

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Topiwala, A; Allan, CL; Valkanova, V; Zsoldos, E; Filippini, N; Sexton, CE; Mahmood, A; Singh-Manoux, A; Mackay, CE; Kivimki, M; Ebmeier, KP (2015) Resilience and MRI correlates of cognitive impairment in community-dwelling elders. The British journal of psychiatry , 207 (5). pp. 435-9. ISSN 0007-1250 DOI: 10.1192/bjp.bp.114.152363

Downloaded from: <http://researchonline.lshtm.ac.uk/2534216/>

DOI: [10.1192/bjp.bp.114.152363](https://doi.org/10.1192/bjp.bp.114.152363)

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by/2.5/>

Resilience and MRI correlates of cognitive impairment in community-dwelling elders

Anya Topiwala, Charlotte L. Allan, Vyara Valkanova, Enikő Zsoldos, Nicola Filippini, Claire E. Sexton, Abda Mahmood, Archana Singh-Manoux, Clare E. Mackay, Mika Kivimäki and Klaus P. Ebmeier

Background

The contribution of education and intelligence to resilience against age-related cognitive decline is not clear, particularly in the presence of 'normal for age' minor brain abnormalities.

Method

Participants ($n=208$, mean age 69.2 years, s.d.=5.4) in the Whitehall II imaging substudy attended for neuropsychological testing and multisequence 3T brain magnetic resonance imaging. Images were independently rated by three trained clinicians for global and hippocampal atrophy, periventricular and deep white matter changes.

Results

Although none of the participants qualified for a clinical diagnosis of dementia, a screen for cognitive impairment (Montreal Cognitive Assessment (MoCA) <26) was abnormal in 22%. Hippocampal atrophy, in contrast to other brain measures, was associated with a reduced MoCA score

even after controlling for age, gender, socioeconomic status, years of education and premorbid IQ. Premorbid IQ and socioeconomic status were associated with resilience in the presence of hippocampal atrophy.

Conclusions

Independent contributions from a *priori* risk (age, hippocampal atrophy) and resilience (premorbid function, socioeconomic status) combine to predict measured cognitive impairment.

Declaration of interest

K.P.E. has received consultation fees from Lilly in relation to Amyvid™.

Copyright and usage

© The Royal College of Psychiatrists 2015. This is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) licence.

One in nine people worldwide is 60 years or older, and this proportion is projected to increase to one in five by 2050.¹ With a prevalence of dementia between 6 and 7% of over 65-year-olds,² cognitive decline in ageing populations is creating an increasing social and financial challenge, although traditional estimates may overestimate the detrimental effects of age in the contemporary population.^{2–4} Advanced imaging techniques, such as magnetic resonance imaging (MRI), allow for detailed investigation of the ageing brain. Visual inspection of structural MRIs is a quick and reliable technique that does not require specialist software pipelines or expertise, and is routinely used in clinical practice, unlike automated analysis. Visual inspections can be used to detect atrophy in the grey matter (particularly the medial temporal lobe), and hyperintensities in white matter, which have been highlighted as correlates of functional impairment and dementia.^{5,6} In people over 60 years, such minor MRI abnormalities are, however, often characterised as 'normal for age'. However, the functional implications of these changes identified by visual inspection are unclear; hence it is difficult for the clinician to ascribe significance to them. Moreover, apart from a few exceptions,⁷ studies of cognitive deficits have ignored factors that may confer functional resilience against structural brain damage.

This paper describes the cognitive profile and routine MRI findings from the first quarter of the Whitehall II imaging substudy of 800 participants.⁸ This sample was recruited from the Whitehall II occupational cohort of 6035 civil servants from 20 UK Government departments in London.⁹ Among 208 participants aged 60–82, we examine the relationship between MRI abnormalities, often described as age-related, and performance on tests estimating premorbid intelligence and cognitive impairment, in relation to factors that may confer resilience against cognitive impairment, including education and premorbid IQ. We define resilience as the positive effect of variables on cognitive

outcome given a certain severity of risk factors or organic changes of the brain. Our hypotheses were that cognitive impairment measured by the Montreal Cognitive Assessment (MoCA) would be associated with brain abnormalities, in particular hippocampal atrophy and deep white matter changes, after controlling for confounders, such as age, gender, education and premorbid IQ. At the same time, we predicted that with a given degree of brain abnormality (hippocampal atrophy or deep white matter changes) and other confounders being equal, higher premorbid IQ and education would predict a higher MoCA score, i.e. a smaller chance of cognitive impairment.

Method

Participants

The Whitehall II study was established in 1985 at University College London, and recruited 10 308 non-industrial civil servants across a range of employment grades. Eight hundred of these were randomly selected for the current Whitehall II imaging sub-study,⁸ from a cohort of approximately 6035 community-dwelling elders (29 were oversampled from participants previously scoring higher (score ≥ 16) on the Centre for Epidemiologic Studies Depression (CES-D) scale and are included in this study). This paper describes results from the first 208 participants recruited to the imaging substudy. Participants gave informed consent and attended the investigation in Oxford, unless MRI was contraindicated.

