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Amyloid Discovery Cohort

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BACKGROUND

Dementia is the leading cause of death in England and Wales, accounting for 11.6% of all deaths registered in 2015 [1]. As the population ages, the burden of neurological diseases and dementia in particular will increase dramatically. Current estimates suggest that 44 million people worldwide are currently living with dementia, and this number is predicted to more than triple by 2050, by which time the annual cost of dementia in the US alone may exceed US\$604 billion [2]. Estimates suggest that a five-year delay in symptom onset would halve prevalence, costs and burden [3].

Understanding the causes of dementia, and lifestyle or pharmacological interventions that can prevent or delay the onset of symptoms is therefore a global priority.

Dementia is a clinical syndrome due to many underlying diseases, of which Alzheimer's disease (AD) is the commonest single cause. AD is characterised histopathologically by the accumulation of senile plaques mainly composed of amyloid β ($A\beta$), neurofibrillary tangles composed of hyperphosphorylated tau [4], and excess neuronal cell loss (atrophy) in vulnerable regions, notably the medial temporal lobe and parietal association cortices. The emergence of techniques for studying biomarkers allows for many aspects of AD pathology to be assessed in vivo. In particular, positron emission tomography (PET) using amyloid-specific tracers allows for quantification of fibrillar amyloid burden; and modern multi-modal magnetic resonance imaging (MRI) offers a non-invasive way of determining brain volumes, cerebrovascular disease, white matter tract integrity, brain perfusion, functional connectivity, and brain microstructure. Applying many of these techniques to cohorts with rare, autosomal dominantly inherited forms of AD, sporadic AD, and healthy older controls suggests that: (1) accumulation of $A\beta$ is seen in a significant proportion (up to a third) of individuals in their 70s; (2) $A\beta$ accumulation occurs prior to, and is likely to trigger, the development of other pathological processes core to AD, including the deposition and spread of abnormally hyperphosphorylated tau through vulnerable networks, microglial activation, brain hypometabolism, and increased rates of atrophy; and (3) these processes all occur several years – and in the case of amyloid deposition perhaps a decade or more – prior to the development of symptoms [5, 6].

These findings have already led to important advances, including (1) a re-conceptualisation of AD to include healthy individuals at risk, with contemporary research criteria now determining that asymptomatic individuals with evidence for brain amyloid, brain amyloid + neurodegeneration, or brain amyloid + neurodegeneration + subtle cognitive impairment can be designated as having preclinical AD [7–9]; and (2) the advent of clinical trials in asymptomatic participants either at risk of AD on the basis of carrying a gene known to cause familial AD [10, 11] or individuals with asymptomatic amyloidosis [12]. These trials aim to modify aspects of AD pathology by slowing or even reversing the development of brain pathology, and delaying the onset of cognitive decline and ultimately the clinical manifestation of AD dementia.

Our understanding of this presymptomatic period is, however, far from complete. Evidence to date comes largely from extrapolation of cross-sectional (or short-interval longitudinal follow-up) studies to infer the sequence of changes that occur over much longer periods [13]. Individuals selected for such studies often are not typical of the population as a whole, with many having genetic risks factors, concerns about cognition, or a family history of dementia [14]. Little is known in the general population about the factors that influence the development, sequence and timing of the different pathologies implicated in AD, and how they interact with other brain pathologies (e.g. cerebrovascular disease) to influence cognitive function. Consequently, the evidence base to inform the design of clinical trials in the presymptomatic phase is currently limited.

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In parallel with the need to identify preclinical AD for interventional trials, it is also vital to understand what influences an individual's risk of developing AD and other forms of late-life cognitive impairment. There are more than 20 identified genetic risk factors for AD, most of which exert only a small influence on risk, but together, by way of a polygenic risk score, have been shown to almost double case prediction from chance [15]. There is evidence that education and physical exercise are protective, whereas mid-life hypertension, obesity and diabetes adversely influence risk [16]. However it is unclear whether these factors act independently, cumulatively or interactively, and how they influence different pathological processes that can lead to dementia; to address these questions requires prospective data across the life course.

The Medical Research Council (MRC) National Survey of Health and Development (NSHD) has followed 5362 individuals since their birth in England, Scotland and Wales during one week in March 1946 [17–19]. Repeated waves of data collection since childhood have enabled detailed cognitive and physical phenotyping of this population-representative cohort. Details of the cohort are provided elsewhere [17, 18]. Now aged 71, members of this intensively-studied cohort are at a critical age to investigate preclinical AD: old enough to be at high risk for amyloid pathology, but several years before the expected exponential rise in dementia prevalence [20].

We describe here the study design and protocol of “Insight 46”, a prospective longitudinal two time-point (0, 24 month) sub-study of 500 study members, incorporating the collection of new clinical, neuropsychological, MRI, PET amyloid imaging, and blood and urine biomarkers. We outline the study's organisation and funding structure, provide an overview of the recruitment criteria, the cognitive, imaging and fluid biomarker protocols, and the duty of care protocol. We summarise the key hypotheses to be tested, and the data that are being collected; these data will in due course be made available to the research community.

