SCIENTIFIC CORRESPONDENCE

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Early changes in visuospatial episodic memory can help distinguish primary age-related tauopathy from Alzheimer's disease

The observation of neurofibrillary tangles (NFTs) without associated amyloid-beta (Aβ) in the brains of cognitively normal and cognitively impaired elderly individuals has, for many years, been a source of discussion and controversy. The term "primary age-related tauopathy" (PART) was introduced in 2014 and consensus guidelines for the condition were published.[1] The clinical manifestations of PART have been described (see Ref.[2] for review). A recent molecular imaging study suggested that mesial temporal tau load is associated with a decline in cognitive performance in those with no Aβ pathology.[3] Neuropsychiatric assessment has shown poor performance of executive function, processing speed, visuospatial ability, semantic memory and language in PART.[2,4] Although the clinical trajectory in PART differs from that of Alzheimer's disease (AD), the very earliest cognitive changes in PART remain unclear.

Seventy-eight eligible participants from The University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age have been investigated for this study. They were assigned to one of four groups based on pathology at death: normal for age (n = 10), AD (n = 27), possible PART (n = 20) and definite PART (n = 21). During mid to late life, participants undertook four batches of cognitive tests assessing various aspects of cognition including memory, processing speed, fluid intelligence and crystallised intelligence. Details regarding assignment of groupings, exclusion criteria, cognitive testing and pathological features have been published by us elsewhere.[5-7] The Memory Circle (MC) test (a test of visuospatial episodic memory) used here has previously been shown to identify individuals at risk of AD approximately 20 years before death.[8]

Demographic information, stratified by test point, can be found in Table S1. Braak stage, Thal phase and CERAD scores for each individual are shown in Table S2. Most subjects (70%) were female and cognitive impairment at death was present in 27% of participants. Mean age at death was 88.3 ± 5.9. Mean age at MC test 1 was 65.0 ± 5.2, test 2 was 70.8 ± 5.1, test 3 was 75.3 ± 5.1 and test 4 was 77.8 ± 5.5. There were significantly more females in the possible PART group compared to the definite PART group (p = 0.008). Cognitive impairment was more likely in AD group when compared to normal for age (p = 0.054), possible PART (χ^2 = 6.031, p = 0.014) and definite PART (χ^2 = 16.970, p < 0.001). Likewise, cognitive

impairment was more likely in possible PART compared to definite PART (χ^2 = 4.654, p = 0.048). Those considered possible PART died at a significantly older age than those with pathology normal for age (t(28) = −2.159, p = 0.040). There were no other significant differences in age at death or age at the various testing points between the groups. MC test 1 was conducted 23.4 ± 4.2 years before death, test 2 was 17.5 ± 4.0 years before death, test 3 was 13.4 ± 4.1 years before death and test 4 was 10.2 ± 3.9 years before death. Although there is no agreed timeline of prodromal stages of AD or PART, the number of years between initial MC tests (time points 1 and 2) and death places these testing periods well before the onset of overt manifestations of cognitive impairment or dementia in AD.

There were no significant differences between the groups in MC test scores at test point 1 (χ^2(3) = 4.045, p = 0.257), but at test point 2 (χ^2(3) = 8.874, p = 0.031) those with AD scored significantly lower than those with definite PART (U = 144, p = 0.006). Similarly, scores were significantly lower in those with possible PART compared to definite PART (U = 128.5, p = 0.051). There were no significant differences in test scores between the groups at test point 3 (χ^2(3) = 1.012, p = 0.798) or test point 4 (χ^2(3) = 3.283, p = 0.350) (Figure 1). When considering the trajectories of test scores within each group, there were no significant differences between time points although there was a tendency for scores to decline over time in the AD group (χ^2(3) = 6.641, p = 0.084). AD pathology, as measured by Braak stage, Thal phase and CERAD score, also correlated with MC test scores at time point 2. In addition, Thal phase correlated with MC test score at time point 1 and time point 4 (see Table S3).