Magnetic resonance imaging

MRI scans were acquired at the University of Oxford Functional Magnetic Resonance Imaging of the Brain (FMRIB) Centre, using a 3 Tesla Siemens scanner (see online supplementary materials and

protocol paper⁸ for further details). Images from the T1-weighted and FLAIR (fluid-attenuated inversion recovery) sequences were used for visual inspection.

MRI analysis

Scans were assessed independently by three medically qualified researchers (A.T., C.L.A. and V.V.) trained in visual inspection techniques, masked to behavioural details and participant identity for: global atrophy, hippocampal atrophy and white matter changes. Global atrophy was assessed viewing supra-ventricular axial slices and rated from absent (0) to severe (3). Standards for each grade had been agreed in advance in consultation with a fourth researcher with expertise in this field (K.P.E.). Hippocampal atrophy was assessed by the Scheltens scale separately for each side according to the width of the choroid fissure, width of the temporal horn and height of the hippocampus (0–4).⁵ White matter changes were graded by the Fazekas scale depending on the presence and size of deep white matter changes (0–3), and the presence or extent of periventricular white matter changes (0–3).¹⁰ This scale provides two different scores each, rated on a 4-point scale.

After recording scores separately, disagreements were settled in consultation with a fourth researcher (K.P.E.) and a consensus score reached. Raters remained masked to all other participant data. Intra- (on a random 10% of 208 scans) and interrater reliability ($n=208$) were assessed by intraclass correlation coefficients (ICCs). For the purpose of the statistical analysis, global atrophy and Fazekas scores were rated as abnormal if >1 ; hippocampal atrophy was only recorded, if both Scheltens scores were >1 .

Cognitive function

Cognitive function was assessed immediately prior to the MRI scan according to a protocol including paper and pencil instruments based on a systematic review¹¹ and extensively piloted in patient groups and healthy volunteers: MoCA, Trail Making Test (TMT A and B), Lexical (letter: 'F') and Semantic Fluency (category: 'Animals'), Rey–Osterrieth Complex Figure (RCF) copying, RCF immediate recall, Hopkins Verbal Learning Test (HVLT-R) immediate recall, Boston Naming Test (BNT), Digit Span and Digit Coding (from the Wechsler Adult Intelligent Scale-IV), Test of Premorbid Function (TOPF), HVLT-R delayed recall and RCF delayed recall (see online supplement for detailed explanation and references). The test battery was administered by trained psychology graduates and psychiatrists.

Statistical analysis

MoCA scores were modelled by logistic regression, as implemented in SPSS 22 for Windows (IBM Corporation, Armonk, New York, USA). After dichotomising variables at the mean (except for 0–3 MRI scales, where the binary cut-off was between 1 and 2, and for the MoCA, where we used the conventional screening cut-off of 25/26), we entered general atrophy, hippocampal atrophy (only if bilateral), deep white matter changes and periventricular white matter changes separately as independent variables. The resulting odds ratios were compared with odds ratios corrected for age, gender, socioeconomic status, education (years of full-time+half years of part-time education, as required for correction of TOPF) and premorbid IQ estimated from TOPF score alone.

Results

The mean age of the 208 participants was 69.2 years (s.d.=5.4), and they were predominantly men 169/208 (81.3%). The imaged

sample was representative of the Phase 11 Whitehall cohort for age, body mass index (BMI) and heart rate, had marginally shorter education (95% confidence intervals (CIs) for difference between means: -0.98 to -0.02 years) and lower CES-D scores (95% CI -2.35 to -0.25 ; see Table DS1 in the online supplement to this paper). Their mean blood pressure was slightly higher (systolic: 95% CI 12.9 to 17.5 mmHg; diastolic: 95% CI 5.8 to 8.6 mmHg). They used more alcohol (95% CI 4.8 to 9.2 units per week). The ratio of men to women was higher in the imaging sample ($\chi^2=13.78$; $P=0.0002$), and there was an excess of executive and a relatively smaller proportion of clerical civil servants ($\chi^2=14.51$; $P=0.0007$; d.f.=2).

In general, participants had relatively good cognitive function. Using the conventional cut-offs, 11/208 (5.3%) had an abnormal (<19) score on the HVLT-R; 46/208 (22.1%) scored <26 on the MoCA. The respective normal distribution values, often used as cut-off for normality (i.e. 1 and 1.5 s.d. below the mean) were 24.6 and 23.4 for the MoCA, and 21.7 and 19.2 for the HVLT-R (for details of cognitive tests and the psychiatric diagnoses recorded after Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-1) interview,¹² see online supplement). Inter- and intrarater reliability for MRI scores was high (ICC 0.8–0.9 and 0.7–0.9 respectively). Scores were approximately normally distributed (Fig. 1), i.e. the majority of participants had higher than minimum (perfect) atrophy and white matter scores.

