Dementias Platform UK Medical Research Council | DATA PORTAL

Whitehall II Imaging Sub-Study Data

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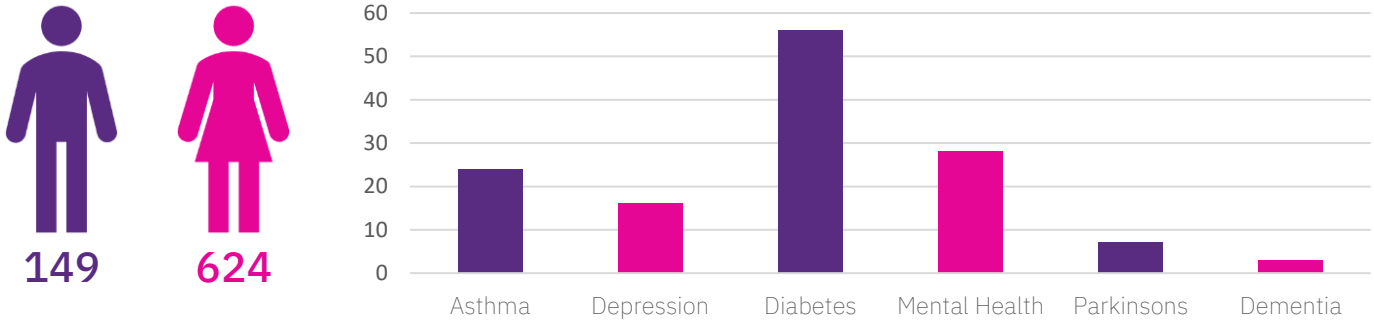
Background

The Whitehall II (WHII) study of British civil servants provides a unique source of longitudinal data to investigate key factors hypothesized to affect brain health and cognitive ageing. This sub study introduces the multi-modal magnetic resonance imaging (MRI) protocol and cognitive assessment designed to investigate brain health in a random sample of 800 members of the WHII study. A total of 6035 civil servants participated in the WHII Phase 11 clinical examination in 2012–2013. A random sample of these participants was included in a sub-study comprising an MRI brain scan, a detailed clinical and cognitive assessment, and collection of blood and buccal mucosal samples for the characterisation of immune function and associated measures. Data collection for this sub-study started in 2012 and was completed by 2016. The participants, for whom social and health records have been collected since 1985, were between 60–85 years of age at the time the MRI study started.

	PHASE 1 (1985-88)	**PHASE 3** (1991-93)	**PHASE 5** (1997-99)	**PHASE 7** (2003-04)	**PHASE 9** (2007-09)	**PHASE 11** (2012-13)
Ages	35-55	39-64	45-69	50-74	55-79	60-85
Participants	10,308	8637	7830	6967	6755	6035
Social circumstances & behaviour, smoking, alcohol, exercise, sleep, diet	✓	✓	✓	✓	✓	✓
Biological measures: blood pressure, BMI, lipids, glucose, insulin, stored blood	✓	✓	✓	✓	✓	✓
2-h oral glucose tolerance test	✗	✓	✓	✓	✓	✓
Inflammatory markers	✗	✓	✓	✓	✓	✗
Autonomic (HRV)	✗	✗	✓	✓	✓	✓
Genetic material	✗	✗	✗	✓	✓	✓
Psychosocial factors: work, social support, – participation, care provision	✓	✓	✓	✓	✓	✓
Health outcomes: CHD, stroke, diabetes, cancer, mortality, medications	✓	✓	✓	✓	✓	✓
Function: physical, social & mental	✓	✓	✓	✓	✓	✓
Cognitive tests, physical/lung function tests	✗	✗	✓	✓	✓	✓

