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PII: S1064-7481(20)30408-5
DOI: https://doi.org/10.1016/j.jagp.2020.07.002
Reference: AMGP 1532

To appear in: *The American Journal of Geriatric Psychiatry*

Received date: 7 February 2020
Revised date: 2 July 2020
Accepted date: 2 July 2020

Please cite this article as: Anya Topiwala DPhil , Sana Suri DPhil , Charlotte Allan MD , Enikő Zsoldos DPhil , Nicola Filippini DPhil , Claire E. Sexton DPhil , Abda Mahmood PhD , Archana Singh-Manoux PhD , Clare E. Mackay PhD , Mika Kivimäki PhD , Klaus P. Ebmeier MD , Subjective cognitive complaints given in questionnaire: relationship with brain structure, cognitive performance and self-reported depressive symptoms in a 25-year retrospective cohort study, *The American Journal of Geriatric Psychiatry* (2020), doi: https://doi.org/10.1016/j.jagp.2020.07.002

Subjective cognitive complaints given in questionnaire: relationship with brain structure, cognitive performance and self-reported depressive symptoms in a 25-year retrospective cohort study

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Keywords: subjective memory, neuroimaging, depression, brain structure

Highlights

What is the primary question addressed by this study?

- Subjective cognitive complaints are common but it is unclear whether they indicate an underlying pathological process or reflect affective symptoms.

What is the main finding of this study?

- This study found no relation between subjective complaints and objective cross-sectional or longitudinal cognitive deficits or neuroimaging markers.
- Subjective cognitive complaints were however associated with self-reported depressive symptoms.

What is the meaning of the finding?

- Psychiatrists should be vigilant for affective disorders in those presenting complaining of poor memory.

Abstract

Background

Subjective cognitive complaints are common but it is unclear whether they indicate an underlying pathological process or reflect affective symptoms.

Method

800 community-dwelling older adults were drawn from the Whitehall II cohort. Subjective cognitive complaint inquiry for memory and concentration, a range of neuropsychological tests and multi-modal MRI were performed in 2012-2016. Subjective complaints were again elicited after one year. Group differences in grey and white matter, between those with and without subjective complaints, were assessed using voxel-based morphometry and tract-based spatial statistics, respectively. Mixed effects models assessed whether cognitive decline or depressive symptoms (over a 25-year period) were associated with later subjective complaints. Analyses were controlled for potential confounders and multiple comparisons.

Results

Mean age of the sample at scanning was 69.8 years (±5.1, range: 60.3-84.6). Subjective memory complaints were common (41%) and predicted further similar complaints later (mean 1.4±1.4 years). There were no group differences in grey matter density or white matter integrity. Subjective complaints were not cross-sectionally or longitudinally associated with objectively assessed cognition. However, those with subjective complaints reported higher depressive symptoms ("poor concentration": odds ratio=1.12, 95%CI 1.07-1.18; "poor memory": odds ratio=1.18, 1.12-1.24).

Conclusions

In our sample subjective complaints were consistent over time and reflected depressive symptoms but not markers of neurodegenerative brain damage or concurrent or future objective cognitive impairment. Clinicians assessing patients presenting with memory complaints should be vigilant for affective disorders. These results question the rationale for including subjective complaints in a spectrum with Mild Cognitive Impairment diagnostic criteria.

Introduction

Subjective cognitive complaints are common, particularly in older adults [1]. Some studies have found these complaints to be associated with later cognitive impairment and dementia [2, 3], but such complaints are also associated with depressive symptoms [4]. Thus, it remains unclear whether subjective memory problems reflect affective symptoms or further indicate an underlying pathological process. Examination of associations between subjective complaints and brain structure may represent a novel approach to clarify this. Neuroimaging measures are useful markers for neurodegenerative disorders and may appear years before memory symptoms[5]. Hence if subjective memory complaints are on a biological pathway leading to dementia, they may well be associated with structural MRI abnormalities. Such associations are likely to be detectable earlier than with clinical measures. To date, there have been no sufficiently powered neuroimaging studies to analyze relationships between subjective memory problems and structural measures across the whole brain. There have been a number of small studies that have reported associations between subjective cognitive complaints and specific neuroimaging measures.