Participants with high (≥ 26) and low (<26) MoCA scores were compared for sociodemographic, clinical and cognitive variables (Table 1). Individuals with low MoCA were slightly older ($F(1,206)=10.6$, $P=0.001$), there was an over-representation of low MoCA in professional (2nd) and clerical (3rd), as opposed to executive (1st) socioeconomic strata ($\chi^2=4.5$, $P=0.03$, d.f.=2), but there were no differences in gender ($\chi^2=0.07$, $P=0.79$, d.f.=1), reported minor neurological history (Guillain-Barre Syndrome; brain cyst; transient ischaemic attack; migraine; epilepsy; multiple sclerosis; Parkinsonism; myalgic encephalopathy; blackout; familial tremor; sleep disorder; $\chi^2=1.63$, $P=0.20$, d.f.=1), history of major depressive episode (from SCID-1; $\chi^2=0.002$, $P=0.97$, d.f.=1) or caseness on CES-D (CES-D ≥ 15 ; $\chi^2=1.04$, $P=0.31$, d.f.=1). There were also no differences in socioeconomic and clinical variables, including alcohol use (Table 1), nor was there a difference in premorbid IQ ($F(1,206)=3.3$, $P=0.07$).

Hippocampal atrophy and deep white matter changes (as defined above) were associated with abnormal MoCA scores. Although the mean odds ratio for both general atrophy and periventricular white matter changes were above 1, confidence intervals indicated no significant effect (Table 2). After correction for potential confounders (age, gender, socioeconomic status, years of education and premorbid IQ), only hippocampal atrophy remained associated with abnormal MoCA. In the presence of hippocampal atrophy, higher premorbid IQ and social class (executive rather than professional or clerical) were independently associated with resilience to cognitive impairment.

Discussion

We observed a significant number of minor MRI abnormalities, in particular whole brain and hippocampal atrophy, as well as white matter changes (Fig. 1). Direct comparison with other published studies is difficult, given the differing imaging protocols, rating scales and rater expertise. Nonetheless, the Rotterdam scan study, for example, reported a slightly lower prevalence of white matter lesions compared with our findings (92% v. 98.5% deep white matter changes, 80% v. 100% periventricular white matter

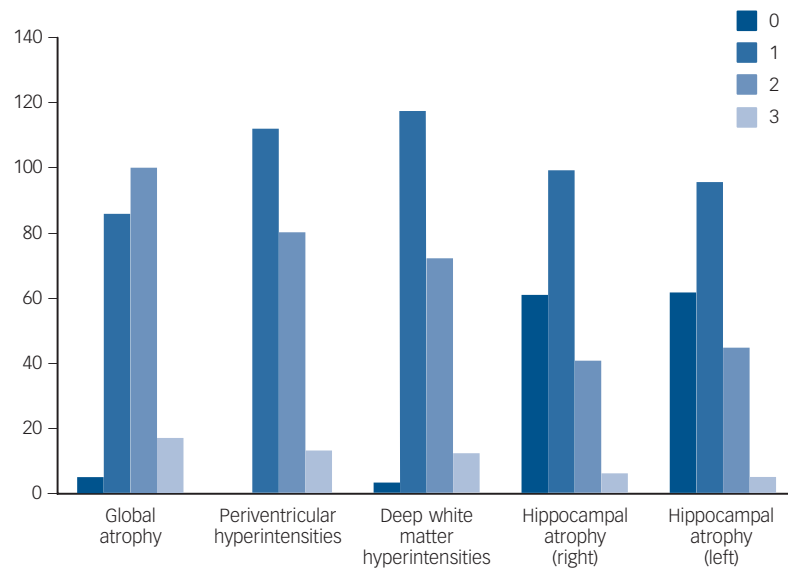


Fig. 1 Distribution (histograms) of global atrophy, Scheltens and Fazekas scores.

changes).⁶ Similarly, hippocampal atrophy in older populations has been reported at lower rates than the 70% we found (e.g. 33%).¹³ This could reflect a true increased burden of pathological changes or increased detection by our higher resolution MRI protocol (all the above studies used a field strength of 1.5T in contrast to 3T in this project).

Compared with previous studies, the proportion of participants with global cognitive impairment was high (20%).¹⁴

Potential health concerns may have induced some participants to attend the testing, so the potential for selection bias cannot be dismissed, as those concerned about memory problems may have been more likely to attend. No participant had an established diagnosis of dementia, which is unsurprising given the study inclusion criteria (community resident and ability to travel to Oxford). Unlike the original MoCA validation study,¹⁵ our sample was not a healthy control group but a community sample, which

