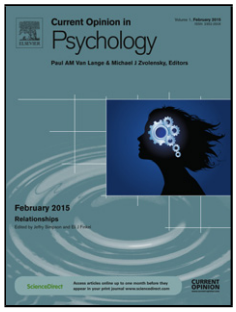

Title: Impairments of Attention in Alzheimer's Disease

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Title: Impairments of Attention in Alzheimer's Disease

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Highlights

- -Multiple aspects of attention are affected in Alzheimer's Disease (AD)
- -The Locus Coeruleus is one of the first brain regions to be affected by tau pathology in AD
- -Deficits in Arousal, Orienting and Executive Control of attention can occur in the early stages of the disease
- -Alzheimer's Disease has a more heterogeneous cognitive profile that previously thought
- -Combination therapy may be more successful than symptomatic treatments aimed at a single neurotransmitter system

Abstract

Alzheimer's Disease (AD) is characteristically perceived as primarily being a disorder of episodic memory, with prominent attentional impairments more typically being associated with other neurodegenerative conditions, such as Dementia with Lewy Bodies. However, attention is also affected early on in Alzheimer's, particularly in individuals with young onset and atypical syndromes. In addition, some initial symptoms that are apparently due to episodic memory loss may be secondary to failures of attentional processes.

This review describes the various attentional impairments that can be observed in patients with AD, and addresses them through the conceptual framework of attention proposed by Posner and Petersen. It also explains how current knowledge of the development of AD has influenced our understanding of how these deficits arise. Finally, there is a brief summary of the effects of current AD treatments on attentional deficits, and how future pharmacological approaches might better target these deficits.

Introduction

Alzheimer's Disease (AD) is typically associated with an impairment of episodic memory early in the course of the disease, with associated atrophy in the hippocampus and dysfunction of connected brain regions [1, 2]. Although symptoms suggestive of episodic memory impairment are the most common presenting complaint of patients with AD, attentional deficits have also been observed early on in the disease process [3-6]. These may be observed on clinical neuropsychological testing but are more likely to be encountered when asking about difficulties that patients encounter in daily life. For example, when patients are asked about everyday problems, they may complain about finding it difficult to pick out relevant conversations when in large groups of people [7]. In addition, relatives and friends may observe that patients might be unable to focus or concentrate on tasks that they are carrying out.

Increasing understanding of the pathophysiology of AD, and the heterogeneity of clinical presentations, has allowed clinicians and researchers to appreciate the importance of attentional deficits in AD [8]. In addition, the use of disease biomarkers, including PET (Positron Emission Tomography) imaging and cerebrospinal fluid (CSF) protein assays (See Box 1), has assisted identification of AD pathology in individuals with less typical syndromes [9]. These patients can present with attentional or perceptual deficits as a key clinical feature, with anatomical patterns of atrophy that do not affect the medial temporal lobes early in in the disease process [10]. This has led to a broadening of the AD phenotype, as well as a better understanding of the spectrum of symptoms that patients can present with, including prominent impairments of attention [11].

One of the most influential accounts of attention is that of Posner and Petersen, who have proposed three discrete, but linked networks, which subserve different aspects of attentional function [12]. These consist of the following: (1) an alerting network, responsible for arousal and for maintenance of attention with increasing time-on task, (2) an orienting network, which allows attention to be targeted to specific spatial locations (3) an executive network that enables the brain to deal with conflicting stimuli. This system was proposed almost thirty years ago, and was partially based on studies with patients who had focal brain lesions leading to attentional impairments, such as spatial neglect [13]. Since then, the general framework has been modified and refined in response to a wealth of new findings, particularly from functional imaging studies [14]. However, the general concept of this tripartite attentional system has remained valid, and can provide a helpful foundation for delineating how different aspects of attention may be affected by Alzheimer's Disease (See Figure 1). In particular, it allows the differentiation of multiple impairments in processes that fall under the general umbrella term of attention. The Posner model does not map precisely onto neuropsychological test batteries or clinical presentations of AD. However, it can be used to delineate which attentional networks may be affected at different stages of AD, and how they can be

disrupted to varying degrees in specific subtypes of the disease. Below I discuss the three Posner networks individually, reviewing recent evidence for AD-related impairments relating to each.

Alerting, Noradrenaline and Sustained Attention

The alerting network is reliant on ascending pathways originating from the brainstem. Arousal and alerting appear to be particularly linked to noradrenergic pathways originating from the locus coeruleus in the pons (See Figure 2) [15]. It has long been known that the locus coeruleus is affected very early on in AD, and recent research has suggested that it is one of the first brain regions to be affected by pathological accumulation of tau protein [16, 17]. Tau is one of the two key proteins which can accumulate in the brain to lead to Alzheimer's, and it builds up within neurons, leading to cell dysfunction and death (the other protein is Beta-amyloid which is deposited in extracellular plaques). In a post mortem study of individuals with AD, locus coeruleus volume loss has been found to correlate with cognitive decline [18], and it has been suggested that locus coeruleus integrity is critical in delaying the development of cognitive impairment in AD [19].

