Recurrent depression has persistent effects on cognition but this does not appear to be mediated by neuroinflammation.

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Abstract

Background

Later-life depression appears to be different to depression in younger adults. The underlying pathology may also differ. Depression is linked to dementia but whether it is a risk factor or an early sign of a developing dementia remains unclear. Neuroinflammation is increasingly recognised in both depression and Alzheimer's Disease.

Aims

To investigate the link between depression, inflammation and dementia. We hypothesised that recurrent depression has adverse effects on performance in cognitive tests in middle to older age and that this effect is modified by anti-inflammatory medication.

Methods

We identified UK based cohort studies which included individuals aged >50, had medical information, results from detailed cognitive testing and had used reliable measures to assess depression. Individuals with recurrent depression had ≥ 2 episodes of depression. Controls had no history of depression. The presence/absence of inflammatory illness was assessed using a standardised list of inflammatory conditions. Individuals with dementia, chronic neurological and psychotic conditions were excluded.

Logistic and linear regression were used to examine the effect of depression on cognitive test performance and the mediating effect of chronic inflammation

Results

Unexpectedly in both studies there was evidence that those with recurrent depression performed better in some cognitive tasks (e.g Mill Hill vocabulary) but worse in others (e.g. reaction time). In UK Biobank there was no evidence that anti-inflammatories moderated this effect.

Limitations

Cross-sectional assessment of cognition

Conclusions

Although previous recurrent depression has small effects on cognitive test performance this does not appear to be mediated by chronic inflammatory disease.

Keywords

Depression, Alzheimer's Disease, cognition, inflammation, depressive disorders

Introduction

Depression and Alzheimer's Disease (AD) are both common mental illnesses. Alzheimer's disease is the most prevalent form of dementia and affects 11.3% of those aged over 65 years. (Association, 2021) Depression has an estimated lifetime prevalence of 13-18%. (de Graaf et al., 2012; Takayanagi et al., 2015) Some authors propose that the syndrome we call depression, which as with most psychiatric conditions is based on symptom clusters, may actually represent several different diseases with differing underlying aetiologies and genetic architectures.(Mullins and Lewis, 2017) Later life depression appears to differ from that earlier in life, with somatic and cognitive symptoms being more prominent. (Hegeman et al., 2012) Although the incidence of depression appears to peak at around 30 years and then decrease with age, there is a second (smaller) peak after the age of 50 suggesting a different pathological process. (Eaton et al., 1997)

The relationship between depression and dementia

Depression was identified by the Lancet commission in 2017 as one of "nine potentially modifiable risk factors at different stages of life that, if eliminated, might prevent more than a third of cases of dementia including AD (Livingston et al., 2017). There is a clear relationship between the two conditions with depression doubling the risk of later dementia (Byers and Yaffe, 2011), but it is unclear whether later life depression is a prodromal manifestation of dementia or if depression is truly a risk factor for dementia. The mechanism for this link remains unknown although multiple aetiologies have been suggested e.g. vascular changes, increased amyloid-β (Aβ), neuroinflammation, changes in levels of nerve growth factors and alterations in the glucocorticoid axis (Alexopoulos et al., 1997; Donovan et al., 2016; Lupien et al., 1999). Cognitive symptoms are increasingly recognised in depression, particularly in the elderly in whom depressive "pseudodementia" is a well-known syndrome. (Lee et al., 2012; Wells, 1979) Although pseudodementia symptoms resolve with treatment of the depressive

illness there is some evidence that the risk of subsequent dementia is raised. (Sáez-Fonseca et al., 2007) It has been shown that hippocampal volume reduces during depressive episodes, with some evidence that this effect is reversed with successful treatment. (Poul Videbech and Barbara Ravnkilde, 2004; Stephanie Campbell et al., 2004) Previous depression, particularly persistent depression, has been shown to impair performance on cognitive tests in several cohorts, with some evidence that this does not return to baseline. (Rock et al., 2014) The mechanism of this effect is unknown (John et al., 2019; Lyall et al., 2019; Singh-Manoux et al., 2010)