Table 1 Descriptive variables for high (≥ 26) and low (< 26) MoCA groups

Variable	Low MoCA group (< 26)			High MoCA group (≥ 26)		
	Mean	s.d.	<i>n</i>	Mean	s.d.	<i>n</i>
Age, years	71.3	6.1	46	68.5	5.0	162
Alcohol units/week	15.9	15.4	45	16.7	15.8	155
Body-mass index, kg/m ²	26.3	4.2	46	26.5	4.4	162
Systolic blood pressure, mmHg	145.7	18.3	46	141.8	17.5	161
Diastolic blood pressure, mmHg	77.3	8.9	45	78.5	10.3	161
Heart rate, beats per minute	66.6	11.7	43	67.9	13.3	161
CES-D score	7.5	7.6	46	5.57	6.8	162
Years of education	16.5	4.3	46	15.5	3.3	162
Premorbid IQ ^a	115.6	12.6	46	118.6	8.9	162
MoCA (correct out of 30)	23	2.0	46	28	1.3	162
Boston naming test (correct out of 60)	54.5	8.6	46	57.8	3.2	162
Digit coding (correct out of 135)	49.3	13.3	46	64.9	12.7	162
Digits backward (correct out of 16)	8.63	2.59	46	10.25	2.57	162
Digits forward (correct out of 16)	10.04	2.17	46	11.16	2.26	162
Digits sequence (correct out of 16)	8.50	2.92	46	10.70	2.49	162
Lexical fluency, words per minute	12.63	5.11	46	16.17	4.31	162
Semantic fluency, words per minute	17.91	5.70	46	22.83	5.63	162
Trail Making Test A, seconds	40.04	17.79	46	29.77	10.97	160
Trail Making Test B, seconds	98.98	49.99	45	58.79	22.85	160
HVLT (delayed recall, correct out of 12)	7.09	3.55	46	9.33	2.71	162
HVLT (immediate recall, correct out of 36)	23.74	5.79	46	27.65	4.48	162
RCFT (copy, correct out of 36)	27.20	6.44	46	30.83	3.78	161
RCFT (delayed recall, correct out of 36)	10.04	5.60	46	15.43	5.99	161
RCFT (immediate recall, correct out of 36)	11.03	6.62	46	15.88	6.07	161

MoCA, Montreal Cognitive Assessment; CES-D, Centre for Epidemiologic Studies – Depression; HVLT, Hopkins Verbal Learning Test; RCFT, Rey–Osterrieth Complex Figure Test. Results with $P < 0.05$ are in bold.

a. Test of premorbid function (IQ corrected for gender and education).

Measure	Odds ratios	95% CI	P
Table 2 Odds ratios for MoCA (≥ 26 / < 26) with normal/abnormal MRI measures			
Uncorrected odds ratio			
≥ 1 normal hippocampi/both hippocampi abnormal	3.43	1.61–7.31	0.001
No general atrophy/general atrophy	1.83	0.92–3.64	0.09
Normal Fazekas/deep white matter changes	2.28	1.16–4.48	0.02
Normal Fazekas/periventricular white matter changes	1.80	0.92–3.53	0.09
Corrected odds ratios ^a			
≥ 1 normal hippocampi/both hippocampi abnormal	2.75	1.16–6.50	0.02
Age (higher/lower)	0.63	0.29–1.37	0.24
Premorbid IQ ^b (higher/lower)	2.19	1.02–4.71	0.045
Gender (female/male)	1.67	0.60–4.64	0.24
Social class (lower/higher)	0.46	0.22–0.99	0.048
Years of education (higher/lower)	0.50	0.22–1.13	0.095
Results with $P < 0.05$ are in bold.			
a. Logistic regression with potential predictor and confounder variables: =1 normal hippocampi, age, gender, social class, years of education and premorbid IQ based on Test of Premorbid Function; $n = 205$.			
b. Premorbid IQ calculated from Test of Premorbid Function scores without correction for gender and years of education.			

included those with a history of major (17% of sample) and minor (9% of sample) depression or bipolar disorder (1% of sample, see online supplement). Deficits in executive function and attention are known to persist in euthymic patients with a history of unipolar depression¹⁶ or bipolar disorder,¹⁷ although there was neither an excess of major depressive disorders nor of current CES-D caseness in the low MoCA group (Table 1). The level of alcohol use in our cohort (mean 16.5 units/week) may also be relevant. Frequent or heavy (>15 units per week) drinkers may be at increased risk of cognitive impairment¹⁸ and dementia,¹⁹ as well as increased ventricle and sulcal size,²⁰ although there was no difference in alcohol use between high and low MoCA scorers (Table 1).

Our sample was representative of the larger Whitehall II cohort for age, BMI and heart rate, but had a marginally shorter length of full-time education. Although they scored a couple of points lower on the CES-D depression scale, they used 5–10 units of alcohol more than the Phase 11 cohort and had a higher blood pressure. There was an excess of men and of executive civil servants relative to clerical staff. One implication of these differences may be that the imaging cohort was more likely to generate associations relying on variability for cardiovascular risk factors.

Of the clinical MRI measures, only deep white matter changes and hippocampal atrophy were significantly associated with cognitive impairment. After correcting for possible confounder variables, only hippocampal atrophy remained associated with MoCA (Table 2). This supports the notion that MoCA may predict pathological deterioration in memory, rather than representing the normal process in ageing.^{21–25} In contrast, global atrophy and periventricular white matter changes appear to have little impact on cognition, which lends credence to their being reported as ‘normal for age’.²⁶ Although a quantitative review found that white matter changes are associated with poorer global cognitive function, speed of processing, immediate-recent memory, delayed memory and executive function,²⁷ not all studies have corroborated these findings.²⁸ Our finding that deep white matter changes are associated with MoCA, but that this association is lost after correcting for potential confounders, may be due to limited power of a study of even 200 participants.