Noradrenergic pathways from the locus coeruleus project throughout the cerebral cortex and have a key role in arousal-they have been found to modulate multiple aspects of attentional function, interacting with the orienting and executive networks. The activity of this alerting network influences perception, and recent work has shown that noradrenaline levels appear to boost visual perception by modulating sensitivity to targets and discrimination accuracy [20]. Mather and colleagues have suggested that noradrenergic signaling during arousal amplifies the activation of prioritized representations in 'hotspots', enabling selective attention [21]. Hence, disruption to the alerting network has the potential to also affect orienting and executive attention as well.

Interestingly, this network may also strengthen memory representations as locus coeruleus activity appears to boost prioritized memories under arousal [22]. Moreover, locus coeruleus volume in older adults is negatively correlated to memory, particularly for salient negative events [23]. Such a link between locus coeruleus dysfunction and impaired memory has been explored through an animal model to show that locus coeruleus dysfunction secondary to amyloid and tau deposition causes cognitive impairment, and that this can be reversed by chemogenetic locus coeruleus activation [24]. Given the close links between arousal and memory that have been shown in healthy individuals, the effects of noradrenaline may well be mediated via attention.

One specific paradigm that has been designed to probe each of the attentional networks described by Posner is the Attentional Network Task [25]. This computerized behavioural test assesses the influence of cues and distractors on performance, specifically reaction time, to assess the efficiency of each network. A number of groups have used the Attentional Network Task (ANT) to test the attentional profile of AD patients. Fernandez-Duque and Black examined patients

with AD and found that alerting effects in patients appeared to be no different from those of healthy elderly controls [26]. In contrast, two other groups have used the ANT to examine attention in AD and Dementia with Lewy Bodies, and found that the alerting effect that they observed in healthy controls was not present in patients with AD, suggesting dysfunction of the alerting network in these individuals [27, 28], with it being suggested that this is likely to be secondary to loss of noradrenergic input from the locus coeruleus.

The ANT is relatively limited in scope and relies on reaction time effects, which do not index every aspect of attentional impairment. One aspect of attention that is not explicitly assessed by the ANT but is particularly dependent on the alerting network is the ability to sustain attention over time (or vigilance). This ability to maintain cognitive performance with increasing time-on-task is reliant on noradrenergic signalling, and associated with a right-lateralised network involving key frontal and parietal regions [29-31]. Vigilance is rarely directly assessed in routine clinical neuropsychological assessments, but can be measured using paradigms such as the continuous performance task, which requires a response to an infrequently occurring target stimulus, or the Sustained Attention to Response Test (SART), which requires the withholding of responses to rare targets [32]. A number of researchers have shown sustained attention deficits in AD but some authors have suggested that these do not appear early on in the disease [4, 33]. However, a recent study employed the Sustained Attention to Response Test to examine sustained attention in AD, and the authors found that patients with early AD performed worse than healthy controls [34]. Critically, AD patients' SART performance correlated with their performance on the MMSE, suggesting that sustained attention deficits do occur at the earliest stages of the disease, and that they may contribute to apparent deficits in other domains.

Orienting and Spatial Attention

The orienting network is particularly important in the selection of relevant information in space and was originally described partly on the basis of impairments observed in patients with focal lesions, particularly individuals with neglect following stroke [12, 35]. Although the orienting network was originally felt to be particularly dependent on parietal lobe integrity, extensive work using functional imaging and with patient groups has demonstrated that orienting appears to involve the interaction between two linked predominantly frontoparietal networks-the ventral and dorsal attention networks [36]. The right-lateralised ventral network includes the inferior frontal gyrus anteriorly and the temporoparietal junction posteriorly. It is closely linked to the alerting network as described above, and appears to be involved in the re-orienting of attention, switching from a previously attended spatial location to a new target. The bilateral dorsal attention network includes the frontal eye fields and the intraparietal sulcus, and is critical to the deployment of spatial attention, with close links to eye movement generation [37].

Orienting and spatial attention can be profoundly affected by AD, strikingly in the syndrome of Posterior Cortical Atrophy (PCA) [38]. This disorder is most frequently

caused by AD, and is more likely to occur in patients with early-onset disease. It is associated with prominent parieto-occipital atrophy with relative sparing of the medial temporal lobe. Thus, this variant of AD directly affects the key anatomical structures that are part of Posner's orienting network and PCA presents with profound visuospatial deficits [39]. Patients often manifest the features of Balint's syndrome (simultanagnosia, oculomotor apraxia and optic ataxia) [38]. Simultanagnosia is an inability to perceive multiple items simultaneously which has been ascribed to a spatial restriction of attention [40] and also to reduced visual processing speed [41]. PCA is often also associated with signs of spatial neglect (See Figure 3), in keeping with asymmetric atrophy and dysfunction [42]. Because of their profound visuospatial impairments, patients with PCA are often unable to reliably perform the ANT, which was developed with healthy individuals. Instead, researchers have explored the attentional deficits in PCA through systematic observation of patients' eye movements and via other sensory modalities.

Careful assessment of eye movements in this patient group shows multiple abnormalities, including an inability to generate saccades to new targets from the current item at fixation [43], suggesting an inability to disengage attention. This is in keeping with the pattern of atrophy observed in this group, and has also been demonstrated with functional imaging, showing hypometabolism of regions involved in the ventral and dorsal attention networks [44]. In addition to visual dysfunction, patients with PCA have been found to have attentional dysfunction in the auditory domain. When assessed with a virtual auditory space paradigm, patients were found to have deficits in auditory motion detection, and stationary sound position discrimination [45]. Importantly, patients with typical AD also manifest these impairments, although results from the PCA group revealed much worse auditory motion processing.