Demographics

Sex & Diagnoses



Clinical & Cognitive Assessments

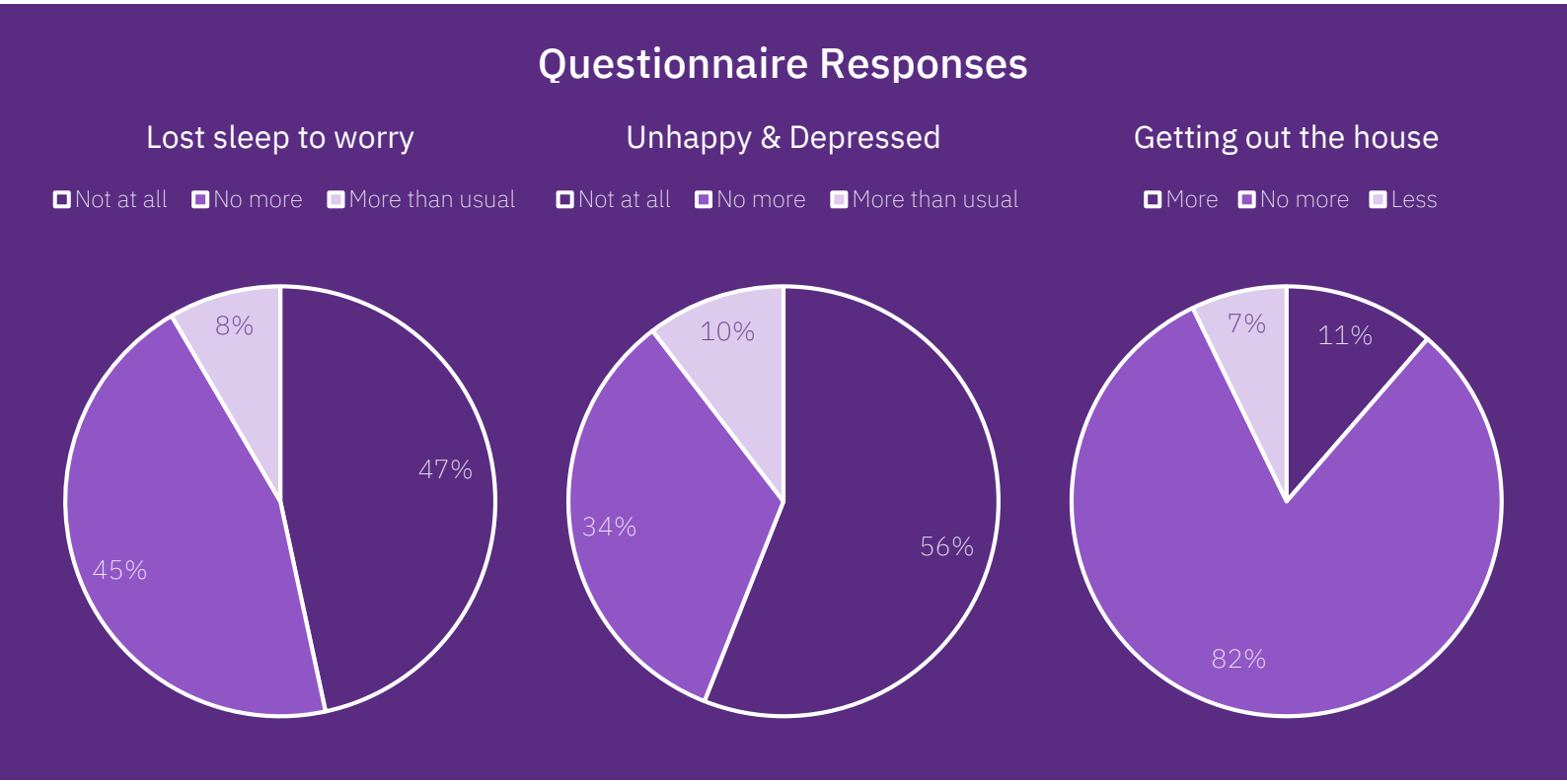
Self-administered questionnaire

Each participant recruited for the WHII imaging sub-study underwent a detailed clinical and cognitive assessment lasting up to two hours.