The role of neuroinflammation

Neuroinflammation has been shown to be associated with both depression and Alzheimer's Disease. For example, there is now meta-analytic evidence from studies measuring peripheral cytokines in individuals with depression versus controls that peripheral pro-inflammatory cytokines are elevated in depression and that some decrease with antidepressant treatment, yet the "precise peripheral immune profile associated with MDD remains a work in progress". (Köhler et al., 2017; Köhler et al., 2018) The literature on neuroinflammation in older adults is much sparser than for younger adults. (Smith et al., 2018) There is marked heterogeneity between studies. A small effect of both IL-6 and C reactive protein (CRP) was seen in older adults with depression, with evidence that elevated IL-6/CRP led to depression rather than vice versa. A large US based study with >20 y of follow-up found that elevated CRP in mid-life was associated with greater later life depression (ß = 0.12; 95% confidence interval [CI]: 0.03, 0.21; t = 2.52, df = 3,354, p = 0.012) (Sonsin-Diaz et al., 2020) but not all studies have reported a single direction of association., e.g. gender differences or attenuation of the effect over time. (Jones et al., 2017; Niles et al., 2018)

Neuroinflammation is increasingly recognised as a key part of the pathology in AD, in particular for its role in accelerating the neurodegenerative disease process. (Calsolaro and Edison, 2016; Chen et al., 2016; Haijun et al., 2019) Ageing itself has been associated with higher levels of circulating pro-inflammatory cytokines, a phenomenon termed "inflammageing" (Ferrucci et al., 2010; Franceschi et al., 2000; Shortanbayev et al., 2014), however this remains controversial. It is possible that depression may exert its effect on increased risk of dementia via increased neuroinflammation. Microglia have been implicated in the pathophysiology of both conditions. (Singhal and Baune, 2017) Microglial activation has been shown to reduce hippocampal neurogenesis. (Singhal and Baune, 2017) In a vulnerable brain this may tip the balance towards the emergence of cognitive symptoms. A study looking at UK Biobank data as a whole found that ibuprofen, a commonly used non-steroidal anti-inflammatory drug, had a beneficial effect on performance on cognitive tasks. (9)

Aims

We aimed to investigate the link between recurrent depression, inflammation and dementia. We hypothesised that recurrent depression has adverse effects on performance in cognitive tests in middle to older age and that this effect is modified by anti-inflammatory medication.

Methods

Study Design

We identified UK based cohort studies available via Dementias Platforms UK (Bauermeister et al., 2020) which; included individuals aged over 50; had information on medical history; had results from detailed cognitive testing; and had used reliable measures to assess depression. Any cohorts without information on medication were excluded, but unfortunately the medication information for Generation Scotland was unavailable for analysis. Ethical approval had been sought by each individual cohort during its set-up and continuing data collection. No specific ethical approval was required for this study as this was secondary analysis of already extant data. Participants in both studied provided written consent to participate. In this paper we examine two cohorts which provided either cross-sectional data (Generation Scotland) or data at only two time-points (UK Biobank).

For all cohorts the presence/absence of inflammatory illness was assessed by establishing whether any of the conditions on a list based on Lyall et al were present. (Lyall et al., 2019) Information was not available on all conditions for each study. We defined anti-inflammatory medications as those within British National Formulary (BNF) categories “non-steroidal anti-inflammatories”, “corticosteroids”, “TNF-alpha inhibitors”. (Commitee, 2021)

UK Biobank Cohort

UK Biobank was established in 2006 as “a very large population based prospective study…to allow detailed investigations of the genetic and nongenetic determinants of the diseases of middle and old age.”(Sudlow et al., 2015) It recruited over 500,000 participants and collection of baseline data was completed in 2010. Efforts were made to recruit a diverse range of participants. At baseline

information was collected via touch screen questionnaire on sociodemographic measures, cognitive function, lifestyle, medical history and environmental factors.(Sudlow et al., 2015) Detailed information was obtained on self-reported diagnoses for a wide range of medical conditions.

Questions on depressive and manic symptoms were added to the baseline assessment in the last two years of recruitment, so detailed information is not available for all participants.(Smith et al., 2013b) Questions on bipolar disorder were derived from the structured interview for DSM-IV Axis 1 disorders (SCID) and questions on current and previous depressive symptoms were derived from the Patient Health Questionnaire (PHQ). Participants were also asked if they had ever sought help with their mental health. A mental health working group developed the definitions for probable bipolar disorder and probable major depression in UK Biobank. Probable single episode major depression was defined as having been depressed/down for at least two weeks plus ever having sought help from a GP/Psychiatrist. Probable recurrent major depression had the same definition but having had at least two episodes.(Smith et al., 2013b) This data is available within UK Biobank as a derived variable and we used this to define caseness for depression.

