactile sensitivity and postural control may be adapted for this purpose.

An alternative position that contrasts with the idea of a 'general factor' or 'central executive' being involved in dual-task decrement is the concept of 'specific interference'. According to this concept, different pairs of tasks interfere for different reasons, such as modality of input (as in two verbal tasks), or interference is produced by two tasks requiring the same stage of processing (e.g. response selection) at the same time, producing a response bottleneck where the processing of one task is delayed. Studies have tended to support the 'general factor' model (Bourke *et al.*, 1996), but the issue is not fully resolved. Hemispheric functional asymmetry may also influence the interference effect of one task upon another. Kinsbourne's functional cerebral distance model predicts that cognitive tasks dependent primarily on one hemisphere, such as language and calculation, will disrupt concurrent right-hand performance more than left-hand performance (Kinsbourne and Hiscock, 1983). As with all dual-task paradigms, a large number of variables may influence outcomes (Pashler, 1994), and this stresses the need to incorporate performance data from both of the concurrent tasks in a combined score which takes account of trade-offs between tasks.

A recent study using functional MRI has shown activation in the prefrontal cortex and anterior cingulate gyrus when two non-working memory single tasks were performed together, but not when they were performed separately (D'Esposito *et al.*, 1995). This activation was interpreted as reflecting CES functioning, although dual-task decrement was relatively small (ranging from 0 to 11%), suggesting that there may have been little stress on the CES. Previous PET studies of the slave systems of working memory have shown activation in similar areas where no dual-task condition was involved (Jonides *et al.*, 1993).

In a test of auditory divided attention by Grady *et al.* (1989), Alzheimer's disease patients were shown to be significantly worse than controls. They used a dichotic listening test called the Staggered Spondaic Word Test, in which attention must be divided between different words that are presented, in parts, to each ear simultaneously. They compared performance on this test with performance in two monotic tests with degraded stimuli consisting of either time-compressed speech or filtered speech presented to one ear at a time. The Alzheimer's disease subjects were impaired to the same degree on both monotic tasks, but were disproportionately poor on the dichotic task. These results were interpreted as showing susceptibility in Alzheimer's disease to the interference effects of competing tasks rather than as a dual-task decrement *per se*. When resting levels of regional glucose metabolism were correlated with performance on a dual-task reaction time paradigm in which Alzheimer's disease subjects performed an auditory simple RT task and a visual-choice RT task in single- and dual-task conditions, Nestor *et al.* (1991) found decreases in metabolism in the right prefrontal and right parietal regions correlated with slowing of RT in the dual task only. Although subjects had to respond to both an auditory stimulus and a visual stimulus within the same trial, the two stimuli were not presented simultaneously but with stimulus onset asynchrony (SOA) varying between 50 and 500 ms. This introduces another factor that may contribute to performance in divided attention paradigms: the time course of interference produced by attending to one stimulus on the effective processing of a subsequent stimulus.

When stimuli are presented to healthy subjects at varying SOAs, either in the same location using Rapid Serial Visual Presentation techniques (Broadbent and Broadbent, 1987; Raymond *et al.*, 1992) or in adjacent spatial locations (Duncan *et al.*, 1994), the detection or identification of one target produces a reduction in the ability to detect or identify a subsequent target that is sustained for periods of ~500 ms. This robust phenomenon in normal subjects, often called the attentional blink or attentional dwell time, has also received

support from ERP studies. In dual-task paradigms, the P300 component of the ERP appears to be reciprocally distributed across the two tasks, i.e. increasing the importance of one task produces a larger P300 response to that task and a smaller P300 to the other task. When subjects had to attend to serial auditory stimuli, Woods *et al*. (1980) noted that the recovery cycle of the P300 was of the order of 600–900 ms, and in a dual task where visual stimuli were presented 400 ms after auditory stimuli the amplitude of the P300 elicited by the first of the two stimuli was inversely related to the amplitude of the P300 elicited by the second stimulus, demonstrating evidence for this phenomenon across modalities rather than only as a result of modality-specific resource competition (Nash and Fernandez, 1996). Such paradigms have interesting possibilities and applications in Alzheimer's disease in examining whether slowed processing of individual stimuli or extended interference between stimuli contributes to the poor performance in tasks of divided attention or dual tasks.