From the few published studies in this field, the most consistent findings are for hippocampal size [6]. Given the robust link between hippocampal atrophy and depression [7] and the frequent lack of control for depressive symptoms in the imaging analyses to date, the relationship between subjective memory complaints, depression and brain atrophy remain unclear. Clarification of the associations between memory complaints and brain structure and function is important given their prevalence and the distress they reflect. Better understanding of these relationships will inform clinicians about the relative weight to be given to perceived problems, objective cognitive testing results, and brain imaging when assessing patients and formulating management plans.

Our objective was to compare multi-modal magnetic resonance imaging (MRI) measures (cross-sectionally), objective cognitive performance prospectively, and self-reported depressive symptoms (both cross-sectionally and longitudinally) between older adults with and without subjective cognitive complaints.

Methods

Sample

Eight hundred participants were randomly selected from the Whitehall II cohort for the Imaging Sub-study (2012-2016) [8]. Compared with the Whitehall II study, the imaging sub-study had significantly more men, were less well educated, had higher blood pressure but lower self-reported depressive symptoms [9]. Twenty individuals were excluded due to missing data on subjective cognitive complaints, cross-sectional cognitive tests or confounders. A further 65 individuals were excluded from the imaging analysis due to incomplete or poor-quality images or gross structural scan abnormality to the degree that subsequent imaging analysis would not run reliably. The sample excluded from the imaging analyses contained significantly more men (difference in percent =17.7, 95% CI: 10.5-21.0, chi-square=12.8 p<0.001, df=1) and subjects had higher Framingham Stroke Risk Scores (Welch two sample t-test: t=-1.48, 95% CI: -5.71-0.85, p=0.14, df=68.69).

Socio-demographic, health and lifestyle variables were measured prior to MRI over a follow-up period of approximately thirty years, in 1985-8 (Wave 1), 1991-3 (Wave 3), 1997-9 (Wave 5), 2003-4 (Wave 7), 2007-9 (Wave 9), 2011-13 (Wave 11) and 2015-6 (Wave 12). Age, sex, smoking, alcohol consumption, and the Framingham Stroke Risk Score (FRS), were assessed by self-report questionnaire or clinical examination. Socioeconomic position was determined according to occupation in 1991-3.

Subjective cognitive complaints

In a questionnaire at the MRI examination two questions assessed the presence of subjective 1) *memory* ("In the past month, have you noticed any problems with forgetting things?") and 2) *concentration* ("In the past month, have you had any problems in concentrating on what you are doing?") complaints. Binary answers (yes/no) were recorded.

Enquiry about subjective cognitive complaints was repeated at Wave 12 of the study 1.4 (mean, S.D.=1.4) years later. Participants were asked to rate the following (not at all/some/quite a bit/very much) in the preceding seven days: 1) forgetfulness, 2) poor concentration, 3) trouble expressing my thoughts, 4) trouble finding the right word, 5) slow thinking speed, 6) trouble figuring things out or solving problems. Responses to these questions were summed to generate a subjective cognitive complaints summary score for Wave 12.

MRI analysis

All MRI scans were acquired between 2012 and 2018 at the University of Oxford Wellcome Centre for Integrative Neuroimaging (WIN), using a 3 Tesla Siemens Magnetom Verio scanner with a 32-channel receive head coil (between April 2012 – December 2014). T1-weighted MPRAGE (TR=2530 ms, TE=1.79/3.65/5.51/7.37 ms, TI=1380 ms, voxel size=1mm^3, FOV=256mm) and diffusion weighted MRI (dMRI; TR=8900 ms, TE=91.2 ms, voxel size=2mm^3, FOV=192mm) sequences were used. The last 250 participants were scanned on a 3T Siemens Magnetom Prisma scanner with 64-channel receive head-neck coil (between July 2015 – December 2016). T1-weighted MPRAGE (TR=1900 ms, TE=3.97 ms, TI=904 ms, voxel size=1mm^3, FOV=192mm) and d-MRI (TR=8900 ms, TE=91 ms, voxel size=2mm^3, FOV=192mm) 3T MRI sequences were used. T1-weighted images were processed using FSL tools (www.fmrib.ox.ac.uk/fsl)[10] and 'fsl_anat (Beta version)' (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fsl_anat).

Group differences in whole brain grey matter density were examined using voxel-based morphometry (VBM)[11]. This is an objective method to compare grey matter density between groups in each voxel (smallest distinguishable image volume) of the T1-weighted image.

