Cognitive and Behavioural Predictors of Alzheimer's Disease Progression

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Abstract

Alzheimer's disease (AD) can be thought of as divided into pre- and post-diagnostic phases. There is evidence that cognitive and behavioural traits influence the risk of AD diagnosis. Following diagnosis, it may be difficult to tangle the causal direction between cognitive and behavioural measures as predictors or manifestations of AD progress, though people with higher lifetime cognitive trait scores appear to be protected somewhat against worsening cognitive scores and behavioural changes. The pre-diagnostic phase can be considered as a state where AD neuropathology is progressing without manifestations of this and a prodromal phase where, typically, episodic memory is impaired. Far fewer data exist that inform about the effects of cognitive or behavioural predictors during this phase, though those from large brain tissue bank collaborations indicate that education, a correlate of cognitive function, does not influence the extent of neuropathology.

Alzheimer's disease (AD) is the commonest cause of dementia. It is characterised by the presence of senile amyloid plaques and neurofibrillary tangles and clinical characteristics consistent with gradual deterioration in memory function of at least six months duration together with other neuropsychological deficits, most typically aphasia, agnosia, apraxia and disturbance in executive function. Although, strictly speaking, AD cannot be diagnosed in the absence of clinical features, it is generally accepted that there is a preclinical phase that can be present for several years during which the underlying pathological features are progressing. Sometimes a further prodromal phase is defined, manifested as amnestic mild cognitive impairment (aMCI)[1]. aMCI is a state where memory function is impaired at least 1.5 standard deviations below the mean, but where other cognitive domains remain relatively unaffected and where there is none or only minimal impairment of social function and activities of daily living (ADL). Once a person has entered the clinical phase of AD, non-memory cognitive domains are progressively involved together with deterioration in ADL. *Figure 1* demonstrates this schema of AD progression.

A Clinical Dementia Rating (CDR) scale[2] has been devised to reflect this progression in both cognition and ADL. The CDR rating can take the value of zero for absence of dementia, 0.5 very mild, 1.0 mild, 2.0 moderate and 3.0 severe dementia.

In addition, progression to clinical AD may also be accompanied by behavioural changes. Such changes may occur at any phase and in some types of AD, such as that seen in adults with Down syndrome (DS), typically occurs at an early stage and may be an initial symptom.[3] Moreover, some psychological or behavioural symptoms may pre-date clinical AD by several years and thus be considered as predictors of progression.

In this review, we will consider cognitive and behavioural predictors relevant to each stage of AD progression as represented in *Figure 1*.

Cognitive and Behavioural Predictors of Alzheimer's Disease Pathology

There are relatively limited *post mortem* samples large enough to be adequately powered to detect all but the largest effects of cognitive or behavioural predictors of AD pathology. The European Clinicopathological Studies in Europe (EClipSE) collaboration[4] studied 872 brains, 486 with dementia derived from the Medical Research Council Cognitive Function and Ageing Studies (MRC CFAS), Cambridge City Over-75s Cohort Study and the 85+ Vantaa study, and found no association between years of education and neuropathological features of AD even though longer education reduced clinical risk of dementia and was also associated with greater brain weight. Education can be used as a proxy for cognition because it occurs at a time when we can be sure that AD neuropathology has not appeared. Cognitive tests, even in mid-life, may be administered when such changes have already started to occur, so for a true cognitive predictor we require mental ability data from childhood or young adulthood. *Post mortem* studies with such data are currently unavailable.

Figure 1: Schema of Progression in Alzheimer's Disease[1,3]
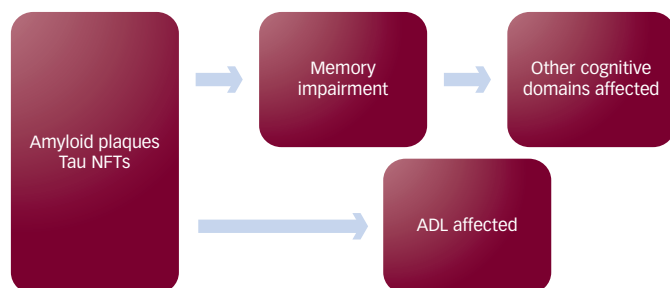
ADL = activities of daily living; NFTs = neurofibrillary tangles.