The theory of dual-task decrement in Alzheimer's disease has been given a more practically orientated investigation by the demonstration of disproportionate slowing of walking speed in Alzheimer's disease subjects when performing a simultaneous verbal fluency test (Camicioli *et al.*, 1997), perhaps helping to explain the greater risk of falls and injuries in the demented compared with non-demented elderly (Alexander *et al.*, 1995). Alberoni *et al*. (1992) devised an experiment in which subjects had to keep track of 'who said what' in a conversation. In everyday situations Alzheimer's disease patients have considerable difficulty following conversations involving more than one other person, and this difficulty is exaggerated in groups to the extent that many Alzheimer's disease patients tend to avoid complex social situations. The given task, which involved watching videotapes of conversations involving increasing numbers of characters and then answering questions on 'who said what', was felt to share features with tests of divided attention that stressed the putative central executive system. While controls performed nearly perfectly, the Alzheimer's disease patients showed a tendency for performance to deteriorate as the number of speakers increased. Results of studies such as this may have a bearing on the suitability of social groups or group therapy for people with Alzheimer's disease.

In summary, impairment of divided attention occurs early in Alzheimer's disease and follows the deficit in episodic memory. What remains controversial, however, is exactly how early this impairment appears relative to other aspects of attentional or executive functioning.

Cognitive slowing in Alzheimer's disease: RT studies

RT tasks are invariably computer-based tasks that measure the time taken for a subject to respond, usually either by pressing a key or by using a voice-activated timing device, to a stimulus that has to be either simply detected or discriminated from other stimuli. Times are recorded in milliseconds and incorporate both processing and response components of a task.

The most basic RT tasks used in Alzheimer's disease are the simple and choice RT paradigms; in the simple RT paradigm the stimulus need only be detected, whereas in choice RT tasks relevant stimuli must be discriminated from irrelevant stimuli. A group of mildly impaired Alzheimer's disease patients showed non-significant slowing on a two-choice visual discrimination task (Lafleche and Albert, 1995), whereas a separate cohort were significantly slower on a simple RT task (Reid *et al.*, 1996). Interpretation of these results is hazardous as the two tasks cannot be compared, having been performed by two separate groups of patients. The importance of subdividing groups of subjects by dementia severity and by comparing performance across different tasks in the same subjects is shown by the results of Pate *et al.* (1994), who demonstrated that while mildly demented patients (CDR = 1 or 2) were impaired in both simple and choice RT tasks, a group of 'very mildly' demented patients (CDR = 0.5) were impaired on the choice RT and performed as quickly as elderly controls on the simple RT task. These results agree with the pattern seen by Pirozzolo *et al*. (1981) and suggest that the element of choice in an RT task significantly affects Alzheimer's disease patients.

The effect that a warning signal, such as a light or a bleep, has upon a subject's response time to a stimulus is used to study phasic changes in alertness. Studies of normal subjects show RT decreasing when a warning signal is given and continuing to decrease as the time between the warning signal and the stimulus (SOA) increases, usually reaching a minimum (RT minimum) between 100 and 300 ms. The difference between the RT minimum and the RT without a warning signal is a measure of the degree of benefit in phasic alertness brought by the warning. Nebes and Brady, using an auditory warning signal before a two-choice task, demonstrated that Alzheimer's disease patients show the same degree of benefit, but the benefit is short lived, and it takes a slightly longer time to reach the RT minimum in comparison with controls (Nebes and Brady, 1993). A similar task with a visual warning signal was used by Pate *et al*. (1994), who also demonstrated that mildly demented patients needed longer to reach an optimal level of alertness.