Diffusion tensor images indicate the directional preference of water diffusion in brain tissue and allow inferences about the structural integrity of white matter tracts. Images were corrected for head movement and eddy currents and brain masks generated using BET. Fractional anisotropy (FA), mean (MD), axial (AD) and radial diffusivity (RD) maps were generated using DTIFit (http://fsl.fmrib.ox.ac.uk/fsl/fdt). Tract-Based Spatial Statistics (TBSS) were used [12] to perform voxelwise statistical analysis. Pre-processing prepared images for registration to standard space. Mean and skeletonized FA, MD, RD and AD images were created and thresholded. Last, each FA, MD, RD and AD image was projected onto the relevant skeleton. To detect group differences between those with and without subject cognitive complaints, a generalised linear model (GLM) was applied using permutation-based non-parametric testing (randomise) [13], correcting for multiple comparisons across space (threshold-free cluster enhancement, TFCE). Mean FA from selected tracts were extracted from the skeletonized FA image using masks from the ICBM-DTI-81 white-matter labels atlas (Table 2).

Cognitive testing

Current cognitive function was assessed at the time of the MRI scan with Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT A and B), Rey-Osterrieth Complex Figure (RCF) copying, RCF immediate and delayed recall, Hopkins Verbal Learning Test (HVLT-R) total immediate (HVLT TR) and delayed (HVLT DR) recall, Digit Span (DSF/DSB/DSS) and Digit Coding (all from the Wechsler Adult Intelligent Scale-IV), lexical and semantic fluency, Boston Naming Test (BNT) and Test of Premorbid Function (TOPF). FSIQ was estimated using the TOPF with sex and education adjustment [14]. Short-term memory (recall of a 20-word list), semantic and lexical fluency were tested during Waves 3-12 inclusive. MMSE was performed during Waves 5-12.

Depressive symptoms

Depressive symptoms were assessed at each study wave using the General Health Questionnaire depression subscale (0 to 12 points), and at Waves 7, 9, 11 and 12 using the Center for Epidemiological Studies-Depression scale (CES-D), a 20 item self-report scale which enquires about the frequency of symptoms [15]. Lifetime history of Major Depressive Disorder was assessed prior to the MRI scan using the Structured Clinical Interview for DSM-IV (SCID-R) [16].

Statistical analyses

All analyses, excluding whole-brain voxelwise analyses, were done with R version 3.4.0 [17]. Descriptive data were summarized for all subjects, and separately by group, according to variable type and distribution (Table 1). Group comparisons were made using the t-test for continuous variables and the chi-square test of proportions for categorical variables. Group comparisons between mean FA for selected white matter tracts were made using the t-test (Table 2). Logistic regression was used to identify significant predictors (independent variables: sociodemographic factors and depressive symptoms) of subjective cognitive complaint status (dependent variable, binary outcome).

Regression models were fitted to check whether cross-sectional performance on a range of objective memory tests performed at the time of scanning (independent variable) were associated with contemporaneous subjective cognitive complaint (dependent variable). Separate models were fitted for subjective memory and subjective concentration complaints. Age, sex, education and FSIQ were included as covariates. The same models were re-fitted with and without memory test score, and a hypothesis test (likelihood ratio) was performed. Calculated p-values were used to test whether objective memory test score made a significant difference to the model.

Multiple regression was used to test whether subjective cognitive complaints at the time of scanning were associated with subjective cognitive complaints (summary score) at Wave 12 (see supplementary materials). Age, sex, education, depressive symptoms and alcohol were included as covariates.

Mixed effects models were used to model longitudinal depressive and cognitive data. For count data (e.g. word recall from list of 20 – 'memory') a binomial regression (logistic link) was used, and for lexical and semantic fluency (performed within a time constraint) Poisson regression. The following fixed effects were included in the initial model: time from study baseline, subjective cognitive complaint status (present or absent), age, sex, social class, FSIQ, alcohol consumption, major depressive disorder and FRS. Separate models were run for subjective memory complaints and subjective concentration complaints. Non-significant variables were removed in the final models presented. In order to test whether cognitive or depressive symptom change over time significantly differed between those with and without memory complaints, interaction terms between time and subjective complaint category were added. Subject ID was included as a random effect. Usual diagnostic checks (residuals plots) were performed on the models, including checking for overdispersion in Poisson models.