The Posterior Cortical Atrophy syndrome is an atypical variant of AD with a striking clinical presentation. However, there is increasing evidence of more parietal involvement with a less memory-related presentation in the broader population of patients with AD. Use of biomarkers such as amyloid PET imaging and CSF analysis has enabled better in vivo identification of the disease [46, 47]. This is providing new evidence to show that that the cognitive and anatomical profiles of AD are likely to be more heterogeneous than previously thought [48, 49]. Rather than PCA being a distinct variant of AD, it may represent the more striking end of a continuum that includes patients with a relatively late medial temporal lobe involvement and earlier non-memory deficits [50]. These individuals have been identified by cluster analysis and other multivariate methodologies in multiple cohorts and are likely to represent a significant proportion of the Alzheimer's population. [51]

Executive Attention Network

In Posner and Peterson's original framework the executive attention network's key role was in target detection or 'focal' attention- the process whereby relevant information might 'enter the conscious state' [14]. Critical roles were assigned to anterior midline regions, and the Anterior Cingulate Cortex in particular has been

demonstrated to be one of the key nodes in this network. Posner and Petersen's view of this network has been elaborated over time, and it has been suggested that there are two separable executive control networks [14]. The set of processes that has been included under the umbrella of 'executive attention' encompasses task monitoring and conflict resolution in addition to attentional processes related to working memory and inhibitory control. Although AD typically tends not to lead to early anterior cingulate pathology or atrophy, patients with AD do have multiple deficits in these processes [52, 53].

In the relatively narrow context of the ANT, which has only been used in small numbers of patients, the executive component of the task is indicated by resolution of conflict. This is operationally as defined by the ability to deal with incongruent flanker stimuli when making a response to a visual target, which has been found to be linked to dorsal anterior cingulate cortex activity. Patients with AD have been found to be impaired on such flanker tasks, with performance that is not significantly different from individuals with behavioural variant Frontotemporal dementia (bvFTD), a neurodegenerative disease which is primarily associated with prefrontal atrophy and early involvement of anterior cingulate cortex [54]. Poor attentional control- as measured by flanker task accuracy- across patients with multiple neurodegenerative diseases including both AD and bvFTD, is associated with prefrontal and anterior cingulate atrophy [55].

The experimental findings from studies employing the Flanker task suggest that the network involved in executive attention can be disrupted by Alzheimer's pathology. On a larger scale, cohort studies, taking a similar approach to the cluster analysis described above, have identified a group with predominantly executive dysfunction relatively early in the course of the disease [49, 56]. Such cohort studies employ standard neuropsychological batteries that include multiple 'classic' pen-and –paper tasks. These standard neuropsychological tests included in the Executive function battery included items such as the WAIS-R Digit Symbol Substitution, Digit Span Backwards, Trails A and B and clock-drawing; these all draw on more than one cognitive domain but do involve an attentional control component. AD patients with impaired performance on this group of tests again have less temporal lobe involvement, and are more likely to have a global atrophy pattern. Thus, the executive attentional network appears to be affected in a significant proportion of patients with Alzheimer's Disease, although these individuals are less likely to conform to the typical amnestic phenotype with early medial temporal lobe atrophy [52]. Rather, their atrophy pattern appears to be more global, and likely to involve anterior cingulate cortex, and/or other nodes of the executive attention network. Further detailed analysis of AD patients with biomarker confirmation of diagnosis will allow a clearer delineation of this AD patient group. In their influential critical review examining attention and executive deficits in AD nearly two decades ago, Perry and Hodges speculated "it is possible that a syndrome of progressive attentional or executive dysfunction exists as a presentation of AD, although to date there have been no such documented cases" [4]. It may be that large-scale studies such as those described above are beginning to allow this to be clarified.

Pharmacological Treatment of Attentional Deficits in AD

Current Symptomatic Treatments for AD

The only licensed drugs for AD are the cholinesterase inhibitors (ChEIs) -donepezil, galantamine and rivastigmine, and the NMDA receptor antagonist, memantine [57]. ChEIs and memantine do improve cognition but only modestly. ChEIs were initially developed as treatments because of the (then) recently described links between cholinergic function and memory, in addition to the observation of degeneration in the cholinergic nucleus basalis of Meynert in the brainstem [58, 59]. However, cholinergic pathways are also important in attentional processes, being linked to the orienting and executive networks in the Posner framework (although dopamine is also associated with the latter) [60]. Interestingly, the ChEIs have a greater clinical effect upon cognition in Dementia with Lewy Bodies than in AD. Given that the former has more prominent attentional impairments, this would be in keeping with an attentional mechanism for ChEIs [61]. There is some evidence to suggest that this is the case [62, 63]), but it is not definitive.

Although there has understandably been a very strong focus on the development of medications that reverse or slow the disease process, there remains a great need for effective symptomatic treatment in AD. One particular problem is that outcome measures are often limited to relatively crude cognitive instruments, and until symptomatic treatment trials regularly employ targeted assessment batteries that are based on a drug's hypothesised neurocognitive mechanism of action, it will not be possible to determine whether it is acting via a specific cognitive domain.

A Role for Combination Therapy?