The phenomenon of cognitive slowing, first applied to the neuropsychology of ageing, is becoming an important factor to be considered in the interpretation of chronometric measurements used to identify deficits in specific cognitve operations. To illustrate this point we can use the two paradigms described above, simple and choice RT tasks. If the difference between choice RT and simple RT is greater for Alzheimer's disease subjects than for controls, this could be interpreted as demonstrating a specific impairment in the processes particular to the choice RT paradigm but absent from the simple RT paradigm. The validity of drawing such conclusions from this subtraction method is challenged by

the phenomenon of cognitive slowing. Meta-analyses of reaction times of normal elderly subjects (Cerella, 1985; Nebes and Brady, 1992) and Alzheimer's disease subjects have shown that the increased duration in RTs shown in these groups can be expressed as a function of the RTs of young normal subjects according to the formula: subject time = $Y + (Z \times$ young normal time), where Y is a constant intercept and Z is a factor supposedly related to generalized cognitive slowing and is of the order of 1.9 for mildly demented and 2.6 for moderately demented subjects. It has been argued that the increased reaction times seen in Alzheimer's disease simply represent a generalized cognitive slowing and that the greater disparity between Alzheimer's disease and control RTs for some tasks is a reflection of different task complexity rather than a specific cognitive impairment on the operation that the task is supposed to test. If, for example, controls perform these two tasks with a mean of 200 ms for simple RT and 300 ms for choice RT, and if we then take Z to be 2.0, then we would expect Alzheimer's disease subjects to perform the simple RT task with a mean of 400 ms (200 ms $\times$ 2). By the subtraction method, a mean choice RT for the Alzheimer's disease subjects of 550 ms would indicate that a specific deficit in choice RT, as the difference between simple and choice RT, is 150 ms (550 – 400 ms) compared with the 100 ms (300 – 200 ms) of controls. According to the cognitive slowing method, to ascertain that a specific deficit occurs in Alzheimer's disease subjects in choice RT requires evidence of increases in RT that are greater than that predicted by cognitive slowing, i.e. choice RT should be >600 ms (300 ms $\times$ 2). Thus, only by identifying specific processes that show slowing that is disproportionate to that predicted by the linear equations of generalized slowing can it be demonstrated that the attentional deficit in Alzheimer's disease is due to a specific effect of the disease process rather than a diffuse process akin to accelerated ageing. Such RT studies in Alzheimer's disease would need to compare Alzheimer's disease subjects with young adults as well as healthy age-matched control groups.

Difficulties with this theory lie in the problems of defining task complexity, agreeing on criteria for the degree of difference from the expected range required, and the lack of supportive data from other measures of attention. As the theory is wholly reliant on RT data, the possibility remains that it is only the response selection and execution elements of RT that are generally slowed in Alzheimer's disease, not the cognitive processing of the components of the actual attentional task. Analysis of measurements such as accuracy and ERP data may help to support or refute this theory in the future, but for now it remains an unresolved issue.

Relationship of attention to other cognitive modules and disease staging

The longitudinal study of mildly demented Alzheimer's disease patients (average MMSE score = 24.5) by Grady *et al*. (1988) was able to examine the issue of when attentional deficits appear in Alzheimer's disease. They examined a subgroup of five patients who, on initial testing, showed deficits in memory functions but no deficits in the domains they referred to as 'attention and abstract reasoning' and 'language/visuospatial'. In follow-up of periods up to 40 months, four out of five of these patients developed deficits in addition to memory impairment. Two of these four had deficits in all three domains and two had deficits in only memory and attention and abstract reasoning. There were no patients in this subgroup, or out of the initial 11, who showed deficits in the language/visuospatial domain without impairments in the attention and abstract reasoning domain. Concurrent functional imaging measuring resting glucose metabolism showed that neocortical metabolic dysfunction preceded deficits in attention and abstract reasoning, thought to be 'neocortically mediated cognitive functions', by 8–16 months, and language/visuospatial impairment by 12–37 months. These results were felt to support the theory of an initial memory loss related to medial temporal pathology which progresses to impairments in attention and abstract reasoning before the appearance of language/visuospatial problems. They postulated that attentional problems become manifest when the spread of pathology from the medial temporal lobes disrupts connections between the frontal and parietal lobes, which maintain a system for directed attention.