METHODS / DESIGN

Participants' recruitment and clinical protocol description

Participants

To capitalise on the life course data and to avoid a priori decisions as to who might be at risk of cognitive decline, entry criteria to the sub-study are based only on maximising the life course data available for analysis. A sample of 500 NSHD study members are being selected at random from those who attended a clinic-based assessment age 60–64, had previously intimated they were willing to attend a clinic visit in London and for whom relevant data in childhood and adulthood are available.

The first 500 study members fulfilling these criteria and agreeing to participate will be included. Excluded are individuals with contraindications to MRI or PET including, but not limited to, claustrophobia, metallic implants such as pacemakers, or research nuclear medicine scans within the last year that would result in an individual exceeding acceptable mandated yearly radiation exposures. Where appropriate, the option to consent to post-mortem brain donation is discussed with participants.

Duty of care

A duty of care protocol building on the NSHD protocol used in 2006–10 and in accordance with the MRC/Wellcome Trust guidelines is being implemented for the purpose of feeding back health-related findings in research [22] to each participant and their GP. Participants are given the option of ‘opting out’ from receiving any correspondence regarding reportable findings, but must consent to their GP receiving the information. Anthropomorphic measures (height and weight), recumbent blood pressure, audiometry and a range of standard clinical blood tests (haemoglobin, platelet count, vitamin B12, urea, creatinine, random glucose and TSH) together with their normal ranges are routinely reported. Participants with results outside the normal range are advised to discuss the

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results with their GP in a timely fashion. If blood results are significantly outside the normal range, falling beyond pre-specified 'Action' levels, the study clinician contacts the participant and GP via telephone within 48 h of receipt of results.

All T1, T2 and FLAIR volumetric MRI sequences are reviewed by a consultant neuroradiologist at the National Hospital for Neurology and Neurosurgery. The study follows guidelines based on the UK Biobank imaging study (www.ukbiobank.ac.uk/wp-content/uploads/2016/11/Incidental-findings-list-of-possible-abnormalities.pdf), and information is only fed back to study members and their GP if there is an MRI abnormality that might require treatment or surveillance. The ethical challenges of providing information regarding amyloid PET results in cognitively-normal individuals has been discussed elsewhere [23], and for this study amyloid PET status is not fed back to study members. In addition, information is fed back to participants and their GP if clinical assessments reveal clear evidence of significant cognitive impairment (based on a MMSE score ≤ 24 and/or significant concern from study clinician) or clinically detectable parkinsonism (i.e. fulfilling Queen Square Brain Bank criteria [24] for Parkinson's disease (PD)) in previously undiagnosed individuals.

Clinical, neurological, cognitive and sensory assessments

All individuals are assessed at a single site (UCL). Participants complete four self-administered questionnaires; undergo a structured clinical interview with a neurologist; have a structured neurological examination; undergo neuropsychological testing, and assessment and testing of auditory, olfactory and visual function. These assessments have been designed to be administered in divided sessions that last less than four hours during a single day (mean duration =199 min based on six pilot visits).

Self-administered questionnaires

The state and trait anxiety inventory [25]: This 40-item questionnaire assesses an individual's thoughts and feelings, and is designed to quantify anxiety levels at the present moment and in general.

A dental health questionnaire [26]: There is growing evidence that periodontitis is a risk factor for sporadic AD and it has been postulated that periodontal pathogens may drive chronic neuro-inflammation contributing to Alzheimer's pathology [27]. This self-administered questionnaire utilises eight questions designed to assess the likelihood of periodontitis.

A handedness questionnaire [28]: Hand preference is closely related to cerebral dominance [29]. This questionnaire assesses hand preference for 12 different tasks using a numerical scale enabling quantification of each participant's handedness (range - 24 to +24).

Screening question for Rapid Eye Movement (REM) sleep behaviour disorder [30]: REM sleep behaviour disorder is a known risk factor for the emergence of Parkinson's disease and related disorders. A yes/no answer is obtained to the question "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?". This has a sensitivity of 93.8% and a specificity of 87.2% for detecting REM sleep behaviour disorder [30].

Clinical interview

A standard personal and family history of neurological illness or cognitive impairment and a medication history is obtained. In addition, participants are screened for measures of self-perceived cognitive decline using the SCD-Q part I (MyCog) questionnaire [31] and are asked questions that enable coding of essential features of subjective cognitive decline as outlined by the working group of the Subjective Cognitive Decline Initiative [32]. A corroborative history regarding each participant's cognitive functioning is obtained using the AD8 screening tool, an informant questionnaire administered in person or via the telephone by the study clinician. The AD8 correlates

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well with the clinical dementia rating scale (CDR), and has high sensitivity and specificity for detecting cognitive impairment [33, 34].

Physical and neurological examination

A physical examination comprises anthropomorphic measures (weight in kilograms and height measured to the nearest mm), and lying and standing blood pressure at three minutes to assess for evidence of orthostatic hypotension (OMRON HEM-905; OMRON Healthcare UK Ltd., Milton Keynes).

Patients with AD and other forms of dementia have more marked decline in motor function, including gait, than healthy controls, with the possibility that these changes may precede the onset of frank cognitive symptoms [35, 36]. This is perhaps not surprising if gait is viewed as a complex cognitive task, requiring an interplay of attention, executive function and visuospatial function, in addition to the motor processing functions of the motor cortex, basal ganglia and cerebellum. It has therefore been suggested that changes in gait and motor skills in general may reflect and correlate with early cognitive change [37].