Multiple neurotransmitter pathways, including both noradrenergic and cholinergic systems, are affected early on in AD. As stated above, noradrenergic pathways from the locus coeruleus appear to play a key role in arousal, and noradrenergic dysfunction leads to impaired cognitive function. There is evidence that noradrenergic agents can improve attention in animals, healthy humans and other patient groups [64], but when noradrenergic medications have also been trialled in AD they have shown no clear effect [65-67].

Given that attentional subsystems work in concert, it may be that combining a noradrenergic agent with standard cholinergic treatment could lead to a synergistic effect on attention and cognition. To date, there has only been one fully-powered randomised controlled trial taking such an approach, investigating the effect of combining atomoxetine with ChEIs, but this did not show any difference between treatment groups [68]. It is possible that such combination therapy will only be helpful for particular patients i.e. those identified by the cohort analyses described above as having a predominantly attentional presentation. Moreover, these individuals may only be responsive at a particular stage in their disease course. It is therefore critical to fully understand the range of cognitive profiles that present in AD, as well as their trajectories. Only then will trials will be able to systematically examine whether these are differentially affected by specific treatment combinations.

Conclusion

The families and friends of patients affected by AD often state that, in addition to their problems with recalling recent information, their ability to concentrate and to focus has decreased. However, the orthodox view of the disease process is that it initially affects episodic memory with associated atrophy of limbic regions, particularly the hippocampus. Research looking at small groups of patients with atypical syndromes, the use of targeted attentional paradigms, and the methodical analysis of large cohorts have all contributed to a more nuanced view of the spectrum of attentional deficits that can be affected early on in AD, which is more in keeping with the observations of individuals affected by the disease.

It may be that the imprecise mapping of the cognitive neuroscience of attention onto its neuropsychological measurement has led to the underestimation of attentional deficits in AD. Although the original framework of Posner and Petersen has required extensive elaboration to fit in with advances in neuroimaging, it provides a general system through which to address the different aspects of attentional dysfunction that clearly affect patients with AD and that are often noted by their families. Moreover, the clinical features of rarer variants of AD such as posterior cortical atrophy validate the systematic fractionation of attention. Impairments of each subsystem of Posner and Petersen's attentional framework are present in AD, and attention can be affected at the earliest stages of the disease. In order to develop effective symptomatic cognitive treatments for patients with AD, it will be essential to consider attentional impairments as an important component of the heterogeneous cognitive profile seen in Alzheimer's Disease. Development of novel symptomatic treatments for AD will need to address these, and may involve the use of combination therapies to target multiple attention networks.

COI

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References

1. Scheltens, P., et al., *Alzheimer's disease.* Lancet, 2016. **388**(10043): p. 505-517.
2. Leech, R. and D.J. Sharp, *The role of the posterior cingulate cortex in cognition and disease.* Brain, 2014. **137**(Pt 1): p. 12-32.
3. Levinoff, E.J., D. Saumier, and H. Chertkow, *Focused attention deficits in patients with Alzheimer's disease and mild cognitive impairment.* Brain Cogn, 2005. **57**(2): p. 127-30.
4. Perry, R.J. and J.R. Hodges, *Attention and executive deficits in Alzheimer's disease. A critical review.* Brain, 1999. **122 (Pt 3)**: p. 383-404.
5. McGuinness, B., et al., *Attention deficits in Alzheimer's disease and vascular dementia.* J Neurol Neurosurg Psychiatry, 2010. **81**(2): p. 157-9.
6. Scinto, L.F., et al., *Impairment of spatially directed attention in patients with probable Alzheimer's disease as measured by eye movements.* Arch Neurol, 1994. **51**(7): p. 682-8.
7. •Kamourieh, S., et al., *Speech Registration in Symptomatic Memory Impairment.* Front Aging Neurosci, 2018. **10**: p. 201.
   Fluctuation in speech registration in patients with probable AD, as tested by a paradigm which used distracting background speech, correlated with activity within a right hemisphere fronto-temporal system associated with sustained auditory attention
8. Finke, K., et al., *A biased competition account of attention and memory in Alzheimer's disease.* Philos Trans R Soc Lond B Biol Sci, 2013. **368**(1628): p. 20130062.
9. Ahmed, R.M., et al., *Biomarkers in dementia: clinical utility and new directions.* J Neurol Neurosurg Psychiatry, 2014. **85**(12): p. 1426-34.
10. Tsai, P.H., et al., *Posterior cortical atrophy: evidence for discrete syndromes of early-onset Alzheimer's disease.* Am J Alzheimers Dis Other Demen, 2011. **26**(5): p. 413-8.
11. Lehmann, M., et al., *Diverging patterns of amyloid deposition and hypometabolism in clinical variants of probable Alzheimer's disease.* Brain, 2013. **136**(Pt 3): p. 844-58.
12. Posner, M.I. and S.E. Petersen, *The attention system of the human brain.* Annu Rev Neurosci, 1990. **13**: p. 25-42.
13. Posner, M.I., et al., *Effects of parietal injury on covert orienting of attention.* Journal of Neuroscience, 1984. **4**: p. 1863-1874.
14. Petersen, S.E. and M.I. Posner, *The attention system of the human brain: 20 years after.* Annu Rev Neurosci, 2012. **35**: p. 73-89.
15. Berridge, C.W. and B.D. Waterhouse, *The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes.* Brain Res Brain Res Rev, 2003. **42**(1): p. 33-84.
16. Braak, H. and K. Del Tredici, *The preclinical phase of the pathological process underlying sporadic Alzheimer's disease.* Brain, 2015. **138**(Pt 10): p. 2814-33.
17. Mann, D.M., et al., *Changes in the monoamine containing neurones of the human CNS in senile dementia.* Br J Psychiatry, 1980. **136**: p. 533-41.

