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# Trajectories of memory decline in preclinical Alzheimer's disease: results from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

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ABSTRACT

Memory changes in preclinical Alzheimer's disease (AD) are often characterized by heterogenous trajectories. However, data regarding the nature and determinants of predominant trajectories of memory changes in preclinical AD are lacking. We analyzed data from 333 cognitively healthy older adults who participated in a multicenter prospective cohort study with baseline and 18-, 36-, and 54-month follow-up assessments. Latent growth mixture modeling revealed 3 predominant trajectories of memory change: a below average, subtly declining memory trajectory (30.9%); a below average, rapidly declining memory trajectory (3.6%); and an above average, stable memory trajectory (65.5%). Compared with the stable memory trajectory, high Aβ (relative risk ratio [RRR] = 2.1), and lower Mini-Mental State Examination (RRR = 0.6) and full-scale IQ (RRR = 0.9) scores were independently associated with the subtly declining memory trajectory; and high Aβ (RRR = 8.3), *APOE* ε4 carriage (RRR = 6.1), and greater subjective memory impairment (RRR = 1.2) were independently associated with the rapidly declining memory trajectory. Compared with the subtly declining memory trajectory group, *APOE* ε4 carriage (RRR = 8.4), and subjective memory complaints (RRR = 1.2) were associated with a rapidly declining memory trajectory. These results suggest that the preclinical phase of AD may be characterized by 2 predominant trajectories of memory decline that have common (e.g., high Aβ) and unique (e.g., *APOE* ε4 genotype) determinants.

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## 1. Introduction

There is consensus that in cognitively normal (CN) older adults, abnormally high levels of amyloid beta (Aβ+), assessed using Aβ neuroimaging or cerebrospinal fluid sampling, herald the start of the preclinical stage of Alzheimer's disease (AD; (Rowe et al., 2014). The finding that Aβ+ is associated with reduced episodic memory has also raised the possibility that in CN older adults, memory

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dysfunction may indicate Aβ+ (Darby et al., 2011; Wagner et al., 2012). However, when compared with normative data, CN older adults with Aβ+ show little to no impairment on tasks of episodic memory, certainly much less than that required to warrant evaluation for possible mild cognitive impairment (MCI; e.g., z score $\leq -1.5$ standard deviations [SDs]). Consequently, the extent to which measures of episodic memory, applied in a single assessment, can be used to identify the presence of Aβ+ in CN older adults is limited.

Results of prospective studies have indicated that Aβ+ is associated reliably with memory decline suggests that objectively defined memory decline, which may provide a more accurate basis for identifying preclinical AD (Doraiswamy et al., 2014; Lim et al., 2014a; Mormino et al., 2014). For example, CN older adults with objectively defined memory decline could be investigated with Aβ neuroimaging or cerebrospinal fluid sampling. However, in Aβ+ CN older adults, memory function also varies as a function of demographic (e.g., premorbid intelligence, cognitive reserve; Duff et al., 2013), genetic (e.g., *APOE*; Mormino et al., 2014; Naj et al., 2014), and *BDNF* rs6265 genotype; Lim et al., 2014b), and psychiatric (e.g., anxiety symptoms; Pietrzak et al., 2014) factors. Therefore, any memory decline detected in CN older adults might reflect one or more of these factors in addition to, or even instead of, early amyloidosis. Furthermore, different trajectories of episodic memory change may reflect different underlying neuropathologic processes (Knopman et al., 2013; Nettiksimmons et al., 2013; Wilson et al., 2010). The conclusion that memory decline is associated with AD risk factors comes from studies of CN older adults stratified according to the risk factor of interest and then evaluated for changes in memory over time (Caselli et al., 2009; Doraiswamy et al., 2014; Lim et al., 2012, 2013b; Mormino et al., 2014; Villemagne et al., 2013). Consequently, associations between AD risk factors and memory decline, observed in these studies, do not take into account the potential that heterogeneity in memory trajectories reflects the simultaneous effects of multiple risk factors (Hayden et al., 2009). Thus, to evaluate how memory decline in CN older adults reflects different AD risk factors it would be useful first to characterize predominant trajectories of memory change from a large cohort studied prospectively, and then to examine the extent to which different AD risk factors predict these trajectories.

The aims of the present study were: (1) to identify predominant trajectories of episodic memory change in CN older adults; and (2) to characterize the AD risk factors that are associated with these trajectories. To evaluate these aims, we applied latent growth mixture modeling to evaluate the nature and determinants of predominant trajectories of episodic memory change over a 54-month period in a well-characterized cohort of CN older adults enrolled in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing.