Participants' self-paced gait is assessed over a 20- m distance in isolation and while performing a cognitive task (single-letter-cued (phonemic) fluency and dual-letter-cued (phonemic) alternate fluency), and wearing an accelerometer on the lower back (LPMS-B inertial measurement unit (Life performance Research Inc.)), with data analysis using a custom program written in LabVIEW2010 (National Instruments, Ireland). Temporal (step time and cadence) as well as spatial (step-, stride-time, walking speed) parameters can be derived. More in-depth analysis utilising temporal-spatial parameters and participant metadata can describe parameters indicating motor control [38]. Non-linear or phase plot analysis can be used to explore subtle gait changes using the whole dataset of a particular participant. Using this approach, it has been demonstrated that changes in gait can be detected in the pre-symptomatic phase of Huntington's disease [39].

Although parkinsonian features are generally considered to be later clinical manifestations in AD, it has been reported that parkinsonian features may precede the onset of frank dementia [40, 41]. A standardised neurological examination includes the MDS-Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Motor) [42], which quantifies presence of tremor, bradykinesia, rigidity, postural instability and gait disorder. Assessments are videotaped for quality control purposes and to enable further review by a senior neurologist if clinically significant parkinsonian features are identified. The Bradykinesia Akinesia Incoordination (BRAIN) test is administered to all participants via a laptop (Lenovo Thinkpad, Lenovo Group Ltd). This computer keyboard tapping task was originally developed for use in assessing the effect of symptomatic treatment on motor function in Parkinson's disease. An online version has been designed and validated which can be utilised as an objective longitudinal measure of emerging motor dysfunction [43]. The outputs of the BRAIN test include a kinesia score (KS30, number of key taps in 30 s), akinesia time (AT30, mean dwell time on each key in ms), incoordination score (IS30, variance of travelling time between key presses) and dysmetria score (DS30, accuracy of key presses).

Cognitive battery

The cognitive assessment battery is based on a review of results and cognitive protocols from several large-scale initiatives and clinical trials involving individuals at risk for AD [10, 12, 44], and is complementary to cognitive assessments performed as part of the most recent (in some cases concurrent) NSHD home visit (that includes the ACE-III [45] and word-list learning [46]).

Complementing ongoing work with the whole NSHD cohort, participants' cognitive trajectories will be assessed prospectively over the two time points, and retrospectively using previously collected cognitive measures.

The battery includes:

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The mini-mental state examination (MMSE) [47]: The MMSE is a widely used 30-point screening tool for cognitive impairment within clinical practice, assessing multiple cognitive domains including: i) orientation to time and place (10 points); ii) registration (3 points); iii) attention +/- calculation (5 points); iv) recall (3 points); v) language (2 points); vi) repetition (1 point); vii) reading (1 point); viii) writing (1 point); ix) visuospatial function (1 point); x) following a 3-stage command (3 points).

Logical memory from the Wechsler Memory Scale-Revised (WMS-R) [48]: The Logical Memory test assesses free recall of a short story that contains 25 details. The participant is asked to recall the story immediately and after a delay of approximately 20 min.

Digit-symbol substitution test, from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [49]: The Digit-Symbol Substitution test explores attention and psychomotor speed. Participants are given a code table displaying the digits from 1 to 9, each paired with a symbol. On a worksheet printed with rows of digits, participants are asked to fill in the corresponding symbol under each digit as shown in the code table, as quickly and accurately as possible. The score is the number of symbols completed correctly within 90 s.

Matrix reasoning from the Wechsler Abbreviated Scale of Intelligence (WASI) [50]: The Matrix Reasoning test assesses non-verbal reasoning. Participants are shown a matrix of geometric shapes with a section missing and are required to select the missing piece from five options. There are 32 matrices, graded in difficulty, and the test is discontinued when participants reach a certain error threshold, as specified in the WASI manual.

Five more novel tests, intended to detect subtle, early cognitive deficits, are also being administered (see Fig. 2).

Task-set switching / response inhibition [51, 52]: A meta-analysis of relationships between amyloid burden and cognition in cognitively-normal older adults found evidence of an association between amyloid burden and executive functioning [53]. This task examines the relationship between two important executive functions – task-set switching and response inhibition – which are vulnerable in early AD [54, 55]. Individuals are presented with a computer screen on which a stimulus is displayed, and a response box with two buttons. The first part of the experiment comprises the simple choice “arrow only” and “word only” conditions, which complements the simple choice reaction time tasks administered at 60–64 years. In the “arrow only” condition, participants are shown the cue ‘arrow’ for 1000 ms, followed by an arrow pointing left or right. In the “word only” condition, participants are shown the cue ‘word’ for 1000 ms, followed by the word ‘left’ or ‘right’. In each case they must press the button that corresponds to the stimulus, using the index and middle fingers of their dominant hand. The second part of the experiment is a switching condition in which the cue may be either ‘arrow’ or ‘word’, and the stimulus is a combined arrow and word. The stimulus is either congruent (e.g. left arrow and the word ‘left’) or incongruent (e.g. left arrow and the word ‘right’). Trials in the switching task are categorised into switch and non-switch. In a non-switch trial the cue is the same as for the immediately preceding trial, whereas in a switch trial the cue differs from the immediately preceding trial. In order to evaluate the effect of preparation time on task-set switching and response inhibition, the cue is shown for either a short (200 ms) or long (1500 ms) interval before the stimulus appears. Outcome measures are reaction time and error rate.