Results

Subjective cognitive complaints, particularly of memory, were common in our sample. Of a total of 780 subjects included in the non-imaging analysis, 157 (20.1%) reported a problem with their concentration, whilst 320 (40.0%) reported a memory problem. 126 (16.2%) subjects reported both a memory and concentration problem. Subjective complaints at the time of MRI were significantly associated with complaints over a year (mean 1.4±1.4) later at Wave 12 (supplementary materials Table 2).

Those with subjective cognitive complaints had significantly greater concurrent self-reported depressive symptoms (CES-D scores) and a higher proportion had a history of Major Depressive disorder (SCID) (Table 1). However, we found no significant group differences with respect to socio-demographics, education, social class, FSIQ, vascular risk or alcohol consumption.

Cross-sectional analysis

In the brain-wide analysis of grey matter density using voxel-based morphometry, we found no significant group differences between subjects with and without subjective cognitive complaints. Similarly, there were no differences in white matter integrity throughout the brain, as assessed using diffusion tensor imaging, related to the presence of SCCs (Table 2). Results were consistent between models adjusted only for age and sex and fully adjusted models.

Similarly, there were no independent cross-sectional associations between cognitive performance, on any domain tested, and a subjective cognitive complaint (supplementary materials).

In logistic regression analysis (supplementary materials Table 1), current depressive symptoms (CES-D) were independently associated with higher odds

of reporting a subjective concentration complaint, as well as higher odds of reporting a subjective memory complaint independently of other variables. Higher age and FSIQ were associated with increased odds of subjective memory, but not concentration, complaints.

Longitudinal retrospective analysis

In our examination of longitudinal scores using mixed effects models, subjective cognitive complaints (of memory or concentration) were not associated with preceding decline in cognitive performance on any of the four tests we did longitudinally during the study (MMSE, memory recall, lexical and semantic fluency, measured repeatedly over the preceding 25 years in Waves 3-12) (Figure 1 & supplementary materials).

Participants with subjective concentration or memory complaints had higher baseline GHQ depression scores. Additionally, those with subjective concentration complaints experienced a greater increase in self-reported symptoms over time compared with those without (see Figure 2 & supplementary materials).

Discussion

Key findings and their context

In this longitudinal study of older adults, subjective cognitive complaints reflected depressive symptoms but not markers of neurodegenerative brain damage or objective cognitive impairment cross-sectionally or retrospectively across a 25-year period prior to subjective cognitive complaints inquiry.

Our finding that increased depressive symptoms were associated with subjective cognitive complaints is consistent with the literature. In the CFAS sample subjective complaints have been associated with both cross-sectional and longitudinal depressive symptoms [18, 19]. Similar relationships have been reported in other studies [4, 20, 21]. Whilst statistically significant, the effect size is small, likely reflecting the multifactorial nature of subjective cognitive complaints. We proposed two hypotheses to explain our observed association between subjective cognitive problems and depressive symptoms, in the absence of objective impairment. First, subjective problems may be reported in those with depressive symptoms as disturbance in self-appraisal and self-doubt are fundamental features of depression. Alternatively, subtle deterioration in cognition (if individuals are more sensitive to it than our cognitive testing) may precipitate depressive symptoms. However, we think this is a less likely explanation, as our neuropsychological battery was comprehensive, and we found no associations with either longitudinal changes in cognition or MRI measures.

In our sample, we found no association between subjective complaints and either cross-sectional or longitudinal objective performance. This is at odds with some research suggesting an increased risk of dementia or cognitive impairment in those with SMC [22-24]. A meta-analysis of 28 prospective longitudinal studies reported an increased risk of conversion to dementia (RR 2) in those with subjective memory complaints [25]. Sample selection is likely to be

important when contextualizing results. Our sample was community dwelling, and subjects needed to provide informed consent and attend Oxford for testing. Thus although not an exclusion criterion, anyone with significant functional impairment, i.e. dementia was unlikely to attend. In contrast, studies recruiting from memory clinics will capture individuals seeking help who may be more likely to have more severe and chronic objective cognitive problems, albeit in some cases not reaching the diagnostic threshold for MCI [26]. The method and wording of the question(s) to elicit SMCs may affect results, too. At the time of scanning, our participants were asked in a written questionnaire about problems in the *last month*, whereas in other studies complaints were elicited by oral questioning and put no time constraints on reported difficulties [22-24]. However, in our participants there was consistency between current and subsequent (Wave 12) reports of subjective complaints. Some specific subjective memory complaints may be more ominous. For example, trouble following a group conversation or finding your way somewhere familiar, may be more sinister [27]. Subjective and objective memory performance reciprocally influence each other at times [28]. In reality, self-awareness and cognitive problem severity are likely to be linked via a U-shaped relationship i.e. with those with either very mild or severe objective deficits being unaware [29].