More recently, Reid *et al.* (1996) studied patterns of early cognitive impairment in 51 patients with mild Alzheimer's disease (MMSE score > 19) and found that the first non-memory deficits occurred on executive/frontal tasks (including category and letter fluencies and the Porteus maze test) and attentional tasks (simple RT measurement and digit span) before deficits in language and visuospatial functions became manifest. This pattern of results replicates that found by Lafleche and Albert (1995), who studied a group of very mildly demented patients with an average MMSE score of 25. Although all these studies have included measures of language and visuospatial abilities, no studies to date have compared the stage of disease at which either working or semantic memory dysfunction becomes apparent in relation to attentional deficits.

An important aspect of all studies of this nature is the criteria that are used to diagnose Alzheimer's disease. It must be born in mind that a progressive memory impairment is a requisite for diagnosis of possible Alzheimer's disease and that impairment of one other cognitive domain is also necessary for a classification of probable Alzheimer's disease to be diagnosed according to the NINCDS–ADRDA criteria (McKhann *et al.*, 1984). Although it is of great interest to study subjects in the earliest stages of Alzheimer's disease, these patients invariably have a progressive amnesia as the presenting symptom. It is only by long-term follow-up, sometimes taking ⩾4 years before other cognitive deficits manifest themselves, that these patients can reach criteria for probable Alzheimer's disease rather than possible Alzheimer's disease. It is also quite possible that Alzheimer's

disease patients could present with isolated language or attentional deficits but would not be included in such studies, having failed to reach current criteria. We know that patients with Alzheimer's disease may occasionally present with an isolated progressive aphasia syndrome (Greene *et al.*, 1996) or with a syndrome of posterior cortical atrophy producing gross deficits in visuospatial function and praxis (Levine *et al.*, 1993; Mackenzie Ross *et al.*, 1996), so it is possible that a syndrome of progressive attentional or executive dysfunction exists as a presentation of Alzheimer's disease, although to date there have been no such documented cases.

Our review of the research into attention function in Alzheimer's disease has found deficits in many attentional and executive processes, but in doing so it has highlighted the difficulty in comparing and collating the results of different studies to reach more general conclusions about which aspects of attention are affected and how early they are affected. Cross-sectional studies benefit from assessing attentional deficits as a function of disease severity and should employ well validated tools for this assessment. Severity scales that are widely used include the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975), the Mattis Dementia Rating Scale (DRS) (Mattis, 1992), the Clinical Dementia Rating Scale (CDR) (Berg, 1988) and CAMCOG (Cambridge Examination for Mental Disorders of the Elderly Cognitive Test) (Huppert *et al.*, 1995). For discussion of their relative merits see Galasko *et al.* (1990) and Salmon *et al.* (1990).