With a given degree of hippocampal atrophy, higher premorbid IQ and socioeconomic status (based on civil service grade) but not education were independently associated with resilience to cognitive impairment. This lends strength to the cognitive reserve²⁹ or compensation hypotheses.³⁰ It may also explain why the Whitehall cohort is resilient to functional deterioration

(several of the mean test scores are higher than published results at similar ages^{14,31,32} despite more prevalent structural brain changes). This cohort has a higher education level³³ and a lower cardiovascular risk profile than those in other studies.³⁴ Finally, there are a number of other determinants of cognitive reserve not explored in this study, such as participation in leisure activities,³⁵ cohesion of social networks,³⁶ occupational complexity³⁷ and personality characteristics that may be responsible for additional variability.³⁸

We were able to combine 3T MRI imaging with comprehensive cognitive testing in a large study drawn from an occupational cohort. Limitations to our study include its cross-sectional design, and further work needs to include longitudinal and diagnostic follow-up data. Although previous work has demonstrated the clinical value of the MRI scales used,³⁹ and our interrater reliability figures were higher than those quoted in several other studies,⁴⁰ it will be valuable to compare our results with automated volumetric measurements to establish whether the key findings (e.g. that hippocampal atrophy is highly functionally relevant and premorbid intelligence and social class confer resilience to functional but not structural deterioration) can be corroborated. In the meantime, our results should contribute to the interpretation of ‘age-related’ MRI abnormalities as they are usually reported in clinical practice.

Anya Topiwala, MBChB, **Charlotte L. Allan**, MBChB, **Vyara Valkanova**, MD, **Enikő Zsoldos**, MSc, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK; **Nicola Filippini**, DPhil, **Claire E. Sexton**, DPhil, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK and Oxford Centre for Functional MRI of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK; **Abda Mahmood**, MSc, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK; **Archana Singh-Manoux**, PhD, Department of Epidemiology and Public Health, UCL, London, UK and INSERM, U1018, Centre for Research in Epidemiology and Population Health, France; **Clare E. Mackay**, PhD, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK; **Mika Kivimäki**, PhD, Department of Epidemiology and Public Health, UCL, London, UK; **Klaus P. Ebmeier**, MD, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

Correspondence: Klaus P. Ebmeier, MD, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK. Email: klaus.ebmeier@psych.ox.ac.uk

First received 18 Feb 2014, final revision 3 Jun 2014, accepted 13 Jan 2015

Funding

‘Lifelong Health and Wellbeing’ Program Grant: ‘Predicting MRI abnormalities with longitudinal data of the Whitehall II Substudy’ (UK Medical Research Council: G1001354), the Gordon Edward Small’s Charitable Trust (SC008962), and the HDH Wills 1965 Charitable Trust (PI: KPE). N.F. and A.M. are funded by the HDH Wills 1965 Charitable Trust. C.L.A., S.C.E. and C.E.M. are supported by the National Institute of Health Research, A.T. and C.L.A. by the Oxford University Clinical Academic Graduate School, and C.L.A. by Wolfson

College, Oxford. A.S.-M. was supported by the National Institute on Aging, NIH (R01AG013196; R01AG034454). M.K. was supported by the UK Medical Research Council (K013351), the US National Institutes of Health (R01HL036310; R01AG034454) and an ESRC professorship. K.P.E. was supported by UK Medical Research Council (G1001354), the Gordon Edward Small's Charitable Trust (SC008962) and the HDH Wills 1965 Charitable Trust.