	Assessment Name	Assessment Description
Mental State, Depression & Anxiety	General Health Questionnaire-30	The GHQ-30 is a 30-item self-administered screening questionnaire for the detection of psychiatric illness that accompanies ill-health, in non-psychiatric clinical and community settings (routinely applied from scan 200).
	Mood Disorder Questionnaire	The MDQ is a brief self-report questionnaire for the assessment of lifetime history of bipolar disorders, based on the DSM-IV.
	Centre for Epidemiological Studies Depression Scale	The CES-D is short self-report scale that measures major depressive symptomatology in the general population.
	State and Trait Anxiety Inventory	The STAI measures both S (state)- and T (trait)-Anxiety in clinical and research settings. It is a self-administered questionnaire that consists of twenty statements assessing how the individual feels at the moment (S-Anxiety) and twenty assessing how they generally feel (administered to n = 15 before routinely applied from scan 200).
	Life-Orientation Revised	The LOT-R was devised to measure individual optimism for future events in the general population.
Stress & Worry	Life Events	A modified version of the List of Threatening Experiences questionnaire (LTE-Q) is used, in which participants are asked about seven types of stressful life events. Participants are asked to remember if any of the events happened to them in the past, and when they happened.
	MacArthur stress reactivity questionnaire	It is a nine-item self-rated questionnaire in which the participant is required to rate nine statements on a 5-point scale, regarding to how they handle their emotions in stressful situations.
	Penn State Worry Questionnaire Ultra-Brief Version	The PSWQ ultra-brief is the 3-item version of the widely used self-report questionnaire for pathological worry, the 16-item long PSWQ. The 3-items capture pathological worry as defined by the DSM-IV; perceived uncontrollability, multiple domains and high frequency of worry. The PSWQ was introduced into the assessment after scan 200.
Exercise	CHAMPS Physical Activity Questionnaire for Older Adults	The CHAMPS is a self-administered physical activity questionnaire for older persons. Participants report the weekly frequency and duration of various physical activities, typically undertaken by older adults, allowing calculation of metabolic equivalent of task (MET) and caloric expenditure values per week.
	Locus for Causality Exercise Questionnaire	The LCE is a 3-item self-administered scale that assesses how much an individual feels that they choose to exercise (internal perceived locus of causality) rather than have to exercise for some reason (external perceived locus of causality). It is thought that individuals are more likely to engage in physical exercise when the perceived locus of causality is internal.

Sleep	Pittsburgh Sleep Quality Index	The PSQI is a self-rated questionnaire made up of seven component scores that assess sleep quality and disturbance over a one-month period in clinical and research settings.
	Jenkins Sleep Questionnaire	The JSQ is a 4-item self-rated questionnaire for the assessment of sleep disturbances over a month period.
Other	Handedness	It is a self-administered questionnaire that assesses which is the participant's preferred hand to complete a list of twelve tasks, as well as left-handedness in the family.

Participants also provide information on medical history (detailing hospitalizations, longstanding illnesses, diseases, or medical conditions), alcohol and nicotine intake, and general information, such as age and education. Their blood pressure is measured twice in a sitting position, after the cognitive protocol.



Further structured assessments

Further tests were performed when the clinical history and SCID data of the participant suggested a diagnosis and indicated that a more detailed assessment was required (the number of each test carried out so far is listed in brackets):

Assessment Name	**Assessment Description**
Hamilton Depression Scale	The HAMD is a 17-item severity scale administered to individuals diagnosed with 'affective disorder of depressive type'. It has been devised to quantify the intensity of the depressive symptoms of the patient, based on the necessary information elicited by the interviewer. This scale was administered to participants currently symptomatic on the SCID-I (n = 16).
Young Mania Rating Scale	The YMRS is an 11-item rating scale for the assessment of manic symptoms based on the subjective report of the patient's experience over the past forty-eight hours. It follows a rating style of symptom severity similar to that of the HAMD and is administered to participants currently symptomatic on the SCID-I (n = 2).
CAGE Questionnaire	Four questions make up this questionnaire to detect dependence on alcohol. They request information on whether the individual needs to "Cut down" their drinking, feels Annoyed by criticism of their drinking, feels Guilty about their alcohol use, and whether they use alcohol first thing in the morning as an 'Eye-opener'. This scale is administered to participants currently symptomatic on the SCID-I (n = 6).