The cognitive tests in UK Biobank were also performed using a touchscreen computer, without supervision. The original tests could be completed in approximately 5 minutes. All participants were invited to complete the pairs memory test, the reaction time test and a sub-sample completed the numeric memory test, a prospective memory task and a numeric and verbal reasoning test. (Fawns-Ritchie and Deary, 2020) The UK Biobank cognitive tests have been shown to correlate with general cognitive ability (r^2 varied from 0.3 to 0.6) and test-retest reliability, although moderate, is generally lower than reference cognitive tasks (r^2 varied from 0.4 to 0.6). (Fawns-Ritchie and Deary, 2020)

Visual memory: The visual memory task involved memorising the positions of pairs of cards and successfully matching them after the cards have been turned face down on the screen. In round one participants had 3 pairs to remember and in round 2 there were 6 pairs. Data are available on the number of correct and incorrect matches. Total data are available for 498,728 participants, Cronbach α reliability =0.62.(Hagenaars et al., 2016). We have focused on the 6 pair version due to its greater difficulty.

Reaction time: Participants were asked to complete a touch screen version of the game snap and the time to match each symbol was recorded. Twelve rounds were completed and the reaction time averaged across rounds. Total data are available for 496,827 participants, Cronbach α reliability =0.85.(Hagenaars et al., 2016)

Prospective memory: Towards the beginning of the cognitive tests participants were shown the message "At the end of the games we will show you 4 coloured shapes and ask you to touch the blue square. However, to test your memory we want you to actually touch the orange circle instead." Data are available on whether the participant selected the right shape and whether this was on the first or second attempt. Total data are available for 211,952 participants.

Numeric memory: This assessed digit backward span starting from a 2 digit number up to a maximum of 12 digits. This task was only performed by 89,000 participants.

Numeric and verbal reasoning test: Participants were asked to complete as many questions as possible requiring local and reasoning ability in 2 minutes. This task was included towards the end of recruitment and so data is only available for 205,333 participants, Cronbach α reliability =0.62. This task is similar to reference tasks which measure crystallised cognitive ability.(Hagenaars et al., 2016)

The cognitive tasks were repeated in a sub-set of just under 34,000 participants who took part in an imaging sub-study (phase 2 of UKBiobank) and the range of tasks extended to include other tasks. Due

to consequent reductions in power we have only examined tasks also performed at baseline in our phase 2 analysis.

Generation Scotland Cohort

Generation Scotland is a family based cohort established in 2003 which selected participants aged between 35 and 65 at random from GP registration lists and asked them to identify at least one first degree relative aged 18+ who would also participate. The age range for probands was subsequently amended to 18-65. Some participants were seen in person at research clinics and other participated via postal samples and questionnaires. In total 5.3% of the 126,000 probands invited to participate took part in the study, another 1288 individuals volunteered to participate and 16,007 family members participated. The mean age of participants was 47 and they were generally healthier and wealthier than the Scottish general population. (Smith et al., 2013a)

Self-reported medical history on a more limited range of conditions was collected including history of depression, severe depression, cancer, rheumatoid and osteoarthritis and stroke. (Smith et al., 2013a) Unlike UK Biobank standardised cognitive tests were performed including the Wechsler memory test, the verbal fluency test, the Mill Hill vocabulary test and the digit symbol test. (Lezak, 1995; Raven, 1983; Wechsler, 1945; Wechsler, 2008) Current depressive symptoms were assessed using the General Health Questionnaire 28 (GHQ) and all participants were screened for a history of mental health problems using the SCID.(Smith et al., 2013a) Twenty one point seven percent of participants screened positive and were invited to complete the mood disorder section of the SCID. (Smith et al., 2013a)

The cognitive tests administered in Generation Scotland were the digit symbol substitution test, the Wechsler logical memory test, 3 letter verbal fluency and the Mill Hill vocabulary scale.(Smith et al., 2013a) In contrast to the bespoke tests in UK Biobank these are all well established cognitive tasks. The primary outcome was the difference between the delayed and immediate logical memory score.

Statistical methods

For each cohort individuals aged under 50 were excluded from the analysis as this study was focused on those aged over 50. As we wished to focus on the effects of recurrent depression, individuals who had only had a single episode of depression were excluded. In both studies individuals with a diagnosis of bipolar disorder were excluded, as were individuals with Alzheimer's disease and Parkinson's disease because both disorders are known to be associated with deteriorations in global cognitive performance that would be likely to overshadow any effect of inflammation. In UK Biobank, which had more detailed information on medical history, individuals with any form of dementia, chronic neurological/neurodegenerative conditions, stroke, epilepsy, neurological trauma, any form of brain tumour, alcohol/drug dependence, motor neurone disease, brain abscess and schizophrenia were excluded in addition to those with bipolar disorder.