18. Theofilas, P., et al., *Locus coeruleus volume and cell population changes during Alzheimer's disease progression: A stereological study in human postmortem brains with potential implication for early-stage biomarker discovery.* Alzheimers Dement, 2017. **13**(3): p. 236-246.
19. Robertson, I.H., *A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease.* Neurobiol Aging, 2013. **34**(1): p. 298-308.
20. Gelbard-Sagiv, H., et al., *Noradrenaline Modulates Visual Perception and Late Visually Evoked Activity.* Curr Biol, 2018. **28**(14): p. 2239-2249 e6.
21. Mather, M., et al., *Norepinephrine ignites local hotspots of neuronal excitation: How arousal amplifies selectivity in perception and memory.* Behav Brain Sci, 2016. **39**: p. e200.
22. •Clewett, D.V., et al., *Locus Coeruleus Activity Strengthens Prioritized Memories Under Arousal.* J Neurosci, 2018. **38**(6): p. 1558-1574.
Locus Coeruleus activity associated with threat, as indexed by pupillometry combined with fMRI, appears to lead to better encoding of visual information in healthy individuals
23. ••Hammerer, D., et al., *Locus coeruleus integrity in old age is selectively related to memories linked with salient negative events.* Proc Natl Acad Sci U S A, 2018. **115**(9): p. 2228-2233.
Neuromelanin-sensitive MRI sequences (also used in (16)) can be used to examine the Locus Coeruleus (Figure 2). Reduced Locus Coeruleus integrity secondary to ageing leads to poorer memory, particularly for emotionally negative events
24. ••Rorabaugh, J.M., et al., *Chemogenetic locus coeruleus activation restores reversal learning in a rat model of Alzheimer's disease.* Brain, 2017. **140**(11): p. 3023-3038.
Reversal of Locus Coeruleus/noradrenergic lesions improves cognitive function in a rodent model of AD (where hyperphosphorylated tau was detected in the locus coeruleus prior to accrual in the medial entorhinal cortex or hippocampus).
25. Fan, J., et al., *Testing the efficiency and independence of attentional networks.* J Cogn Neurosci, 2002. **14**(3): p. 340-7.
26. Fernandez-Duque, D. and S.E. Black, *Attentional networks in normal aging and Alzheimer's disease.* Neuropsychology, 2006. **20**(2): p. 133-43.
27. Fuentes, L.J., et al., *Attention network functioning in patients with dementia with Lewy bodies and Alzheimer's disease.* Dement Geriatr Cogn Disord, 2010. **29**(2): p. 139-45.
28. •Firbank, M., et al., *Neural correlates of attention-executive dysfunction in lewy body dementia and Alzheimer's disease.* Hum Brain Mapp, 2016. **37**(3): p. 1254-70.
When carrying out the ANT whilst undergoing fMRI scanning, patients with Alzheimer's disease and Lewy body dementia patients had greater activation of a fronto-parieto-occipital network than healthy controls for incongruent and more difficult trials, and these changes were also accompanied by behavioural changes (slower reaction times).

29. Fortenbaugh, F.C., J. DeGutis, and M. Esterman, *Recent theoretical, neural, and clinical advances in sustained attention research.* Ann N Y Acad Sci, 2017. **1396**(1): p. 70-91.
30. Oken, B.S., M.C. Salinsky, and S.M. Elsas, *Vigilance, alertness, or sustained attention: physiological basis and measurement.* Clin Neurophysiol, 2006. **117**(9): p. 1885-901.
31. Aston-Jones, G., et al., *Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task.* J Neurosci, 1994. **14**(7): p. 4467-80.
32. Robertson, I.H., et al., *'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects.* Neuropsychologia, 1997. **35**(6): p. 747-58.
33. Weintraub, S., A.H. Wicklund, and D.P. Salmon, *The neuropsychological profile of Alzheimer disease.* Cold Spring Harb Perspect Med, 2012. **2**(4): p. a006171.
34. ••Huntley, J.D., et al., *The importance of sustained attention in early Alzheimer's disease.* Int J Geriatr Psychiatry, 2017. **32**(8): p. 860-867.
Sustained attention, as tested with the SART, is affected in very early AD, and this deficit correlates with overall cognitive function.
35. Li, K. and P.A. Malhotra, *Spatial neglect.* Pract Neurol, 2015. **15**(5): p. 333-9.
36. Corbetta, M. and G.L. Shulman, *Spatial neglect and attention networks.* Annu Rev Neurosci, 2011. **34**: p. 569-99.
37. Corbetta, M. and G.L. Shulman, *Control of goal-directed and stimulus-driven attention in the brain.* Nat Rev Neurosci, 2002. **3**(3): p. 201-15.
38. Crutch, S.J., et al., *Posterior cortical atrophy.* Lancet Neurol, 2012. **11**(2): p. 170-8.
39. Andrade, K., et al., *Visuospatial deficits in posterior cortical atrophy: structural and functional correlates.* J Neurol Neurosurg Psychiatry, 2012. **83**(9): p. 860-3.
40. Dalrymple, K.A., J.J. Barton, and A. Kingstone, *A world unglued: simultanagnosia as a spatial restriction of attention.* Front Hum Neurosci, 2013. **7**: p. 145.
41. Neitzel, J., et al., *Neuro-cognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy.* Brain, 2016. **139**(Pt 12): p. 3267-3280.
42. Andrade, K., et al., *Visual neglect in posterior cortical atrophy.* BMC Neurol, 2010. **10**: p. 68.
43. Shakespeare, T.J., et al., *Abnormalities of fixation, saccade and pursuit in posterior cortical atrophy.* Brain, 2015. **138**(Pt 7): p. 1976-91.
44. Kas, A., et al., *Neural correlates of cognitive impairment in posterior cortical atrophy.* Brain, 2011. **134**(Pt 5): p. 1464-78.
45. •Golden, H.L., et al., *Auditory spatial processing in Alzheimer's disease.* Brain, 2015. **138**(Pt 1): p. 189-202.
Spatial processing of auditory information is affected in atypical (PCA) and more typical AD. Across both groups, auditory spatial processing deficits is related to atrophy of posterior cortical regions.