Searching across the whole brain, stringently correcting for multiple comparisons, but using voxel-wise approaches not to miss unexpected associations, we found none between subjective memory complaints and cross-sectional brain structure, as measured by grey matter density and white matter integrity (FA and MD). This is at odds with reported associations between subjective cognitive complaints and cortical thinning in middle aged people at risk for Alzheimer's disease (AD) [30], as well as with AD-like grey matter atrophy [31] including smaller hippocampal volume [6, 32]. However, unlike in this study, previous analyses have usually not controlled for depressive symptoms, which are also associated with hippocampal atrophy [33]. Indeed Cherbuin et al. found adjusting for affective symptoms reduced the association [34]. This raises concerns about residual confounding underlying reported associations between subjective complaints and hippocampal size. Findings with

regard to white matter lesions have been contradictory. Subjective memory complaints were correlated with white matter lesion volume in memory clinic attendees with normal cognition, independent of depression or cognition in one small sample [35]. However, a large study found no association with white matter hyperintensities, as rated by the Fazekas score [36]. Similarly, links with Alzheimer's biomarkers remain unclear. Increased amyloid on postmortem has been reported amongst those with subjective cognitive complaints [37], but others have not replicated this [38].

Limitations and strengths

In a large sample, we were able to simultaneously examine relationships between subjective cognitive complaints, objective cognitive performance, depressive symptoms and brain structure, whilst controlling for multiple potential confounders. Most studies to date have been more limited in their scope. The 25-year duration of follow up, with respect to affective and cognitive data, is a further strength.

The definition of subjective memory complaints has no standard operationalization for assessment, and there is heterogeneity in the literature with regards to what they entail [39]. Our study relied on self-report in a binary fashion (present or absent) on a single occasion, followed by further questions after an interval of approximately one year. We were, therefore, unable to investigate how chronicity or severity of subjective complaints affect associations with objective impairments.

Due to the nature of recruitment from the British civil service in the mid 1980's, our sample is not representative of the wider UK population in terms of sex, ethnicity and social class. This may limit the generalizability of our findings.

We had single time point MRI so our analyses with respect to brain outcomes were only cross-sectional. It would be informative in the future to examine longitudinal change. Additionally, we had only one time point with cognitive data

after the enquiry about subjective cognitive complaints (at Wave 12). We can therefore not exclude the possibility of decline subsequent to our study period.

Clinical relevance

Subjective cognitive complaints are often seen as being on a continuum with definitions of Mild Cognitive Impairment (MCI) [40, 41]. Our data, which offered no evidence for an association between subjective complaints and objective deficits, question the rationale for this. The association with affective symptoms suggests clinicians should be vigilant for depression in patients who present complaining of poor memory. Our findings, namely that subjective complaints were not linked to objective deficits in cognition or brain structure, should be reassuring to such individuals.

Acknowledgements

Financial support

This work was supported by the UK Medical Research Council (G1001354, K013351, MR/S011676, MR/R024227), the Gordon Edward Small's Charitable Trust (SC008962; KPE), the HDH Wills 1965 charitable trust (charity No: 1117747; KPE), NIH (R01AG056477, R01AG034454), and the National Institute Health Research (NIHR) Oxford Health Biomedical Research Centre. The Wellcome Centre for Integrative Neuroimaging is supported by core funding from the Wellcome Trust (203139/Z/16/Z). AT is supported by a Wellcome Trust fellowship (CSR00190). MK is supported by the UK Medical Research Council (MR/S011676, MR/R024227), NIH (R01AG056477), NordForsk, the Academy of Finland (311492).

Author contributions

AT planned the study and acquired and analysed data. EZ and AM acquired data. NF and CS acquired and analysed data. AS-M, CEM, and MK also planned the study. KPE planned the study and analysed data. All authors contributed towards writing the paper by revising it critically for intellectual contact, and have given final approval of the version to be published. All authors have given agreement to be accountable for all aspects of the work.