Data for psychological and behavioural predictors of AD pathology are even scarcer. However, regarding delusions and hallucinations, there is some evidence, based on small studies, that psychotic symptoms may be associated with more severe pathological changes in the frontal and temporal lobes.[5]

Cognitive and Behavioural Predictors of Memory Impairment

In the non-demented population, around 50 % of variance in cognitive ability in old age is explained by a stable lifetime cognitive trait already manifest in childhood.[6] For English-speaking populations, this stable trait can be well estimated using tests of pronunciation of irregular grapheme-phoneme lemmas, such as the National Adult Reading Test (NART).[7] Hence NART-estimated IQ influences normative mini-mental state examination (MMSE) scores in healthy cohorts[8] so that cut-off scores for dementia need to take this into account. NART also correlates with specific cognitive domains such as memory and fluid intelligence.[9] The corollary is that cut-off population norms for memory, as used in defining aMCI, for example, also need to be corrected for this life-long cognitive trait. Memory impairment is also associated with other psychological factors, such as low mood and some of the drugs used to treat depression. Older anti-depressant drugs had more anti-cholinergic effects which are associated with impaired cognition in older adults, though not progress to dementia.[10]

Depression itself can affect memory in a number of ways. Older depressed individuals have frequent somatic complaints and, in addition, can be preoccupied with perceived memory impairment. Subjective memory complaints, in addition to being associated with depression are associated with personality, particularly neuroticism.[11] Such complaints have a complex relationship with dementia and do not seem to be associated with current cognitive impairment but may relate more strongly to risk of later cognitive decline.[11] Furthermore impaired attention and concentration associated with a depressive illness can, in themselves, result in poorer performance on cognitive tests than would be anticipated. In practice this is not a great problem since a full assessment will identify such deficits and make allowances for them.

However depression may also itself be a risk factor for later memory impairment and dementia, but the long period of development of AD neuropathological changes[12] complicates the picture. Depression in earlier life is consistently associated with a markedly increased dementia risk.[13,14] Later life depression does not seem to be associated with dementia in an identical way, though many studies report an increased risk of dementia, particularly for severe depression.[13,15,16] This may suggest depression at this stage of life is an independent

risk factor for dementia, as it appears to be in earlier life, but it may also reflect reverse causality – symptoms of anxiety and depression in response to the early, preclinical changes associated with dementia. There is also evidence that there is a dose-response association, with even mild, subclinical symptoms of anxiety and depression – commonly called psychological distress – being associated with memory impairment and dementia.[17] Again the question of reverse causality remains to be fully resolved.

There are numerous hypothesised mechanisms, presumably reflecting the multifactorial nature of this association.[13] All these models have in common a direct pathological effect on the brain, for example a toxic effect of the hypercortisolaemia of depression on the hippocampus.[18] One particularly interesting possibility is that vascular disease may play a role in the development of both depression and dementia. Some vascular lesions do seem to be associated with an increased risk of depression, leading to the concept of 'vascular depression'[19,20] and the association of vascular risk factors with AD, as well as vascular dementia, is well accepted.[21]

Cognitive and Behavioural Predictors of Clinical Alzheimer's Disease

Although memory impairment typically precedes clinical AD, at present it is inadequate on its own to predict progress to clinical AD with any certainty. However, in a study of 22 patients with familial AD caused by the E280A single presenilin-1 mutation, thirty carriers of the mutation who did not meet AD criteria (asymptomatic carriers) and 30 healthy relatives (non-carrier healthy controls), a test of visual shape-colour binding was sensitive for detecting both early-onset familial AD carriers (sensitivity = 77 %, positive predictive value [PPV] = 77 %, negative predictive value [NPV] = 83 %) and asymptomatic carriers (sensitivity = 73 %, PPV = 81 %, NPV = 76 %) and for separating them from healthy controls (specificity = 83 %), performing much better at identifying the asymptomatic carriers who would progress to clinical AD about 10 years later than other cognitive tests.[22] It remains to be seen whether visual short-term memory binding, that is where it is the ability to remember a combination of shapes and colours relative to the ability to remember the single features on their own, predicts progression in sporadic AD: prospective studies of people with aMCI are required to evaluate this.