‘What was where?’ visual short-term memory binding task [56, 57]: This test requires participants to view one or three fractal objects, presented simultaneously in random locations on the screen. Participants are asked to remember both the objects and their locations. After a delay of one or four seconds they are required to make a forced choice between two fractals, one of which was displayed in the initial memory array (the target) and the other of which is a ‘dummy’ fractal. Participants are required to touch the object they think has been previously presented and ‘drag’ it on the touch screen to its remembered, original location. Outcome measures are the proportion of fractals correctly identified, and the localisation error (i.e. the distance between the location reported by the

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participant and the true location of the target in the initial memory array) and the proportion of 'binding errors'. A binding error occurs when a participant chooses the correct fractal but drags it to the location of one of the non-target (unprobed) fractals from the initial array. The binding of such featural information has been shown to be vulnerable in asymptomatic familial AD mutation carriers [58, 59]. There is evidence that binding ability is relatively preserved in normal ageing despite the age-related decline in memory for object identification and localisation, making it a promising target for sensitive tests to detect preclinical AD [60].

Visuomotor integration: This is a circle-tracing task which includes both direct and indirect visual feedback conditions. The task is presented on a tablet laptop, with the screen placed flat on the table in front of the participant, with an additional free-standing monitor behind it. Participants are asked to use a stylus to trace round a circle on the tablet as quickly and accurately as possible. In the direct condition, participants can see their hand and the path they are tracing on the tablet. In the indirect condition, participants put their arm under a box so they cannot see their hand, but they are instructed to look at the free-standing monitor to view a copy of the circle and their tracing path. Continuous performance measures are provided including accuracy, speed and speed of error detection and correction. The test has revealed changes in speed and accuracy in Huntington's Disease mutation carriers more than 10 years before expected age-of-onset [61].

12-item Face-Name Associative Memory Exam (FNAME- 12A): The FNAME-12A is a modified version of the 16-item Face-Name Associative Memory Exam (FNAME-16). The FNAME-12A has fewer stimuli and additional learning trials which are well tolerated by those with mild cognitive impairment (MCI), while remaining challenging in cognitively-normal older adults [62]. It has demonstrated psychometric equivalence with the FNAME-16, which is related to β -amyloid burden in cognitively normal older people [63]. The FNAME-12A requires the participant to learn 12 face-name and face-occupation pairs. Participants are given two exposures to all 12 face name/ occupation pairs. After each exposure and following a 10-min delay they are asked for the name and occupation associated with each face. After a 35-min delay they are shown three faces and asked to identify each previously learned face from two distractors (facial recognition) and to recall the name and occupation. If they cannot remember the name or occupation, they are provided with three recognition choices.

Irrelevant distractor paradigm [64, 65]: Participants are given a computerised letter-search task and are required to make a rapid decision as to which target letter ('X' or 'N') has appeared in the search display. There are three load conditions, high (four letters), medium (three letters) and low (one letter). On some of the trials, a distractor appears on the outside of the search display. This distractor can either be task irrelevant (a cartoon character) or task-relevant (the letter X or N). The task-relevant distractors can be congruent or incongruent to the target letter. Outcome measures are reaction time and error rate. The task evaluates the extent to which attention is captured by the different distractors, and the role of perceptual load in this process.

These tasks give weight both to response accuracy and latency to maximize detection of subtle cognitive change and discriminate cortical/subcortical dysfunction. Cognitive performance at the 2-year follow up in the sub-study will be evaluated against study baseline performance and cognitive performance in childhood, adolescence and adulthood.

Sensory function

There is increasing interest in the possibility that impaired visual function, sense of smell and hearing may provide signals of preclinical AD [66–70]. As such, participants will have comprehensive sensory assessments of vision, olfaction and both peripheral and central auditory function.

Basic parameters of visual function, an important factor contributing to deficits experienced in elderly patients with cognitive impairment, are assessed using The Portable Eye Examination Kit

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(PEEK), a smartphone application that measures visual acuity, colour vision and contrast sensitivity [71].

The University of Pennsylvania Smell Identification Test (UPSIT) is a commercially-available, well-established, reliable, and standardized olfactory test that can be self-administered [72]. The 'British' version is being used as it is the most culturally appropriate to the NSHD. Each test comprises four 10-page booklets with one odorant (embedded in 10–50- μm diameter microcapsules fixed in a proprietary binder and positioned on brown strips) at the bottom of each page. Accompanying each strip is a multiple-choice question with four responses following an alternative forced-choice paradigm. Packs are provided to participants to complete at home and returned using a pre-paid envelope provided. Participants are also asked prior to testing whether they have subjectively noticed a decline in their sense of smell.

Peripheral hearing is assessed using air conduction threshold audiometry, with pure tones presented to each ear at different frequencies covering the range of human speech perception (0.5 kHz - 4 kHz). A testing procedure in keeping with British Society of Audiology recommendations [73] is used in which the sound level of the tones are varied and hearing thresholds for each ear at each frequency to be obtained.