46. de Souza, L.C., et al., *Cerebrospinal fluid biomarkers in the differential diagnosis of Alzheimer's disease from other cortical dementias.* J Neurol Neurosurg Psychiatry, 2011. **82**(3): p. 240-6.
47. Carswell, C.J., et al., *Clinical utility of amyloid PET imaging with (18)F-florbetapir: a retrospective study of 100 patients.* J Neurol Neurosurg Psychiatry, 2018. **89**(3): p. 294-299.
48. Lam, B., et al., *Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome.* Alzheimers Res Ther, 2013. **5**(1): p. 1.
49. Dong, A., et al., *Heterogeneity of neuroanatomical patterns in prodromal Alzheimer's disease: links to cognition, progression and biomarkers.* Brain, 2017. **140**(3): p. 735-747.
50. ••Scheltens, N.M.E., et al., *The identification of cognitive subtypes in Alzheimer's disease dementia using latent class analysis.* Journal of Neurology Neurosurgery and Psychiatry, 2016. **87**(3): p. 235-243.
Latent cluster analysis examining cognitive profile in >900 patients with probable AD identified several subtypes, including a group with memory-sparing and moderately affected visuopatial function.
51. Kolanko, M. and P. Malhotra, *Exploring Alzheimer's disease subtypes at the prodromal stage.* Brain, In Press.
52. Stopford, C.L., et al., *Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia.* Cortex, 2012. **48**(4): p. 429-46.
53. Baddeley, A.D., et al., *Attentional control in Alzheimer's disease.* Brain, 2001. **124**(Pt 8): p. 1492-508.
54. Possin, K.L., et al., *Dissociable executive functions in behavioral variant frontotemporal and Alzheimer dementias.* Neurology, 2013. **80**(24): p. 2180-5.
55. Luks, T.L., et al., *Atrophy in two attention networks is associated with performance on a Flanker task in neurodegenerative disease.* Neuropsychologia, 2010. **48**(1): p. 165-70.
56. ••Zhang, X., et al., *Bayesian model reveals latent atrophy factors with dissociable cognitive trajectories in Alzheimer's disease.* Proc Natl Acad Sci U S A, 2016. **113**(42): p. E6535-E6544.
Bayesian modelling of atrophy patterns in the earliest stages of Alzheimer's Disease reveals distinct patterns of atrophy which influence decline across different cognitive domains. A 'cortical' (frontal, parietal, lateral temporal, and lateral occipital cortices) atrophy factor showed the strongest association with executive dysfunction whereas a temporal (medial temporal cortex, hippocampus, and amygdala) factor showed the strongest association with memory impairment.
57. Cummings, J.L., *Alzheimer's disease.* N Engl J Med, 2004. **351**(1): p. 56-67.
58. Drachman, D.A. and J. Leavitt, *Human memory and the cholinergic system. A relationship to aging?* Arch Neurol, 1974. **30**(2): p. 113-21.
59. Whitehouse, P.J., *Clinical and neurochemical consequences of neuronal loss in the nucleus basalis of Meynert in Parkinson's disease and Alzheimer's disease.* Adv Neurol, 1987. **45**: p. 393-7.