On first sight, these results might appear counter intuitive. Loss of significance at the later time points may simply be due to fewer available test scores as participants die or drop out of the study. However, when considering prodromal-stage pathological changes and their effect on cognition, another possible explanation emerges. It is presumed that at time point 1 (23.4 ± 4.2 years before death), Aβ pathology is either absent or insufficient in all groups to affect cognitive performance. By time point 2 (17.5 ± 4.0 years before death), Aβ pathology (and possibly tau pathology) will have increased in AD and possible PART to a level where subtle cognitive changes can
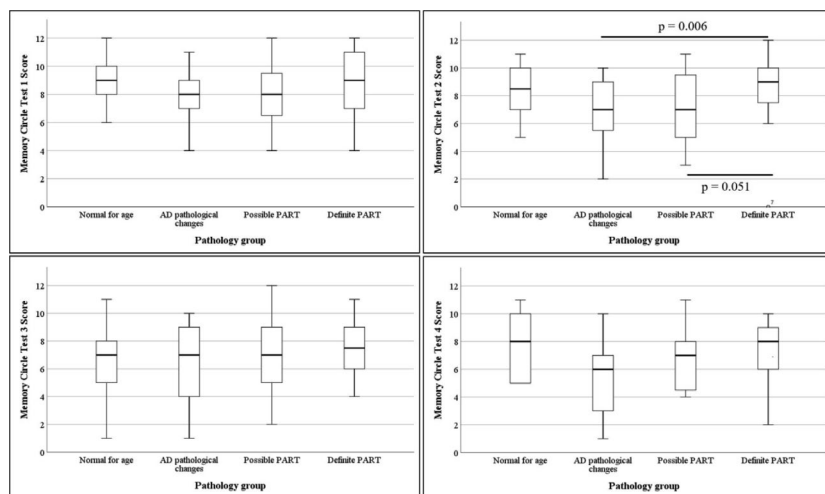
FIGURE 1 Boxplots comparing MC scores between pathology groups at the four testing time points. The boxes represent the interquartile (IQ) range which contains the middle 50% of the records. The whiskers represent the highest and lowest values which are no greater than 1.5 times the IQ range. The line across the boxes indicates the median. Differences between pathology groups for MC scores were analysed with the Mann-Whitney U test

be detected. As no Aβ pathology will be present in definite PART their cognition will remain intact and scores will remain comparable to those with pathology normal for age. However, by time points 3 (13.4 ± 4.1 years before death) and 4 (10.2 ± 3.9 years before death), tau may be present in all pathology groups, along with Aβ in the AD and possible PART groups. There may also be a degree of Aβ pathology present in those normal for age. Thus, the combination of these early pathologies may lead to a convergence in MC test scores again. If later time points had been available, a more severe decline in MC scores in AD compared to possible/definite PART would have been anticipated as the rate of both Aβ and tau pathology accelerates compared to PART.

In this short correspondence, we are raising the possibility that PART can be differentiated from AD very early on in the disease course using a simple cognitive test. To further elucidate these findings, replication in a larger cohort will be needed and questions regarding co-morbidities will need to be more extensively considered. With these points in mind, we tentatively conclude that Aβ deposition has a subtle effect on visuospatial episodic memory in early AD and possible PART. This finding enables a "window of opportunity" to distinguish those who will develop AD from those who will develop definite PART. This early detectable difference in cognition however is transient, being overcome by onset and progression of Aβ and tau pathology in AD and possible PART, and tau pathology in definite PART. Present findings indicate that PART is a separate entity to AD.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

AUTHORS' CONTRIBUTIONS

AR devised and designed the study, performed all statistical analysis and wrote the paper. YD performed immunochemistry and assisted with preparation of the manuscript. FR finalised neuropathological diagnosis and assisted with preparation of the manuscript. JM performed immunochemistry and assisted with preparation of the manuscript. PT provided data for cohort and assisted with preparation of the manuscript. MH helped to finalise clinical cognitive impairment diagnosis, provided clinical data for cohort and assisted with preparation of the manuscript. AP provided data for cohort assisted with preparation of the manuscript. NP finalised clinical cognitive impairment diagnosis and assisted with preparation of the manuscript. DM finalised neuropathological diagnosis and assisted with preparation of the manuscript.

ETHICAL APPROVAL

The study was approved by Manchester Brain Bank Management Committee (REC reference 19/NE/0242). Under conditions agreed with the Research Ethics Committee, The Manchester Brain Bank can supply tissue or data to researchers, without requirement for researchers to apply individually to the REC for approval.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/nan.12726.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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EARLY CHANGES IN VISUOSPATIAL EPISODIC MEMORY CAN HELP DISTINGUISH PRIMARY AGE-
RELATED TAUOPATHY FROM ALZHEIMER'S DISEASE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.