Central auditory processing is tested by using a word identification in background noise paradigm [74]. This involves presentation of high-frequency monosyllabic words embedded in a multi-talker babble noise composed of 20 voices. The background noise is presented at a fixed level of 65 dB SPL, while the sound level of each individual word is varied according to an adaptive staircase procedure based on whether participants are able to identify the word correctly. This is designed to obtain a "speech reception threshold", which quantifies participants' ability to identify spoken words in background noise.

Imaging protocol description

Imaging is performed on a Biograph mMR 3 T PET/ MRI scanner (Siemens Healthcare, Erlangen), allowing for simultaneous acquisition of dynamic amyloid PET and MR data whilst minimising scanning time and exposure to radiation (compared with the use of PETCT). Participants will have one scanning session at each time point. The neuroimaging protocol comprises both structural and functional acquisitions, and is designed to be completed within a 60-min scanning session.

Amyloid load is assessed using the 18F amyloid PET ligand, florbetapir. Amyloid positivity on florbetapir- PET imaging is correlated with post-mortem A β burden, neuritic amyloid plaque density, and neuropathological diagnosis of AD [75]. After intravenous cannulation, 370 MBq florbetapir F18 (Amyvid) is injected. PET data are acquired continuously during and following injection to allow florbetapir uptake dynamics to be assessed. Final amyloid burden is assessed over a 10-min period, ~50 min after injection, with scope for the previous 10-min period to be used if longer scan periods are not tolerated. PET data, acquired in list-mode, is reconstructed using a 3D ordered-subset expectation-maximisation algorithm with three iterations and 21 subsets, and smoothed with a 4 mm Gaussian kernel. Attenuation maps are computed by default from the ultra-short echo time (UTE) sequences provided by the vendor as well as from the T1-weighted and T2-weighted volumetric scans using a multi-atlas CT synthesis method [76], also known as pseudo-CT (pCT). The latter approach significantly improves PET reconstruction accuracy when compared to the UTE-based correction [77].

For the MR acquisitions, a body coil RF transmitter is used in conjunction with a 12-channel receiver array head coil. The maximum gradient strength is 45mT/m along each direction. The MR sequences are:

- (i) high resolution 3D T1-weighted, T2-weighted and FLAIR volumetric scans;
- (ii) resting state functional MRI (rs-fMRI);

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- (iii) multi-shell high angular resolution diffusion-weighted MRI (DW MRI);
- (iv) a multi-echo 3D gradient echo sequence for simultaneous T2*-weighted/susceptibility-weighted imaging (SWI), quantitative susceptibility mapping and b₀ field mapping; and
- (v) arterial spin labelling (ASL) for quantitative mapping of cerebral blood flow (CBF).

An additional b₀ field map is also acquired for distortion correction of the rs-fMRI and DW MRI images.

3D volumetric scans (T1, T2 and FLAIR)

Three volumetric scans are acquired with matched spatial coverage, resolution and complementary contrasts, to aid tissue segmentation, delineation of the intracranial vault, and white-matter lesion visualization. 3D T1-weighted images are obtained using an MPRAGE sequence [78]. This is optimized to provide strong contrast between white matter and grey matter and enable quantification of grey matter macroscopic structures in both cortical and subcortical brain regions. 3D T2-weighted images use a long echo train turbo spin echo sequence (SPACE) [79]. FLAIR images are acquired using the same SPACE sequence as T2-weighted images but with the addition of an inversion preparation pulse to null signal from cerebrospinal fluid. T2-weighted and FLAIR images are sensitive to white-matter lesions and hyperintensities, which are typically seen in association with cerebrovascular disease.

Images undergo manual QC in line with protocols developed for commercial trials, by a trained team who assess motion, coverage and other issues. T1 scans are additionally checked specifically for blurring, image wrap-around and contrast problems, and FLAIR for good CSF suppression. Pre-processing of structural (T1, T2, FLAIR) images is carried out by applying a correction for gradient non-linearity [80] followed by brain-masking (by registration of MNI template to the scan) N4-bias correction [81]. An automated multi-region parcellation of the T1 images is carried out using geodesic information flow (GIF) [82] – demonstrated in Fig. 4. The parcellation is transferred to microstructure, PET, ASL and fMRI maps for the purpose of region-of interest (ROI)-based analysis following registration of those images to the T1 image.

Resting state fMRI (rs-fMRI)

Resting state, or task-free, fMRI (rs-fMRI) allows for assessment of functional cortical connectivity through analysis of resting state networks (i.e. disparate brain regions which exhibit synchronised fluctuations in local cerebral blood flow while the brain is not engaged in any specific task), which are thought to represent cortical networks critical to the functional organisation of the brain [83]. rs-fMRI is acquired using a T2*-weighted gradient echo EPI acquisition scheme. A resolution of 3x3x4mm³ was chosen to ensure whole brain coverage (defined as 144 mm coverage in the inferior-superior direction for angled transverse slice orientation [84]) within a reasonable relaxation time (TR) (~2 s). Parallel imaging is also used to accelerate the imaging and reduce image distortions (GRAPPA with acceleration factor 2). At the beginning of the rs-fMRI acquisition, participants are asked to “close their eyes and not to fall asleep” for the duration of the scan.