Neural correlates of attentional dysfunction in Alzheimer's disease

The earliest pathological changes of neurofibrillary tangles in Alzheimer's disease appear to involve the transentorhinal region; the changes then encroach upon the entorhinal cortex and the hippocampus before spreading to the neocortex (Hyman *et al.*, 1984; Braak and Braak, 1991, 1995). This pattern is in keeping with the first neuropsychological deficit in Alzheimer's disease being episodic memory loss (Huff *et al.*, 1987; Welsh *et al.*, 1992), and there is sufficient evidence, including *in vivo* MRI evidence, to link neuropsychology with the site of pathology (Squire, 1992; Deweer *et al.*, 1995; Fox *et al.*, 1996). In the same way that converging lines of evidence have linked the early loss of episodic memory in Alzheimer's disease to medial temporal pathology, visuospatial dysfunction to parietal pathology (Levine *et al.*, 1993) and temporal neocortex damage to semantic memory (Hodges and Patterson, 1995), it may be possible to predict which attentional processes are likely to be affected in Alzheimer's disease based on current knowledge of the pattern of spread of pathology in Alzheimer's disease and from what is known about the neural substrates of attentional networks. Following involvement of the medial temporal structures, pathological changes of neurofibrillary tangles spread to the basal forebrain and anterior cingulate (Braak and Braak, 1991; Vogt *et al.*, 1992) before encroaching on the neocortical association areas. Within these regions the earliest and heaviest burden of pathology is found in the temporal and parietal lobes, and involvement of the prefrontal cortex appears to occur even later (Reed *et al.*, 1989; Tikofsky *et al.*, 1993). The primary motor, sensory and visual cortices are typically spared until the very severe stages of the disease, and the thalamus and superior colliculus also remain relatively unaffected. The majority of resting measurements of rCBF and glucose metabolism by SPECT or PET imaging of Alzheimer's disease subjects have also shown early temporal and parietal perfusion deficits, with frontal changes occurring as the disease progresses (Jagust *et al.*, 1987, 1997; Johnson *et al.*, 1987; Rapoport, 1991; Brown *et al.*, 1996). Although some studies have demonstrated a degree of heterogeneity in the cortical sites of hypoperfusion and hypometabolism (Zimmer *et al.*, 1997; Stein *et al.*, 1998), the combined pathological and imaging evidence suggests relative preservation of the frontal lobes in Alzheimer's disease. It is, therefore, somewhat surprising that Alzheimer's disease produces the marked impairment in attentional and executive functions that have been linked with frontal lobe function before deficits in language and visuospatial function occur (Haxby *et al.*, 1986, 1990; Lafleche and Albert, 1995; Reid *et al.*, 1996). To link attentional dysfunction in Alzheimer's disease to disease pathology in circumscribed brain regions may be an oversimplification, and the pathological process of Alzheimer's disease may cause attentional deficits in other ways.

Current research points to two neural systems whose disruption may contribute to the attentional deficit: (i) the basal forebrain cholinergic system and (ii) corticocortical tract integrity.

The basal forebrain cholinergic system consists of the medial septum, the diagonal band of Broca and the nucleus basalis of Meynert, and provides the major cholinergic innervation to the neocortex (Mesulam and Geula, 1988), including areas such as the prefrontal cortex, the thalamus and the parietal lobes, which are known to be involved in attention. Although the relative role that cholinergic deficiency in Alzheimer's disease plays in the impairment of memory or attention is controversial (Christensen *et al.*, 1992; Geula and Mesulam, 1994; Lawrence and Sahakian, 1995; Raffaele *et al.*, 1996), cholinergic disruption certainly causes attention deficits (Wesnes *et al.*, 1988; Voytko, 1996), and animal studies in which the nucleus basalis of Meynert is lesioned with cholinergic excitotoxins have shown predominant attentional rather than mnemonic deficits (Muir *et al.*, 1993, 1995) that can be reversed with nicotine and cholinesterase inhibitors such as physostigmine. Pathological studies in Alzheimer's disease have revealed that, after the medial temporal lobe, the most heavily involved regions are the accessory basal nucleus of the amygdala and the nucleus basalis of Meynert (Arnold *et al.*, 1991). Neurofibrillary tangle density in the nucleus basalis of Meynert has the strongest correlations with dementia severity (Samuel *et al.*,