Conflicts of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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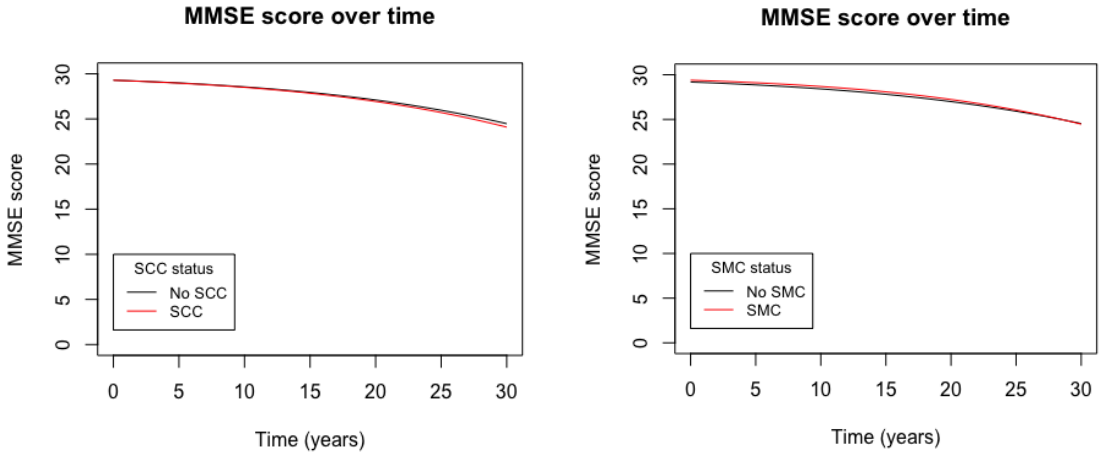

Figure 1: Graphs showing predicted change in MMSE scores over time (years) according to subjective concentration complaint (SCC) and subjective memory complaint (SMC) status, for a man of average age (40 years at baseline) and alcohol intake (10 units weekly). Predictions generated on the basis of mixed effects models.

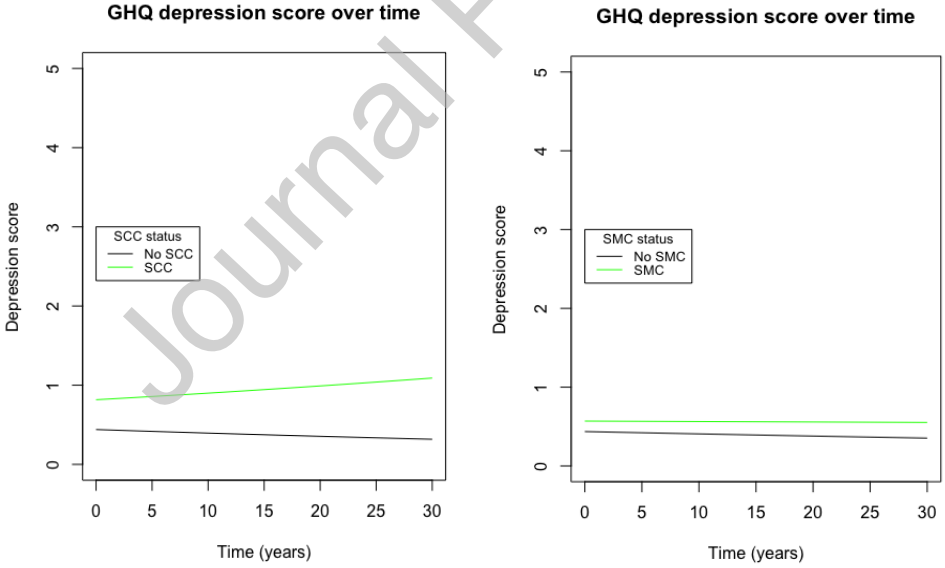

Figure 2: Graphs showing predicted change in GHQ depression scores over time (years) according to subjective concentration complaint (SCC) and subjective memory complaint (SMC) status, for a man of average age (40 years at baseline) and alcohol intake (10 units weekly). Predictions generated on the basis of mixed effects models.