Individual fMRI time series are visually checked for head coverage, motion, signal dropout and other artefacts. All fMRI volumes are realigned to correct for motion between individual points in the time course. A plot of the registration parameters computed in the motion correction is provided for manual review to ensure that the level of motion is not severe enough to adversely affect the resulting analysis. Signal quality metrics such as signal-to-noise ratio (SNR), variance of signal change from average signal (DVARs) and spike levels are also plotted over the length of the time course [85]. Time points that are outliers are automatically removed from the analysis.

The motion-corrected fMRI time course is then registered to the corresponding anatomical T1 image. A cohort specific group template discretised in MNI space is iteratively computed by mapping all T1 images with 10 (1 rigid, 9 affine) and 10 non-linear registrations into the MNI image space [86]. The fMRI scan is then transformed into the template space by combining the affine registration from

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fMRI to T1 image with the transformation that maps the individual T1 image into the group template in MNI space. A Generalised Linear Model (optimised with restricted maximum likelihood estimation (REML) [87]) is used to account for signal drifts and physiological noise using cosine basis functions (high pass filtering of frequencies >0.01 Hz), the demeaned motion-realignment estimates and their derivatives, and RETROICOR regressors, where appropriate [88].

Two methods of analysing the pre-processed data will be used: a seed-based method and independent component analysis (ICA) [89]. In brief, the remaining residuals Fig. 4 Volumetric T1 pre-processing and segmentation in Insight 46. Examples of axial (top row), coronal (middle row) and sagittal (bottom row) slices from an original MPRAGE volumetric T1 scan (left column), pre-processed T1 (distortion and bias field corrected) (middle column), and with the GIF parcellation overlaid on top (right column) are smoothed (Gaussian smoothing kernel with 5 mm FWHM) and mapped into the subsampled group space to create spatial correspondence among individual brains. A seed region is chosen to extract an average time course that is correlated with the time course of every individual voxel. The resulting correlation map per participant is Fisher z-transformed to enable t-test hypothesis testing among participants. For the ICA, time courses of the motion realigned fMRI scan within a mask of the brain are extracted, centred and variance-normalized, resulting in one voxel-time matrix per participant. All participant matrices are then concatenated in time. The obtained group matrix is reduced to its principal components and whitened. The independent component analysis [90] is applied to the whitened group matrix to obtain spatial components. The representation of all group independent components in each participant is required for group comparison. Dual regression will be applied to obtain group-independent component representations in each participant.

Diffusion-weighted MRI

Diffusion-weighted MRI is a technique that enables characterisation of the microstructural integrity of white and grey matter. The majority of studies investigating neurodegeneration utilise the diffusion tensor model [91], which aggregates the differential diffusion profiles of water molecules in extra- and intracellular spaces to produce an array of metrics including fractional anisotropy (FA), axial diffusivity (AxD), radial diffusivity (RD) and mean diffusivity (MD). These metrics have been used to demonstrate change in white-matter tract integrity and grey-matter microstructure in AD [92]. However, this model does not account for multiple fiber orientations or tissue compartments within a voxel, making interpretation of changes in these metrics ambiguous. Neurite orientation dispersion and density imaging (NODDI) [93] is a recently-developed multi-shell diffusion technique which allows for the estimation of tissue microstructure at the sub-voxel level by assuming that water protons in neuronal tissue can be considered to be in three different pools: i) free water, modelling CSF space; ii) restricted water, modelling dendrites and axons; and iii) hindered water, modelling diffusion within glial cells, neuronal cell bodies and the extracellular environment. This more complex modelling enables estimation of neurite density (neurite density index (NDI)) and neurite orientation dispersion (orientation dispersion index (ODI)) in both white and grey matter.

Diffusion MRI is acquired using a twice-refocused spin echo EPI sequence [94, 95] with two non-zero b-values (700 and 2000 s/mm^2) and multiple directions (32 and 64 directions for the $b = 700/2000$ s/mm^2 scans respectively). The b-vector directions were calculated to be uniformly distributed over a hemisphere, and images with $b = 0$ s/mm^2 are interspersed throughout the acquisition (12 obtained overall). Images are acquired with an isotropic $2.5 \times 2.5 \times 2.5mm^3$ resolution, with 58 slices to ensure whole brain coverage.

Visual review is performed for identification of poor quality images by checking for: (i) full brain coverage; (ii) inter-acquisition motion (using motion plots over the acquisition); (iii) sufficient correction of geometric distortion; and (iv) slice-wise signal dropout (using correlation plots between adjacent slices). Images failing this quality-control process are removed before running the diffusion

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analysis. For each participant, if the number of acquisitions that have failed is high enough that it might affect the consistency of the analysis between subjects, then these data are marked as a 'failed acquisition'.

Pre-processing of diffusion-weighted images involves first correcting for inter-volume motion registration and eddy currents using FSL's Eddy tool [96]. This is followed by correction for EPI susceptibility distortion using field maps to the structural T1 [97] and phase encode direction constrained non-linear registration to the T1 volume, with modulation based on the Jacobian determinants. The separate diffusion weighted shells (together with their associated $b = 0$ volumes) are fitted with a diffusion tensor model using NiftyFit [98]. The NODDI model is then fitted to the combined shells [93] (see Fig. 5 for an example of the diffusion-weighted images and corresponding parameter maps).