The life-long cognitive trait provides, as in the case of memory impairment, a backdrop for crossing the threshold for a clinical diagnosis of AD to be made. An early study suggested that lower childhood IQ increased the risk of dementia,[23] but a subsequent study indicates that this is probably accounted for by its effect on vascular dementia, probably through mid-life vascular risk factors and not AD.[24] These studies were carried out in narrow-age cohorts at ages where dementia would have had time to manifest. It is possible that the life-long cognitive trait may delay clinical AD onset in keeping with the idea or ideas of cognitive reserve.[25] Since the life-long cognitive trait correlates fairly highly with education, the EClipSE collaboration data described above[4] support this paradigm. However, some caution is required in attributing reduced dementia risk to higher pre-morbid intelligence. The case of adults with DS illustrates this. People with DS generally have lower IQ scores than the general population, many falling below 70 and thus consistent with a diagnosis of intellectual disability. People with DS are also at very high risk of an Alzheimer-type dementia. However, this risk is due to increased beta-amyloid production as a consequence of trisomy 21,

since the *APP* gene is located on chromosome 21. It is thus possible that cognitive scores are markers for underlying genetic predispositions. An example in the general population is *APOE* ε4 carriage. This leads to impaired cognition in the non-demented population.[26] *APOE* ε4 carriage also increases AD risk, so again lower cognitive scores may be just an indicator of an underlying predisposition. Other genes that predispose to AD, such as *TRAPPC6A*, have also been shown to be associated with cognitive ageing.[27]

For behavioural and psychological predictors, there is a suggestion that psychopathology, measured by the neuropsychiatric inventory, may be associated with a higher risk of conversion to dementia.[28] Other studies tautologously suggest that functional deterioration in general is associated with conversion to dementia from aMCI, when the absence of functional decline is the least defined part of diagnostic criteria for aMCI. Indeed, one study found that no ADL predicted conversion from 'cognitively impaired not demented' to AD; only the social and occupational component of the Functional Rating Scale did so.[29] However, even though ADL may not predict who will develop dementia, a case-control study found that individuals who went on to develop AD began to become differentiated from controls in terms of their functional ability five to six years before diagnosis.[30]

Cognitive and Behavioural Predictors of Clinical Alzheimer's Disease Progression

Perhaps unsurprisingly, the life-long cognitive trait continues to influence cognitive scores and thus clinical AD progression, beyond diagnosis. Measuring the life-long cognitive trait in people with dementia might appear problematic, but the NART has been validated against true pre-morbid IQ scores and is impervious to the effects of dementia, at least in the mild-to-moderate stages.[31] NART-estimated IQ accounts for 19.5 % of the variance in MMSE scores at the point of diagnosis.[32] Moreover, during follow-up over 78 weeks, one study found that for every 10 IQ points increase as estimated by the NART, there is a corresponding increase of 2.7 % in cognitive abilities as measured by a range of memory tests and verbal fluency.[33] Moreover, there is a trend for people with AD with higher NART scores to have a less steep decline in cognitive abilities over time.[33] A 10 IQ points increase in NART is also associated with a 2 % increase in ADL scores, but this is all explained by the life-long cognitive trait's effect on contemporaneous cognitive function. This suggests that although CDR staging comprises both cognitive and ADL items, it is actually measuring a single underlying trait of disease progression driven largely by cognitive ability. Such a model assumes that disease progression is uni-dimensional. This assumption is open to testing using item response theory (IRT).

IRT-based analyses allow examination of a scale to determine whether there is one or more underlying traits; in this it closely resembles factor analysis. However, in addition it also enables a hierarchy of item difficulty to be determined; that is it tests whether some items are more difficult than others and ranks items according to difficulty. This is particularly useful for assessing disease progress.[34] IRT has been applied to the MMSE[35] and indicates that the MMSE can be thought of as comprising an age-related sub-scale (orientation to time, attention/calculation, naming, repetition and three-stage command) and a non-age-related subscale (orientation to place, registration, recall, reading and copying).[36] The corollary of this is that since people age as their disease progresses, some items are likely to

change more than others and these changes will be partly attributable to age rather than disease progression. This demonstrates the importance of recording cognitive scores at the item level if possible.