Acknowledgements

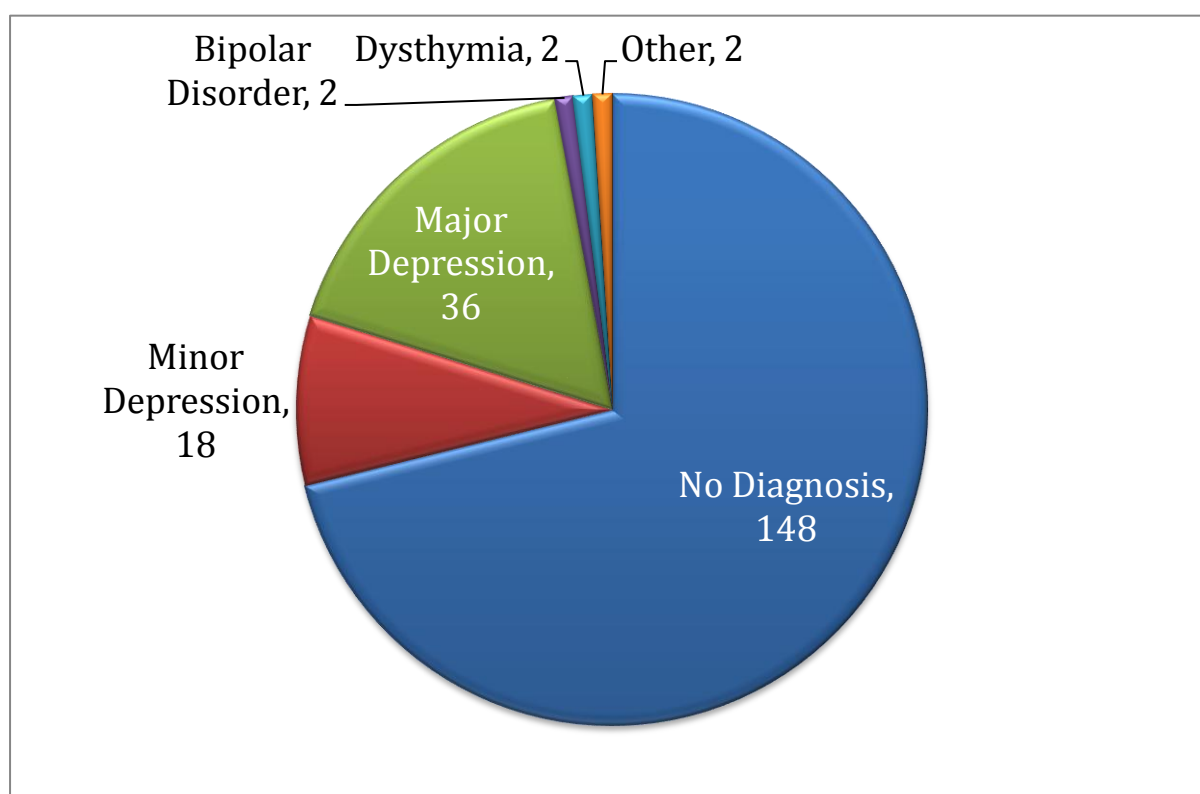
The Multi-Echo MPRAGE sequence is a Works-in-Progress package, developed by Siemens AG, Healthcare Sector, Erlangen, Germany in collaboration with the Athinoula A. Martinos, Center for Biomedical Imaging, Massachusetts General Hospital. Preliminary results were published in a poster at the Royal College of Psychiatrists' International Congress 2013.

References

- Guzmán JM, Pawliczko A, Beales S, Till C, Voelcker I. *Aging in the 21st Century, a Celebration and a Challenge*. United Nations Population Fund (UNFPA) & HelpAge International, 2012.
- Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet* 2013; **382**: 1405–12.
- Spijker J, MacInnes J. Population ageing: the timebomb that isn't? *BMJ* 2013; **347**: f6598.
- Christensen K, Thinggaard M, Oksuzyan A, Steenstrup T, Andersen-Ranberg K, Jeune B, et al. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. *Lancet* 2013; **382**: 1507–13.
- Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein H, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 1992; **55**: 967–72.
- Breteler MM, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology* 1994; **44**: 1246–52.
- Karama S, Bastin ME, Murray C, Royle NA, Penke L, Munoz Maniega S, et al. Childhood cognitive ability accounts for associations between cognitive ability and brain cortical thickness in old age. *Mol Psychiatry* 2014; **19**: 555–9.
- Filippini N, Zsoldos E, Haapakoski R, Sexton CE, Mahmood A, Allan CL, et al. Study protocol: the Whitehall II imaging sub-study. *BMC Psychiatry* 2014; **14**: 159.
- Marmot MG, Smith GD, Stansfeld S, Patel C, North F, Head J, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet* 1991; **337**: 1387–93.
- Fazekas F, Chawluk JB, Alavi A, Hurtig H, Zimmerman R. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol* 1987; **149**: 351–6.
- Herrmann LL, Goodwin GM, Ebmeier KP. The cognitive neuropsychology of depression in the elderly. *Psychol Med* 2007; **37**: 1693–702.
- First MB, Gibbon M, Spitzer RL, Williams JB. *User's Guide for the Structured Clinical Interview for DSM-IV-TR Axis I Disorders – Research Version – (SCID-I for DSM-IV-TR, November 2002 Revision)*. American Psychiatric Association, 2002.
- Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood-pressure levels and late-life cognitive function – the Honolulu-Asia aging study. *JAMA* 1995; **274**: 1846–51.
- Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* 1997; **349**: 1793–6.
- Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatrics Soc* 2005; **53**: 695–9.
- Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med* 2014; **44**: 2029–40.
- Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord* 2006; **93**: 105–15.
- Anttila T, Helkala EL, Viitanen M, Kareholt I, Fratiglioni L, Winblad B, et al. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. *BMJ* 2004; **329**: 539.
- Saunders PA, Copeland JR, Dewey ME, Davidson IA, McWilliam C, Sharma V, et al. Heavy drinking as a risk factor for depression and dementia in elderly men. Findings from the Liverpool longitudinal community study. *Br J Psychiatry* 1991; **159**: 213–6.
- Mukamal KJ, Longstreth Jr WT, Mittleman MA, Crum RM, Siscovick DS. Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the cardiovascular health study. *Stroke* 2001; **32**: 1939–46.
- Glomb J, Kluger A, de Leon MJ, Ferris SH, Mittelman M, Cohen J, et al. Hippocampal formation size predicts declining memory performance in normal aging. *Neurology* 1996; **47**: 810–3.
- Dickerson BC, Goncharova I, Sullivan M, Forchetti C, Wilson R, Bennett D, et al. MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiol Aging* 2001; **22**: 747–54.
- Barnes J, Bartlett JW, van de Pol LA, Loy CT, Scahill RI, Frost C, et al. A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. *Neurobiol Aging* 2009; **30**: 1711–23.
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *NeuroImage* 2001; **14**: 21–36.
- Driscoll I, Davatzikos C, An Y, Wu X, Shen D, Kraut M, et al. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology* 2009; **72**: 1906–13.
- Leys D, Soetaert G, Petit H, Fauquette A, Pruvo JP, Steinling M. Periventricular and white matter magnetic resonance imaging hyperintensities do not differ between Alzheimer's disease and normal aging. *Arch Neurol* 1990; **47**: 524–7.
- Gunning-Dixon FM, Raz N. The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. *Neuropsychology* 2000; **14**: 224–32.
- Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. *Neurology* 1999; **53**: 132–9.
- Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 2002; **8**: 448–60.
- Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron* 2004; **44**: 195–208.
- Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol* 2004; **19**: 203–14.
- Boone KB, Miller BL, Lesser IM. Frontal lobe cognitive functions in aging: methodologic considerations. *Dementia* 1993; **4**: 232–6.
- van Velsen EF, Vernooij MW, Vrooman HA, van der Lugt A, Breteler MM, Hofman A, et al. Brain cortical thickness in the general elderly population: the Rotterdam Scan Study. *Neurosci Lett* 2013; **550**: 189–94.
- Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ* 2012; **344**: d7622.
- Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* 2002; **287**: 742–8.
- Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* 2000; **355**: 1315–9.
- Staff RT, Murray AD, Deary IJ, Whalley LJ. What provides cerebral reserve? *Brain J Neurol* 2004; **127**: 1191–9.
- Wilson RS, Schneider JA, Arnold SE, Bienias JL, Bennett DA. Conscientiousness and the incidence of Alzheimer disease and mild cognitive impairment. *Arch Gen Psychiatry* 2007; **64**: 1204–12.
- Wahlund LO, Julin P, Johansson SE, Scheltens P. Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: a comparative study. *J Neurol Neurosurg Psychiatry* 2000; **69**: 630–5.
- Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, Vermersch P, et al. A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci* 1993; **114**: 7–12.