3D T2/SWI*

T2*/SWI are iron-sensitive sequences that allow for detection of cerebral micro bleeds, associated with cerebral small vessel disease or cerebral amyloid angiopathy, generally distinguished by their distribution within the brain parenchyma. Micro bleeds are more common in AD than controls [99], and may independently impact on cognitive function with potential mechanisms including tissue necrosis in strategic white-matter tracts [100], or via the initiation of an inflammatory cascade [100]. A 3D multi-echo gradient echo sequence is acquired to generate T2*-weighted images, T2* maps, SWI, and quantitative susceptibility maps (qSM). This sequence can also provide b_0 field mapping at higher resolution than the GRE-based field maps that are currently often used for processing geometric distortion correction of the DWI and fMRI. The sequence acquires magnitude and phase images at three echo times: TE = 4.92, 9.84, and 19.7 ms (chosen to keep fat and water signals in phase). Magnitude images from the longest TE (19.7 ms) provide the T2*-weighted volume, which are combined with the phase images from the same echo time to generate SWI [101]. T2* maps are generated by fitting the three magnitude images to a monoexponential decay $S = S_0 \cdot \exp(-TE/T2^*)$, and qSM are obtained from the three phase images using the superfast dipole inversion (SDI) method [102]. The images are visually checked for coverage, motion, and artefacts.

Arterial spin labelling (ASL)

ASL is a non-invasive method for determining regional cerebral blood flow (CBF). In brief, blood flowing through the neck vessels is labelled via spin inversion. After a delay period to allow this labelled blood to perfuse into the brain, images are acquired, and compared with equivalent images acquired without prior spin labelling (unlabelled images). The signal difference between labelled and unlabelled images is proportional to blood flow, thus enabling calculation of a quantitative cerebral blood flow map.

ASL data are acquired using a 4-shot segmented 3D GRASE pCASL sequence [103]. The ASL timing parameters were chosen based on the recommendations of the recent ISMRM Perfusion Study Group consensus paper [104]: labelling duration = 1800 ms; post labelling delay = 1800 ms. Ten averages are acquired and saved separately, in order to allow image realignment prior to averaging. Background suppression is used to reduce static tissue signal, and an accompanying set of three saturation recovery data sets (TR = 1 s, 2 s, /2/4 s) are acquired using the same 3D GRASE acquisition scheme for estimation of tissue T1 and M0 (total scan time ~ 50s).

During pre-processing, CBF maps are calculated using the recommended model for ASL images acquired with a single post-labelling delay [104], implemented in NiftyFit [98] and assuming blood T1 at 3 T of 1650 ms and an overall labelling efficiency of 0.833 (blood inversion efficiency of 0.85 and two background suppression pulses with inversion efficiency 0.99 each). The saturation recovery data are fitted to a monoexponential recovery curve to estimate the underlying tissue magnetisation (M0) and receiver coil sensitivity variation, enabling generation of quantitative CBF maps [98]. Error

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maps are also provided to allow inference of how precisely CBF in different regions has been estimated.

Primary imaging pipelines and analyses

All imaging data, derived results, visual quality checks, and radiological reads are stored on a customised web-based server running XNAT 1.6.5 (www.xnat.org). As protected health information (PHI) is stored in the proprietary listmode format, but difficult to remove, the decision was made not to enter any PHI on the scanner console of these participants. After data are acquired on the PET/MR scanner they are transferred to a study-specific waypoint. This includes both the DICOM-compliant imaging format used for MRI and PET images that are reconstructed on the scanner and raw listmode data that consists of a customised DICOM file which contains the Interfile header and a corresponding binary data file generated from the full 60 min of PET acquisition. Twice daily, all recent data are securely synchronised between the study-specific waypoint and the XNAT server, where separate import processes are done for both the DICOM and listmode data. DICOM data are checked for completeness before formally importing the data into the Fig. 5 Representative diffusion images in Insight 46. Examples of diffusion images at the two b values, $b = 700$ and 2000 s/mm², with their corresponding derived MD and FA maps (left) and NODDI metrics (right) XNAT database. Once the DICOM data have been imported, listmode data are then added to the PETMR imaging session in the database and automatic checks are performed to ensure that they contain the full 60-min acquisition, including some small amount of time before the tracer was injected. Next, an in-house workflow management system automatically starts the modality-specific pre-processing steps mentioned in the previous section. Key derived images generated during these pre-processing steps are stored on the XNAT server by attaching them to the original imaging session. Once pre-processing is complete, visual review for each modality is performed and a customised modality-specific webform of the quality checking is stored on the XNAT server.

A consultant neuroradiologist reviews all T1, T2 and FLAIR sequences as outlined in the “Duty of Care” section by downloading the key imaging data from the server and completing a customised radiological read web-form within XNAT. Customised reports are provided to the neuroradiologist which identify the PET-MR imaging sessions where a read needs to be completed.

Primary analyses of T1 images include automated segmentation of whole-brain [105] and hippocampal regions [106], followed by manual checking and editing, semi-automated ventricle segmentation, automated total intracranial volume (TIV) measurement [107] and semi-automated cortical thickness calculation [108]. White-matter burden and micro haemorrhages are assessed using visual rating scales [109, 110], and automated quantification [111, 112].

Volume loss between serial scans will be determined using the robust boundary shift integral (BSI) [113] following affine registration of repeat and baseline scans. Regional BSI calculation is performed using a fully affine whole-brain registration followed by rigid registration of masked local structures. Tensor-based morphometry is used as a non-region-based measure of volume loss.