	Poor Concentration Mean (SD) or N (%)		**T-test/chi-squared test statistic (95% confidence interval difference in means/proportions), degrees of freedom (df), p-value (p) [1]**	**Poor Memory Mean (SD) or N (%)**		**T-test/chi-squared test statistic (its 95% confidence interval difference in means/proportions), degrees of freedom (df), p-value (p) [1]**
	SCC (n=157)	***No SCC (n=623)***		***SMC (n=320)***	***No SMC (n=460)***	
Age, years	70.3 (5.5)	69.6 (5.1)	t=-1.40 (-1.62 to 0.28) df =227, p=0.2	70.4 (5.6)	68.3 (5.01)	**t=-2.76 (-1.80 to -0.30), df=636, p=0.006**
Sex, female	19 (12.1)	81 (13.0)	χ^2=0.03 (-0.07 to 0.05), df=1, p=0.9	47 (14.9)	53 (11.5)	χ^2=1.42 (-0.02 to 0.08), df=1, p=0.2
FSIQ	119.4 (9.5)	117.6 (10.5)	t=-0.91(-2.54 to 0.93), df=246, p=0.4	119.33 (9.48)	116.8 (10.8)	**t=-2.22 (-3.01 to -0.18), df=720, 11p=0.03**
CESD	9.9 (7.4	5.0 (5.6)	**t=-10.94 (-8.06 to -5.60), df=192, p<0.001**	6.72 (6.52)	3.6 (4.7)	**t=-6.40(-3.79 to -2.01), df=582, p<0.001**
Alcohol, current units weekly	11.1 (8.7)	11.9 (10.2)	t=-0.05 (-2.77 to 2.64), df=232, p=1	12.33 (9.20)	12.4 (10.9)	t=-0.12 (-2.28 to 2.02), df=696, p=0.9
Framingham Stroke Risk [%] at scan	12.7 (11.6)	11.2 (7.0)	t=-1.51 (-3.24 to 0.43), df=201, p=0.1	11.71 (9.05)	11.2 (7.1)	t=-0.79 (-1.82 to 0.78), df=583, p=0.43
Education [years full time]	15.0 (3.3)	14.5 (3.3)	t=-0.09 (-0.63 to 0.57), df=236, p=0.9	14.87 (3.22)	11.3 (3.3)	t=-0.91 (-0.70 to 0.26), df=690, p=0.4
SCID_R MDD history N (%)	41 (26.1)	86 (13.8)	**χ^2=13.1 (0.05 to 0.20), df=1, p<0.001**	67 (20.9)	60 (13.0)	**χ^2=8.06 (0.02 to 0.14), df=1, p=0.005**

[1]For continuous variables independent samples Welch's t-test was used, for categorical variables chi-square test for proportions.

Table 1: Group comparisons subjective cognitive complaint status. Abbreviations: CESD – Centre for Epidemiological Studies Depression, FSIQ – full-scale intelligent quotient, GHQ – general health questionnaire, MDD – major depressive disorder, SCC – subjective concentration complaint, SMC – subjective memory complaint.

	SMC mean FA	No SMC mean FA	Welch's T-test statistic (95% confidence interval difference in means), degrees of freedom (df), p-value (p)	SCC mean FA	No SCC mean FA	Welch's T-test statistic (95% confidence interval difference in means), degrees of freedom (df), p-value (p)
Corpus callosum	0.724	0.727	-0.99(-0.008 to 0.003), df=634, p=0.3	0.721	0.727	1.97 (0.00002 to 0.001), df=218, p=0.05
Right cingulum	0.621	0.623	-0.62(-0.007 to 0.004), df=617, p=0.5	0.622	0.622	-0.02(-0.007 to -0.007), df=214, p=1
Left cingulum	0.666	0.669	-1.10(-0.008 to 0.002), df=635, p=0.3	0.666	0.668	0.52 (-0.005 to 0.009), df=215, 0.6
Right corticospinal tract	0.670	0.667	1.50(-0.001 to 0.009), df=638, p=0.1	0.666	0.669	0.69(-0.004 to 0.008), df=233, p=0.5
Left corticospinal tract	0.674	0.677	1.20(-0.002 to 0.008), df=643, p=0.2	0.674	0.676	0.79(-0.004 to 0.009), df=216, p=0.4

Table 2: Comparison of white matter integrity between groups with and without subjective memory (SMC) and subjective concentration (SCC) complaints. Mean fractional anisotropy values (FA) were extracted JHU histological atlas masks using from a skeletonized FA image generated from tract-based spatial statistical analysis.