Cognitive assessments

Assessment Name	Assessment Description
Montreal Cognitive Assessment	The MoCA is a 30-point cognitive screening test assessing multiple cognitive domains: a) visuo-spatial abilities (4 points), assessed using a three-dimensional cube-drawing (1 point) and a clock-drawing task (3 points); b) short-term memory recall task (5 points), which involves learning 5 nouns and recalling them approximately 5 minutes afterwards; c) executive function (3 points), which include an alternation task (1 point) and a verbal abstraction task (2 points); d) attention, orientation and working memory (6 points), which are evaluated using a forward- and backward-digit task (2 points), a sustained attention task (1 point), and a serial subtraction task (3 points); e) language (6 points), which is measured using a three-item naming task (3 points), the repetition of two syntactically complex sentences (2 points) and a phonemic fluency task (1 point); and f) orientation to time and space (6 points). Participants receive an additional (1 point) if their education level is ≤ 12 years. Since the MoCA assesses multiple cognitive domains, it is a useful cognitive screening tool for several neurological diseases, such as Parkinson's disease, vascular cognitive impairment, Huntington's disease, multiple sclerosis, and other conditions, such as traumatic brain injury, depression and schizophrenia.
Trail Making Test (TMT) versions A and B	The TMT is a visual attention and task-switching test consisting of two parts in which the subject is instructed to connect a set of twenty-five consecutive dots (A: numbers and B: numbers and letters) on a sheet of paper as fast as possible while still maintaining accuracy. It provides information about visual search speed, speed of processing, mental flexibility, as well as executive functioning. It is sensitive to the detection of cognitive impairment including Alzheimer's disease.
Rey Complex Figure Test and Recognition Trial	The RCF involves copying and then recalling a complex geometric diagram at increasing time intervals. Different cognitive abilities are needed for a correct performance, including visuo-spatial abilities, memory, attention, planning, and working memory. It is used to investigate the effects of brain injury and to test the presence of neurodegenerative conditions.
Verbal fluency test (adapted from the Addenbrooke's Cognitive Examination Revised)	The verbal fluency test requires participants to say as many words as possible from a category (animals) in a specified time (60 seconds). It is used to investigate the presence of cognitive impairment, neurodegenerative and psychiatric disorders.
Hopkins Verbal Learning Test-Revised	The HVLT-R test provides a measure of verbal learning and memory ability. The participant is required to learn a list of twelve words over the course of three trials, and recall and recognise them at increasing time intervals. It is widely used to test the presence of amnestic disorders.
Boston Naming Test	The BNT-60 is a 60-item test graded in difficulty used to measure semantic memory ability and requires naming of a series of images shown to the participant. It is used in individuals with aphasia or any language disturbance caused by neurological insults, such as stroke or neurodegenerative disorders.
Digit Span (DS) and Coding (DC) tests from the Wechsler Adult Intelligence Scale - Fourth Edition	The DS test is used to investigate short-term memory abilities. It includes recall of a lengthening list of digits forwards, backwards, and rearranged in ascending sequence (DSF, DSB, DSS). In the DC test participants have to write the appropriate novel symbol for each number within a given time.
Test of Premorbid Functioning	The TOPF consists of a list of seventy written words, which must be read aloud and is marked according to pronunciation. The TOPF is used to estimate an individual's level of intellectual functioning before the onset of injury or illness. Premorbid IQ can be calculated from the raw score, adjusted for sex and years of education.
Dots and letters (adapted from the Addenbrooke's Cognitive Examination III)	The participant is asked to count four sets of dots without pointing to them and identify four partially drawn letters. These tasks assess perceptual abilities.
CLOX	The CLOX is a clock drawing task; in the first part the participant is given a set of instructions to draw a clock and in the second part the examiner draws a clock face, which the participant then has to copy. The CLOX was designed to assess executive impairment and non-executive failure, and is used to discriminate dementia sub-groups.
Cambridge Neuropsychological Test Automated Battery Reaction Time touchscreen version	The CANTAB RTI is a computerised (touchscreen) latency task that measures latency and movement time without having to control for tremor. The task is divided into a simple and 5-choice reaction time stage. During the task the participant must react as soon as a yellow dot appears; moving their finger on the screen from a pre-defined location to the location of the yellow dot. In the simple stage the yellow dot always appears in the same location, and in the five-choice stage in one out of five potential locations. The CANTAB RTI is often used to assess visuo-spatial and visuo-motor coordination abilities, motor speed, and understand sustained attention and reaction time.

Imaging Data

Scan Types

Scanning is carried out at the Oxford Centre for Functional MRI of the Brain (FMRIB) using a 3 T Siemens Magnetom Verio (Erlangen, Germany) Scanner with a 32-channel receive head coil. The neuroimaging protocol comprises both structural and functional sequences and lasts approximately 50 minutes. MRI sequences include: a) high-resolution T1-weighted, b) diffusion MRI (dMRI), c) resting-state functional MRI (rfMRI), d) Fluid Attenuated Inversion Recovery (FLAIR) and e) T2*.