IRT can also be applied to ADL scales. As already noted, ADL are a crucial component of AD diagnosis and progression. Correlations between ADL scores and cognitive tests have been found ranging between 0.5 to 0.8 indicating that performance on these functional tasks can be predictive of overall disease severity.[37] That is, AD progression in terms of cognition will be reflected in ADL performance and vice versa. Since a hierarchy of cognitive decline has been established for the MMSE, it is also likely that there will be a hierarchy of functional decline.[38] Confirming a hierarchy of functional decline is more informative than the typical summation of functional deterioration as a confirmed sequence of decline can be used to monitor progression, such that any deviations from the usual progression or changes in rates of progression can be identified and investigated.[39]

However research attempting to expose a pattern of decline has resulted in conflicting hierarchies and some attempts to combine ADL and instrumental ADL into a hierarchical scale have resulted in disagreement over whether it is, in fact, possible to reveal a hierarchy.[40,41] This difficulty replicating hierarchies across different studies can be alleviated by the application of item response models providing invariant item ordering, defined as the extent to which items have the same ordering in terms of item difficulty for all individuals regardless of their total score or latent trait value.[42]

Where hierarchies based on summation of means have been established, such hierarchies will not hold at the individual level, however. "Any set of items can be ordered by item mean scores, but whether such ordering holds for individuals has to be ascertained by means of empirical research. Only when the set of items has an invariant item ordering can their cumulative structure be assumed to be valid at the lower aggregation level for individuals."[42] As such, invariant item ordering is essential for establishing a hierarchy that can be replicated across samples. Applying item response models providing invariant item ordering can enable items to be ordered unequivocally on a hierarchy of item difficulty.

Invariant item ordering of ADL scales is beneficial to clinicians and researchers providing increased understanding of the progression, rate and sequence of the disease and its natural course of decline in ageing.[39,43] Investigating these trajectories in this way can help anticipate subsequent decline in both functional and cognitive abilities and the associated care requirements of patients with cognitive decline. This has the potential therefore to enhance the quality of life of patients and their care-givers and add to our understanding of disease progression.

A recent systematic review sought to identify studies that applied IRT to formally establish a formal hierarchy of functional decline in ADL and instrumental ADL scales in non-demented populations.[44] The number of scales accurately reporting invariant item ordering was rather limited and only four studies were identified that met the requirements for establishing hierarchies at the individual level rather than simply confirming hierarchies at the more general population level. As a result, common items between the scales were relatively scarce allowing only modest patterns in the disablement process to

surface. In line with previous findings, basic ADL such as feeding and personal care were found to be the least challenging items. The lack of studies meeting criteria to establish invariant item ordering may be the result of the assumption held by researchers that the application of any IRT model is sufficient to create an invariant ordering of items. This is not true, as only select models meeting specific assumptions imply an invariant item ordering.

The prognostic relationship between cognitive and functional abilities and how each relates to the progression of AD can be better understood by establishing an invariantly ordered hierarchy. Establishing hierarchies showing which functional abilities are most susceptible to the early effects of cognitive decline can be helpful in diagnosing early dementia.[45,46] In this way, IRT methods increase the interpretative power of ADL scales by establishing item hierarchies which enable researchers to detect minor changes in difficulty for the items most vulnerable to the effects of cognitive decline and consequently indicate the potential onset of progressive cognitive decline.

Conclusions

There is very limited evidence identifying cognitive or behavioural predictors on the underlying disease processes in AD. There is some evidence that a higher lifetime cognitive trait and education protect against the development of clinical AD and may also modulate its course. Psychological stress appears to be a risk factor for subsequent dementia, with an effect size similar to that of vascular risk factors. If there were AD biomarkers that were relevant and reliable as measures of disease progress from the onset of pathology to the terminal stages of clinical AD, these would offer the opportunity to study the effects of cognitive and behavioural variables as potential predictors of progress in greater detail. At present, there is no agreement on such biomarkers and their accuracy as diagnostic tests is unknown.[47–49] There is a clear distinction between tests that aid both diagnosis and prediction of AD and biomarkers which act as indices of progression in addition. Instead, more refined methods are required to assess AD progress using existing measures. In particular, IRT approaches to cognitive and ADL scales promise a more robust index of AD progress that, although it may not stretch back to the inception of neuropathology, may be able to pick up subtle changes before clinical diagnosis. This, together with the development of more AD-specific and sensitive neuropsychological tests, such as short-term visual memory binding, should assist researchers in further investigation of the cognitive and behavioural predictors of AD. ■

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