SCID-Diagnoses in 208 participants:



Psychometric tests used:

- SCID¹
- Montreal Cognitive Assessment (MoCA)²
- Trail Making Test (TMT A and B)^{3,4}
- Ray-Osterrieth Complex Figure (RCF) copy, immediate, delay, recognition⁵
- Category fluency⁶
- Hopkins Verbal Learning Test (HVLT-R) immediate, delay, recognition⁷
- Boston Naming Test (BNT)⁸
- Digit span⁹
- Digit coding¹⁰
- Test of Premorbid Function (TOPF)¹¹

The MoCA is a 30-point cognitive screening test with subtests for verbal recall, clock-drawing, cube copying, phonemic fluency, attention task, naming and orientation, amongst others. The TMT requires subjects to ‘connect the dots’ of twenty-five consecutive targets on a sheet of paper as fast as possible. In TMT A the targets are numbers, and in TMT B alternating numbers and letters. The RCF involves initially copying and then recalling a complex geometric diagram at increasing time intervals. In the HVLT-R task the subject must recall a list of twelve words over the course of three trials immediately and after a delay. The BNT examines semantic memory and requires naming of a series of images shown to the participant. Digit Span includes recall of a lengthening list of digits forwards, backwards, and rearranged in ascending order (DSF, DSB, DSS). In Digit Coding, participants have to write the appropriate novel symbol for each number under time pressure. The TOPF consists of a

list of written words, which must be read aloud and is marked according to pronunciation. Premorbid IQ can be calculated from the raw score, adjusted for sex and years of education.

MRI acquisition

Multi-modal MRI scans were acquired at the FMRIB centre, University of Oxford using a 3 Tesla, Siemens scanner with a 32-channel head coil. Structural images were acquired using a high-resolution three-dimensional T1-weighted sequence: repetition time 2530 ms, echo time 7.37 ms, flip angle 7°, field of view 256mm and voxel dimensions 1.0x1.0x1.0 mm. T2-weighted FLAIR (Fluid Attenuated Inversion Recovery) images, used to characterise white-matter changes were acquired with: repetition time 9000 ms, echo time 73.0 ms, flip angle 150°, field of view 220 mm and voxel dimensions 0.9x0.9x3.0 mm. For further information see Filippini et al.¹²