60. Moore, T. and M. Zirnsak, *Neural Mechanisms of Selective Visual Attention.* Annu Rev Psychol, 2017. **68**: p. 47-72.
61. Sharma, K., T. Davis, and E. Coulthard, *Enhancing attention in neurodegenerative diseases: current therapies and future directions.* Transl Neurosci, 2016. **7**(1): p. 98-109.
62. Bracco, L., et al., *Do cholinesterase inhibitors act primarily on attention deficit? A naturalistic study in Alzheimer's disease patients.* J Alzheimers Dis, 2014. **40**(3): p. 737-42.
63. Bentley, P., J. Driver, and R.J. Dolan, *Cholinesterase inhibition modulates visual and attentional brain responses in Alzheimer's disease and health.* Brain, 2008. **131**(Pt 2): p. 409-24.
64. Chamberlain, S.R. and T.W. Robbins, *Noradrenergic modulation of cognition: therapeutic implications.* J Psychopharmacol, 2013. **27**(8): p. 694-718.
65. Crook, T., et al., *Noradrenergic intervention in Alzheimer's disease.* Psychopharmacol Bull, 1992. **28**(1): p. 67-70.
66. Schlegel, J., et al., *Guanfacine treatment of Alzheimer's disease.* Clin Neuropharmacol, 1989. **12**(2): p. 124-8.
67. Mohr, E., et al., *Clonidine treatment of Alzheimer's disease.* Arch Neurol, 1989. **46**(4): p. 376-8.
68. Mohs, R.C., et al., *Atomoxetine augmentation of cholinesterase inhibitor therapy in patients with Alzheimer disease: 6-month, randomized, double-blind, placebo-controlled, parallel-trial study.* Am J Geriatr Psychiatry, 2009. **17**(9): p. 752-9.

Figure Legends

Figure 1
Attentional Networks, Key Anatomical Structures and Related Attentional Impairments in AD
Schematic image showing attentional networks and related impairments of attention in patients with AD. IPS: Interparietal Sulcus; TPJ: Temporoparietal Junction; Frontal Eye Fields; dACC: dorsal Anterior Cingulate; PFC: Prefrontal Cortex; SPL: Superior Parietal Lobe.

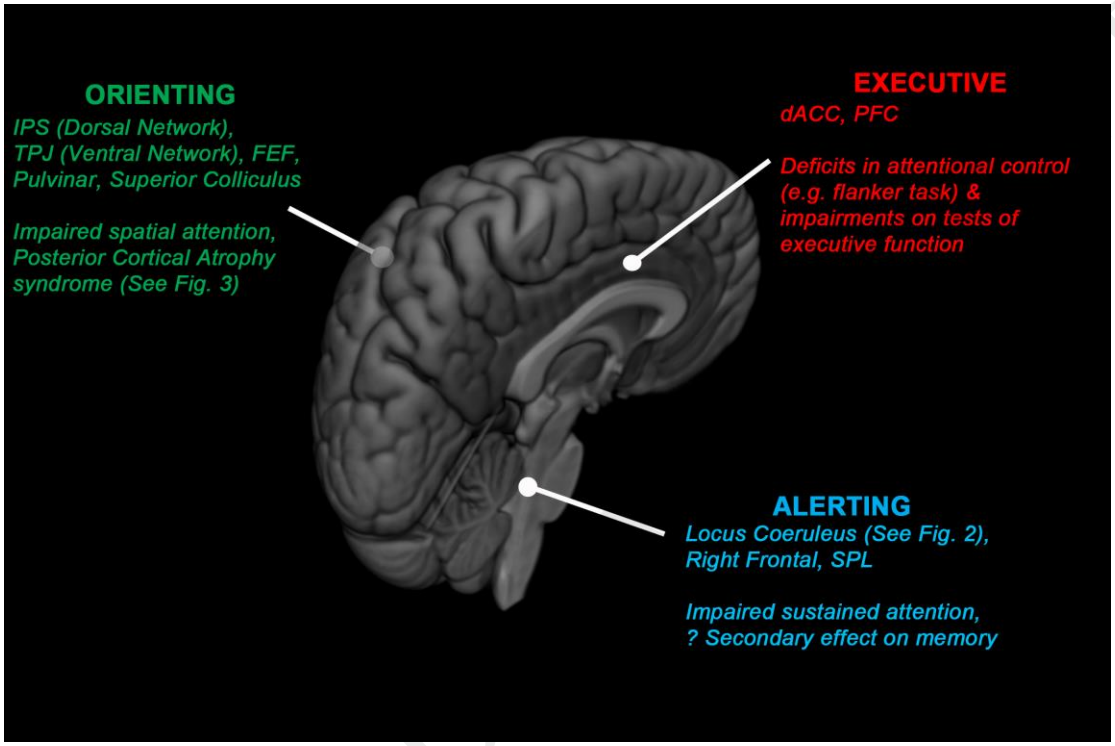


Figure 2
Imaging the Locus Coeruleus in vivo
Image shows axial (A) and coronal (B) view of t1-weighted neuromelanin-sensitive scan in exemplary individual. The LC (arrows) is evident as hyperintense areas. Until recently the locus coeruleus has been hard to image and quantify in vivo. By employing MRI sequences sensitive to neuromelanin, a by-product of noradrenaline synthesis, researchers are now able to image and localise the LC, enabling them to assess the impact of LC changes in health and neurodegenerative diseases (Images courtesy of Dr Dorothea Hämmerer).