## 2. Methods

### 2.1. Sample

The participants were 333 CN older adults who had undergone Aβ neuroimaging as part of the AIBL Study (Ellis et al., 2009; Rowe et al., 2010). Selection into this cohort was controlled to ensure: (1) a wide age distribution from 60 years through to the very elderly; (2) enrollment of approximately 50% with a subjective memory complaint; and (3) enrollment of approximately 30% *APOE* ε4 carriers (Rowe et al., 2010). Exclusion criteria included: schizophrenia; depression (15-item Geriatric Depression Score $\geq$6); Parkinson's disease; cancer (except basal cell skin carcinoma) within the last 2 years; symptomatic stroke; uncontrolled diabetes; obstructive sleep apnea, previous head injury with >1 hour of posttraumatic amnesia; current regular alcohol use >2 standard drinks per day for women or 4 per day for men. For each assessment, a clinical review panel, blinded to Aβ neuroimaging data, considered all available medical, psychiatric, and neuropsychological data to confirm the cognitive health and clinical classification of each participant. The study was approved by the institutional research and ethics committees of Austin Health, St. Vincent's Health, Hollywood Private Hospital, and Edith Cowan University. All participants provided written informed consent (Ellis et al., 2009).

### 2.2. Positron emission tomography imaging and genotyping

Aβ imaging with positron emission tomography (PET) was conducted using 11C-Pittsburgh Compound B (PiB), 18F-florbetapir, or 18F-flutemetamol. A 30-minute acquisition was started 40 minutes after injection of PiB, whereas 20-minute acquisitions were performed 50 minutes after injection of florbetapir and 90 minutes after injection of flutemetamol. For PiB, PET standardized uptake value (SUV) data were summed and normalized to the cerebellar cortex SUV, yielding a region-to-cerebellar ratio termed SUV ratio (SUVR). For florbetapir, SUVR was generated using the whole cerebellum as the reference region (Clark et al., 2011), whereas for flutemetamol, the pons was used as the reference region (Vandenberghe et al., 2010). In line with previous studies, SUVR was classified dichotomously as either negative or positive (i.e., Aβ− or Aβ+). For PiB, an SUVR threshold $\geq$1.5 was used. For florbetapir and flutemetamol, an SUVR threshold of $\geq$1.11 and $\geq$0.62 were used, respectively. An 80-mL blood sample was also obtained from each participant, 0.5 mL of which was sent to a clinical pathology laboratory for genotyping. DNA was isolated from whole blood using a QIAamp DNA blood Midi or Maxi kit (Qiagen) according to the manufacturer's protocol. *APOE* genotype was determined through TaqMan genotyping assays (Life Technologies) for rs7412 (assay ID: C__904973_10) and rs429358 (assay ID: C__3084793_20). The *BDNF* polymorphism, rs6265 (Val66Met), was genotyped either via a custom Illumina GoldenGate assay, performed by the Beijing Genomics Institute, or through inclusion of the TaqMan genotyping assay (assay ID: C__11592758_10) in a custom designed OpenArray assay (Life Technologies). All TaqMan and OpenArray assays were performed on a QuantStudio 12K-Flex real-time PCR system (Applied Biosystems). Participants were split by the presence or absence of a Met at amino acid position 66 in the *BDNF* gene ($BDNF^{Met}$).

### 2.3. Anxiety and depressive symptoms

Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983).

### 2.4. Vascular risk factors

A count of vascular risk factors was obtained by summing whether respondents met criteria for hypertension (blood pressure $\geq$140/90 mm Hg or currently undergoing treatment with an antihypertensive medication), dyslipidemia (fasting serum total cholesterol $\geq$6.22 mmol/L, fasting serum triglycerides $\geq$2.26 mmol/L, or currently undergoing treatment with statin or fibrate medications), obesity (BMI >30 kg/m$^2$), smoking (smoked >20 cigarettes per day for over 1 year), diabetes (fasting plasma glucose >7 mmol/L or currently undergoing treatment with diabetes medication), high homocysteine levels (males >16.2 μmol/L; females >13.6 μmol/L), or chronic kidney disease (estimated glomerular filtration rate <45 mL/min; (Yates et al., 2014).

### 2.5. Subjective memory complaints

Subjective memory complaints were assessed at the 18-month assessment using the Memory Complaint Questionnaire (MAC-Q;