1994), although no correlations were made with attentional tasks in this study. In keeping with this, drugs which modify the cholinergic system, such as the acetylcholinesterase inhibitor Tacrine®, have been shown to significantly improve accuracy and speed on a choice reaction time test but not on a test of visuospatial working memory (Lawrence and Sahakian, 1995). The recent introduction of cholinergic therapies for the symptomatic treatment of Alzheimer's disease may be helpful in assessing the role that cholinergic deficits play in attentional dysfunction, but unfortunately the large multicentre therapeutic trials to evaluate cholinergic drug efficacy in Alzheimer's disease have so far failed to use measures of attention (Davis *et al.*, 1992; Rogers *et al.*, 1998). Recent advances in *in vivo* imaging of cholinergic function in Alzheimer's disease subjects (Kuhl *et al.*, 1994, 1996; Efange *et al.*, 1997; Iyo *et al.*, 1997) present the possibility of examining the relationship of deficits on attention tasks known to be linked with certain brain regions with regional measurements of cholinergic activity. It will also be of interest to examine the particular attentional deficits, and the therapeutic effect on these deficits of acetylcholinesterase inhibitors, in subjects with cortical Lewy body disease, a condition known to be associated with low cortical cholinergic activity (Perry *et al.*, 1994).

An alternative explanation for the attentional deficits found in Alzheimer's disease relates to disruption of corticocortical pathways. In addition to the association between neurofibrillary tangle density in the nucleus basalis of Meynert and dementia severity, it has been shown that neocortical synaptic density correlates highly with dementia severity (Terry *et al.*, 1991; Samuel *et al.*, 1994). It is also known that Alzheimer's disease neuropatholgy selectively affects certain laminae and cell types within the cortex, in particular layers II, III and IV and the pyramidal neurons, which participate in corticocortical connections such as the superior longitudinal fasciculus, a dense fibrous tract connecting the parietal and frontal cortices. These neuropathological findings led to theories of Alzheimer's disease being a disconnection syndrome with disrupted communication between different neocortical association areas (Morrison *et al.*, 1986). More functional evidence of a corticocortical disconnection syndrome comes from EEG measures of cortical synchronicity demonstrating impaired coherence between the anterior and posterior cortices in Alzheimer's disease patients but not in multi-infarct dementia, whose subcortical pathology causes predominantly subcortical–cortical disruption (Leuchter *et al.*, 1992). It is thought that the cognitive deficits of Alzheimer's disease can be explained in terms of these pathological processes disrupting the exchange of information between neural circuits linked by corticocortical tracts. Many attentional and executive tasks require the rapid and simultaneous integration of multiple types of information, and such disconnection, for instance between the parietal and frontal lobes, as postulated by Haxby *et al.* (1990), may account for attentional deficits. As well as supporting evidence from neuropsychology and functional imaging, further neuropathological studies are needed to examine the neuronal, tangle and synapse density of specific areas of the cortex and of tracts between specific cortical areas.

Conclusions

The evidence from standard and computer-based neuropsychological tasks would seem to support the clinical observations of an attentional impairment relatively early in the course of the illness. The accepted pattern of an initial amnesic stage, which may be the only cognitive deficit for several years, is supported by cross-sectional and longitudinal studies which include tests that may be considered to tap attentional functioning. The current diagnostic criteria for Alzheimer's disease, which require a progressive memory deficit for diagnosis of probable or possible Alzheimer's disease, make such an argument hard to refute, as a subject with attentional or executive impairment but normal memory could not be considered to have Alzheimer's disease. Long-term follow up of such subjects may show progression to a generalized dementia with memory deficits, but to our knowledge there have been no pathologically confirmed cases of Alzheimer's disease presenting as a pure attentional or dysexecutive syndrome. On the other hand, subjects with severely impaired memory have been examined over periods of 3 years or more and have shown no impairment on attentional tests. It is possible that such subjects may have subtle attentional deficits that would be picked up by more specifically designed information processing tasks. A number of cross-sectional and longitudinal studies have suggested that attentional and dysexecutive impairments are the first non-memory domains to be affected, usually before problems with language or visuospatial tasks become apparent.

When different facets of attention are examined, it is clear that not all components are affected at the same stage of the disease. In the area of selective attention it would seem that attentional focusing, at least in the visual domain, is relatively preserved, whilst the disengagement and shifting of attention is differentially affected, whether the shift is by location of a stimulus or across features within the same stimulus. Research with the Stroop test, which appears to be sensitive to even minimally affected subjects, may reveal a particular attentional problem in Alzheimer's disease.