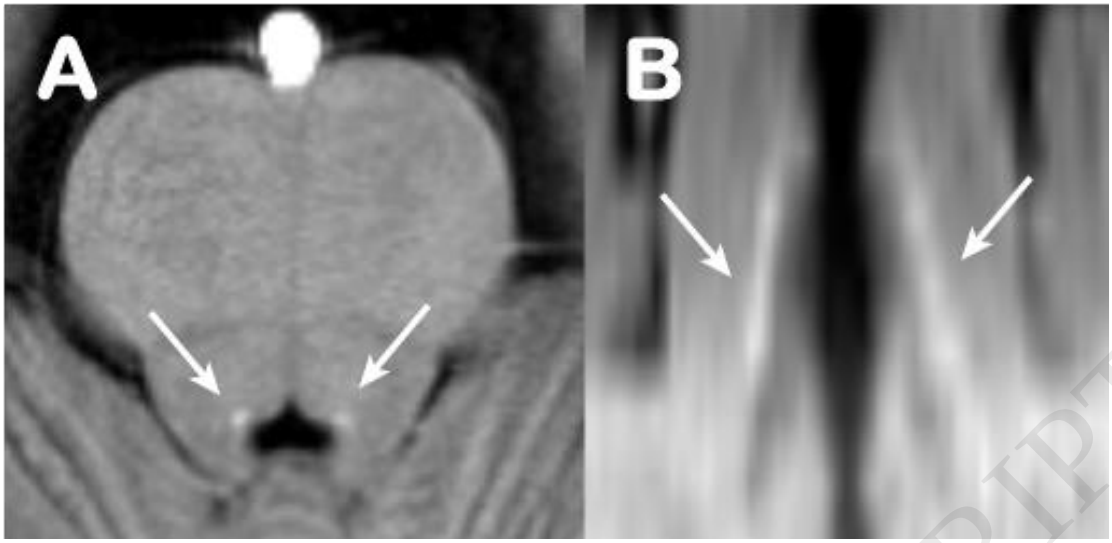
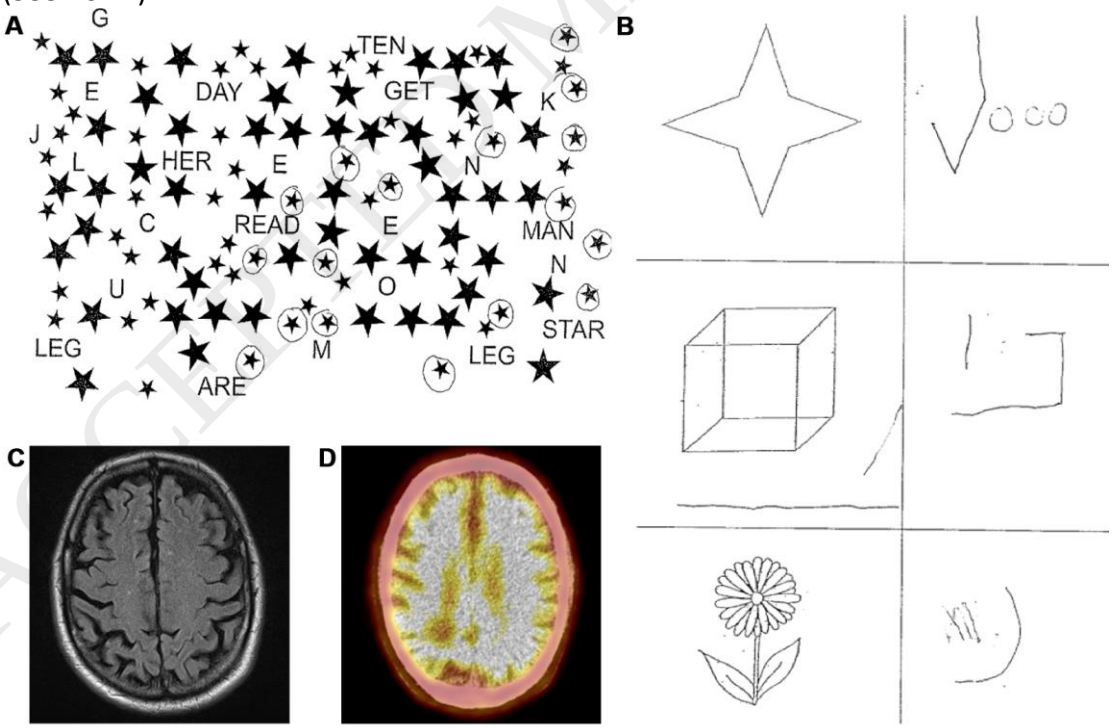


Figure 3

Images showing clinical and radiological findings from a patient presenting with Posterior Cortical Atrophy

(A) Cancellation task (Behavioural Inattention Test star cancellation) performance shows features of left neglect. The participant is required to find and circle all the small stars but is unable to find targets towards the left side, even when given unlimited time. (B) Copying is also affected with left-sided elements of each item omitted. (C) Axial slice from a clinical MR scan demonstrating widening of sulci in a posterior-to-anterior gradient. (D) Amyloid PET imaging with florbetapir showed widespread tracer uptake, indicative of underlying Alzheimer's Disease pathology (See Box 1).



Box 1 Clinical Biomarkers in Alzheimer's Disease

CSF Tau and Aβ1-42*: Low levels of the Aβ1-42 peptide in CSF are a marker for amyloid pathology, suggestive of underlying Alzheimer's Disease. Raised CSF tau and phosphotau levels are more generally indicative of neuronal injury and tend to be raised in AD.*

MRI and PET Imaging*: Amyloid PET imaging can be used to detect the presence of amyloid deposition in patients with Alzheimer's Disease. Structural MRI can be used to demonstrate typical patterns of atrophy and FDG (fluorodexyglucose)-PET will show regions of hypometabolism but these modalities are not-specific for Alzheimer's Disease. Tau PET imaging is currently primarily a research tool and not used in standard practice.*