T1w T2w FLAIR dMRI fMRI ASL

T1w: For the T1-weighted scans, a Multi-Echo MPRAGE (MEMPR) with motion correction was employed. This sequence has the advantage of combining the properties of the classical MPRAGE sequence, which has high contrast aiding cortical segmentation, with Multi-Echo FLASH, which improves segmentation of subcortical regions.

dMRI: A number of strategies were used to minimise distortions caused by, for example, magnetic susceptibility, eddy-currents, and subject-motion. Monopolar diffusion encoding gradients were employed with parallel imaging (GRAPPA) to minimise echo time, which increases the signal to noise ratio (SNR), at the cost of a small increase in eddy-current distortion. A recently developed dMRI correction strategy was used that takes advantage of the complementary information from pairs of diffusion images acquired with reversed phase-encoding (PE) directions to correct for susceptibility-induced distortions. A single non-diffusion weighted (b-value = 0 s/mm2) volume with reversed PE was combined with the non-reversed dMRI data to estimate an off-resonance field, which is then applied to correct susceptibility distortions.

fMRI: A recently developed Multiband MRI sequence was compared with 'standard' EPI. Multiband provides a considerable improvement in temporal (Multiband: 1.3 seconds vs. Standard EPI: 3 seconds) and spatial (Multiband: 2 mm isotropic vs. Standard EPI: 3 mm isotropic) resolution, which allows: a) better definition of the spatial maps, b) wider frequency range exploration in time-series analyses and c) more detailed network analyses. To ensure that the new multiband sequence was robust in the older population, both sequences (standard and multiband) were acquired on a subset of participants (N = 76). In all cases subjects were instructed to lie in dimmed light with their eyes open, blink normally, but not to fall asleep.

Study Protocol

	STRUCTURAL				**FUNCTIONAL**	
Sequence	MEMPR	FLAIR	T2*	dMRI	Multiband	Standard
Condition	-	-	-	-	Resting	Resting
TR in ms	2530	9000	36	8900	1300	3000
TE in ms	1.79/3.65/5.51/7.37	73	30	91.2	40	30
Flip angle	7	150	15	-	66	90
Voxel in mm^3	1x1x1	0.9x0.9x3	0.7x0.7x1.5	2x2x2	2x2x2	3x3x3
FoV read	256	220	220	192	212	192
FoV phase	100%	100%	81.3%	100%	100%	100%

Base resolution	256	256	320	96	106	64
Phase resolution	100%	100%	100%	100%	100%	100%
TI in ms	1380	2500	-	-	-	-
Bandwidth	651 Hz/Px	283 Hz/Px	170 Hz/Px	1680 Hz/Px	1814 Hz/Px	2368 Hz/Px
Orientation	Sagittal	Transversal	Transversal	Transversal	Transversal	Transversal
b-value	-	-	-	1500 s/mm^2	-	-
N. of volumes	-	-	-	-	460	200
N. of directions	-	-	-	60 + 5 b=0 s	-	-
Acquisition time	6m 12s	4m 14s	4m 17s	9m 56s	10m 10s	10m

Data Structure

BIDS Format

BIDS formatting is used to structure the folders and files of the imaging data. The data is split across scan types for each subject, with all scans being in NIFTI format and having an accompanying JSON sidecar containing metadata. The structure of the data is set out below, using subject 01 as an example:

Whitehall Dataset/

sub-01/

anat/

sub-01_T1w.nii.gz
sub-01_T1w.json
sub-01_T2starw.nii.gz
sub-01_T2starw.json
sub-01_FLAIR.nii.gz
sub-01_FLAIR.json

func/

sub-01_task-rest_bold.nii.gz
sub-01_task-rest_bold.json

dwi/

sub-01_dir-AP_dwi.nii.gz
sub-01_dir-AP_dwi.bvals
sub-01_dir-AP_dwi.bvecs
sub-01_dir-AP_dwi.json
sub-01_dir-PA_dwi.nii.gz
sub-01_dir-PA_dwi.json

asl/

sub-01_asl.nii.gz
sub-01_m0scan.nii.gz
sub-01 _acq-ref_m0scan.nii.gz