Table DS1 Comparison of MRI sample of 208 with Phase 11 sample

Variable	MRI Sample			Phase 11 Participants		
	N	Mean	S.D.	N	Mean	S.D.
Age [years]	208	69.2	5.3	6306	69.8	5.9
Sex	207	100%		6306		
<i>Female</i>	39	18.8%		1947	29.3%	
<i>Male</i>	169	81.3%		4459	70.7%	
Socio-economic Stratum	206	100%		5771		
<i>Executive</i>	121	58.7%		2743	47.5%	
<i>Professional</i>	77	37.4%		2470	42.8%	
<i>Clerical</i>	8	3.9%		558	9.7%	
Full time education [years]	208	14.6	3.4	5101	15.1	4.2
CES-D	208	6.0	7.0	5855	7.3	7.6
Alcohol [U/week]	200	16.5	15.6	6227	9.5	11.2
BMI [kg/m²]	208	26.5	4.4	5615	26.7	4.5
Heart Rate [BPM]	204	67.7	13.0	5634	68.1	12.2
Systolic BP [mmHg]	207	143	17.7	5652	127.8	16.5
Diastolic BP [mmHg]	206	78	10.0	5652	70.8	9.9

95% confidence intervals for difference between means are: Age: -1.34 to 0.14 years; Education: -0.98 to -0.02 years; CES-D: -2.35 to -0.25; Alcohol: 4.8 to 9.2 units/week; BMI: -0.82 to 0.42 kg/m²; HR: -2.11 to 1.31 BPM; Systolic BP: 12.9 to 17.5 mmHg; Diastolic BP: 5.8 to 8.6 mmHg. Sex: Chi² = 13.78; p = 0.0002. Social Class: Total Chi² = 14.51; |Chi| = 3.81 (2 DF); p = 0.0007.

References

1. Michael B, Spitzer R, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV TR Axis I Disorders, Research Version, Non-patient Edition. Biometrics Research, New York State Psychiatric Institute, 2002.
2. Nasreddine Z, Collin I, Chertkow H, Phillips N, Bergman H, Whitehead V. Sensitivity and specificity of the montreal cognitive assessment (MoCA) for detection of mild cognitive deficits. *Can J Neurol Sci.* 2003; 30(2): 30.
3. Lezak MD, Howieson DB, Bigler ED, Tranel D. *Neuropsychological Assessment 5e.* Oxford University Press, 2013.
4. Gaudino EA, Geisler MW, Squires NK. Construct validity in the Trail Making Test: what makes Part B harder? *Journal of Clinical and Experimental Neuropsychology.* 1995; 17(4): 529-35.
5. Meyers JE, Meyers KR. Rey complex figure test under four different administration procedures. *The Clinical Neuropsychologist.* 1995; 9(1): 63-7.
6. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry.* 2006; 21(11): 1078-85.
7. Brandt J, Benedict RH. *Hopkins Verbal Learning Test--Revised: Professional Manual.* Psychological Assessment Resources, 2001.
8. Kaplan E, Goodglass H, Weintraub S, Segal O, van Loon-Vervoorn A. *Boston Naming Test.* Pro-Ed, 2001.
9. Wechsler D. *WMS-III: Wechsler memory scale administration and scoring manual.* Psychological Corporation Pearson Education Inc., 1997.
10. Wechsler D. *WAIS-IV Manual.* Psychological Corporation Pearson Education Inc., 2008.
11. Wechsler D. *Test of Premorbid Functioning.* Psychological Corporation Pearson Education Inc., 2011.
12. Filippini N, Zsoldos E, Haapakoski R, Sexton CE, Mahmood A, Allan CL, et al. Study Protocol: The Whitehall II imaging sub-study. *Biomed Central Psychiatry.* 2014; 14: 159.

BJPpsych

The British Journal of Psychiatry

Resilience and MRI correlates of cognitive impairment in community-dwelling elders

Anya Topiwala, Charlotte L. Allan, Vyara Valkanova, Eniko Zsoldos, Nicola Filippini, Claire E. Sexton, Abda Mahmood, Archana Singh-Manoux, Clare E. Mackay, Mika Kivimäki and Klaus P. Ebmeier
BJP 2015, 207:435-439.

Access the most recent version at DOI: [10.1192/bjp.bp.114.152363](https://doi.org/10.1192/bjp.bp.114.152363)

Supplementary Material

Supplementary material can be found at:
<http://bjp.rcpsych.org/content/suppl/2015/08/25/bjp.bp.114.152363.DC1.html>

References

This article cites 38 articles, 9 of which you can access for free at:
<http://bjp.rcpsych.org/content/207/5/435#BIBL>

Reprints/permissions

To obtain reprints or permission to reproduce material from this paper, please write to permissions@rcpsych.ac.uk

You can respond to this article at

[/letters/submit/bjprcpsych;207/5/435](http://bjp.rcpsych.org/letters/submit/bjprcpsych;207/5/435)

Downloaded from

<http://bjp.rcpsych.org/> on March 8, 2016
Published by The Royal College of Psychiatrists