The amyloid PET images are registered to the T1-scan and visually rated as positive/negative by experienced nuclear medicine specialists [114]. Standardised uptake value ratios (SUVR) are calculated globally and locally from a T1-parcellation [115]. Regional grey matter amyloid load is calculated with appropriate partial volume correction [116].

Blood and urine specimen protocol for clinical samples and biomarker identification

Blood samples are collected for haemoglobin, platelet count, urea and creatinine, random glucose, vitamin B12, and TSH, as potential modulators both of cognition and progression of Alzheimer’s pathology. Samples will also be stored for biomarker exploration (both serum and plasma) and genetic analysis. Blood is collected using a Vacutainer system in a single venepuncture procedure. Samples are inverted Fig. 6 Brain volumes derived from first 100 Insight 46 volumetric T1 scans.

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Violin plots demonstrating total brain and lobar volumes (left) and regional lobar volumes (right) calculated on the first 100 T1 scans in Insight 46 using the automated segmentation pipeline eight times to ensure adequate mixing of blood with tube additives. All samples are processed within two hours of collection, as per recent working group guidelines on biomarker pre-processing [117]. One 4.0 ml EDTA sample is collected for haemoglobin and platelet count and the remaining sample is stored at -20 °C prior to genetic extraction. One 2.5 ml SST sample is collected for urea, creatinine, TSH, vitamin B12 and random glucose. Two 10 ml EDTA samples and two clotted 8.5 ml SST samples are spun at 2000 g for 10 min to generate up to 8.0 ml plasma stored as 16 × 0.5 ml aliquots and up to 7.0 ml serum stored as 14 × 0.5 ml aliquots, all at -80 °C, for later analysis. Aliquot tubes are made from polypropylene. Urine is collected in a 100 ml polypropylene pot and transferred on ice for storage. A total of 24 ml urine is stored across 5 aliquots at -80 °C. Planned analyses include measurement of serum neurofilament light [118], plasma tau [119] and plasma Aβ40 and Aβ42 [120] using ultrasensitive Single molecule array (Simoa) assays [121].

Genetics

DNA from each participant is extracted from whole blood using standard methods (phenol-chloroform). Existing genotyping data are available from the MetaboChip [122] and the DrugDev Consortium Array (Illumina, Inc.) and samples are further assayed on NeuroX2 (Infinium NeuroConsortium Array, Illumina, Inc.) according to the recommended protocol. This genotyping platform is the second iteration of a neurological disease-specific array. It covers approximately 500,000 genetic markers, many of which will have a role in neurodegenerative disease, and improves on NeuroX which was designed and released in 2014 [123]. NeuroX2 includes an up-to-date content, with the latest signals from the most recent genome-wide association study (GWAS) in neurodegenerative diseases, such as PD and AD. As an example, all known genome-wide associated and suggestive loci for AD are present in the array, which enables the creation and ascertainment of polygenic risk scores for that disease [15], which can then be improved by using biomarker and imaging data from the same participants.

Analysis plan

Overarching themes of the study include better characterisation of the prevalence and incidence of cerebral amyloidosis in a British birth cohort; examining how biological, genetic, psychological and social factors across life influence cerebrovascular burden, amyloid burden, and neurodegeneration (as measured by cortical network breakdown and cerebral atrophy), and their interplay on cognition; and in doing so establishing metrics that are sensitive for detecting early neurodegeneration. Specific research questions we will address include: the extent and variability of amyloid deposition and proportion of this representative cohort who will be amyloid positive (estimated at 15–25%); the relationships between amyloid load, standard and more advanced MR metrics and vascular burden; the influence of childhood cognitive and motor ability, educational attainment, lifetime mental health, physical activity, physical function and cerebrovascular risk profiles and genetic factors on the development of brain pathology, cognitive health, gait and motor skills; the cognitive tests – both established and novel – that are most associated with cross-sectional biomarkers of brain pathology and have most power to detect change over time and thus to be outcome measures for clinical trials; the extent to which genetic risk scores and blood-based biomarkers can detect asymptomatic amyloidosis; and how best to recruit to presymptomatic AD trials and which imaging and other biomarkers will maximise power to detect treatment effects in the preclinical and very early stages of cognitive decline.

DISCUSSION

Insight 46 intends to integrate the NSHD data on the socioeconomic environment and on physical, psychological and cognitive function from 0 to 69 years, coupled with data on genetics, structural and molecular imaging, and intensive cognitive and neurological phenotyping, to inform what

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influences the entire spectrum of changes that occur as the brain ages: from healthy through to pathological ageing, with a specific focus on AD. Combining the cohort's uniquely rich life course data with the metrics collected in Insight 46, at an age when overt dementia is rare, provides an unprecedented opportunity to explore pre-symptomatic neurodegeneration and to evaluate very subtle cognitive decline. Prospective follow up in the sub-study allows for the consequences of these changes to be quantified. These analyses, initially performed in house, with subsequent data dissemination in line with the MRC Policy on data sharing, have the potential to provide fundamental insights into the factors that influence healthy and pathological brain ageing, provide an evidence base to inform how best to identify individuals at high risk for AD and other forms of dementia, and contribute to practices for monitoring change over time for clinical trials.

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