Clinical observation of patients suggests that while they may be able to perform well-rehearsed and routine tasks competently, they have difficulty in performing novel tasks or old tasks in a novel way. Such well-rehearsed tasks become virtually automatic and require very little effort or attention to perform, but when such automatic processes have to be inhibited to allow tasks to be performed in a novel and hence more attentionally demanding way, this failure of inhibition leads to a breakdown in performance. This failure of inhibition of more automatic responses, reflected in the tendency to read words instead of name colours in the Stroop test, may cause particular problems for Alzheimer's disease patients and be a characteristic of their attentional deficit. Response

inhibition, competing response tendencies, habituation and the response to novelty constitute a seemingly fruitful area for future research in Alzheimer's disease.

Another area in which Alzheimer's disease subjects seem to show specific deficits in attention is in the performance of dual-task paradigms, which reflect a higher level of attentional performance where attention must be shared. This has been investigated in terms of a breakdown in Alzheimer's disease of the 'central executive' or 'supervisory attentional' system, which is purported to co-ordinate and allocate attentional resources in non-routine and non-automatic processes. It would be of great interest to see such dual-task paradigms extended to investigate the effect of sharing attention between modalities including tasks in the auditory, tactile and possibly postural modalities.

The conclusions are far less clear when interpreting the evidence for impairment or preservation of sustained attention. While the majority of studies suggest the preservation of sustained attention, at least in mild Alzheimer's disease, few studies have looked at the more theoretical aspects of sustained attention by examining sensitivity decrements across tasks lasting $\geqslant$30 min.

Although the examination of attention in Alzheimer's disease is still clearly in its infancy, there are already implications for the direction of future research. Neuropsychological tests have great advantages in quantifying attentional deficits, and it can already be suggested that some facets of attention are differentially impaired in Alzheimer's disease, but few studies have compared this relative impairment or preservation of subtypes of attention within a single group of subjects. Many studies report attentional deficits in Alzheimer's disease without referring to the disease severity of the subjects. If moderate to severely demented patients are tested, they are likely to be in a stage of global cognitive impairment and will be poor at all tasks. Thus the relevance of performing poorly on a particular task of attention is lost. Studies should be designed so that different stages of disease severity are compared by using common and well-validated measures such as the MMSE or the DRS. This design could show when in the disease process the different subtypes of attention are affected, such as whether sustained attention is preserved whilst the same patients are performing poorly on dual tasks.

Despite the apparent restrictions of the currently used criteria for Alzheimer's disease diagnosis, it is of great theoretical importance to test subjects in the earliest stages of Alzheimer's disease when only memory is impaired and they can still attempt tasks without being hindered by visuospatial or language difficulties. There are still very few longitudinal studies of patients followed from the earliest stages of the disease with a broad range of tasks, and none which include pathological verification of the diagnosis. Future research should concentrate on qualifying attentional impairment by using information processing tasks to examine specific components of attention in minimally or mildly affected patients.

Chronometric studies of attention in Alzheimer's disease should incorporate the notion of generalized cognitive slowing when reporting RTs and should compare ratio scores in addition to difference scores derived from subtractions. The issue of identifying qualitative and quantitative differences from the attentional deficits of normal ageing can be addressed by comparing the performance of Alzheimer's disease subjects with that of both age-matched controls and young controls.

Recent advances in functional imaging using cholinergic markers may in future be combined with neuropsychological assessment, EEG coherence techniques and event-related potentials to evaluate the contribution of cholinergic deficits and corticocortical disconnection to the attentional impairment in Alzheimer's disease. The use of these techniques in different cortical dementias may provide supporting evidence for the involvement of different brain regions or systems in different components of attention. For example, comparing the profile of attention in Alzheimer's disease and frontotemporal dementia (Brun *et al.*, 1994; Gregory and Hodges, 1996) may illuminate the role of the frontal lobes, whereas comparisons with cortical Lewy body disease could provide evidence about the importance of the basal forebrain cholinergic system in particular aspects of attention.

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