Summary variables were derived as to the presence or absence of inflammatory illnesses using the list in supplementary table 1, derived from Lyall et al. (Lyall et al., 2019) A range of possible confounders including age, gender, ethnicity, BMI, smoking, years of education and level of socioeconomic deprivation were assessed for inclusion as co-variates using the whole sample for analysis. (Sabia et al., 2008) Following analysis of differential missingness of data, a known problem with cohort studies, (Cornish et al., 2015) a complete case analysis was performed for each study after exclusion of

individuals with missing data for either the primary outcome measure or any of the key co-variates. These key covariates, in UK Biobank, were age, gender, ethnicity, smoking status, alcohol use status, BMI, educational qualifications, socioeconomic status, employment at baseline, current depressive symptoms, anti-inflammatory use at baseline and anti-depressant use at baseline. For Generation Scotland data on ethnicity, BMI and employment status were not available but all other co-variates were examined. It has been previously reported that this cohort was 99% of white ethnic origin.(Smith et al., 2013a)

The primary outcome measure for UK Biobank was accuracy in round 2 of the pairs matching task (6 pair version) and for Generation Scotland was the difference between delayed and immediate recall on the Wechsler logical memory test. Logistic regression was used to examine the effect of depression on cognitive test performance in UK Biobank and linear regression in Generation Scotland where logistic regression could not be used due to collinearity. Model 1 was the crude regression output, model 2 included age, gender, ethnicity, BMI, smoking and alcohol as co-variates, model 3 additionally included education, deprivation and employment and model 4 included all co-variates.

Data Availability

The data that support the findings of this study are available from https://www.dementiasplatform.uk/ (Project ID 248). Restrictions apply to the availability of these data, which were used under license for this study. DPUK is an MRC funded resource which is free for the dementia research community to use for approved research projects. More detailed information on DPUK and the cohorts included in this resource is available at https://www.dementiasplatform.uk/research-hub/data-portal

(Bauermeister et al., 2020)

Results

UK Biobank

As shown in Table 1, there were 14, 369 individuals in UK Biobank with recurrent depression and 316,635 without recurrent depression who had complete case information. Nearly 37% of those with recurrent depression had previously seen a psychiatrist (supplementary table 2). The missing data analysis is shown in supplementary tables S19 and S20. The data appeared to be missing at random. Data was missing most frequently for mood in the last two weeks, gender, qualifications and for the presence/absence of recurrent depression. Individuals with recurrent depression were more likely to be female, to have smoked, to take anti-inflammatory medications, to report a chronic inflammatory illness at baseline and to have had a low mood in the previous two weeks.

Table 1

As shown in Table 3, individuals with recurrent depression made a higher number of correct matches with no evidence of a change in the number of incorrect matches, suggesting that they were more accurate. This association persisted despite adjustment for multiple co-variates (model 4 for correct matches OR 1.310 (SE 0.088) p <0.001. They tended to score slightly higher on the numeric and verbal reasoning test in the crude analysis (0.07 difference, p=0.034) but the evidence for this association did not survive correction for co-variates. There was strong evidence that recurrent depression was associated with slower mean reaction times (mean difference 11.13 ms, p<0.001). There was no evidence that the presence of recurrent depression affected performance in the numeric memory task (model 4 OR 1.482, SE 0.356, p=0.100). There was evidence in the crude analysis that recurrent depression was associated with poorer performance on the prospective memory task, but this again did not survive correction for co-variates (model 4 OR 1.068, SE 0.050, p=0.163).

Although there was evidence that recurrent depression was associated with changes in cognitive function at baseline, when the effect of taking anti-inflammatory medication was examined (see supplementary Tables 3 &4) there was no evidence that anti-inflammatory use affects the relationship between depression and cognitive performance. However, there was some evidence that anti-inflammatory use improves mean reaction time in individuals without depression (model 4 β- 0.006, SE0.001, $p<0.001$).

As shown in supplementary Tables 5 & 7, the number of individuals with cognitive task data from phase 2 was greatly reduced (n=703 for recurrent depression and 13,453 for controls) meaning that the study power was commensurately much lower. There was no strong evidence that recurrent depression affected either performance in the cognitive tasks in phase 2 or the change from phase 0 to phase 2. As shown in see supplementary Table 17, we replicated the finding of Lyall et al. that chronic inflammation itself has a detrimental effect on cognition. (Lyall et al., 2019)

Generation Scotland

As shown in Table 2, there were 491 individuals with recurrent depression and 6,868 individuals without recurrent depression in Generation Scotland with complete case information. Individuals with recurrent depression were more likely to be female, have a chronic inflammatory illness, be a current smoker, to live in a more deprived area and were less likely to own their own home. The data appeared to be missing at random (see supplementary Tables 31 & 32).

As shown in Table 4 individuals with recurrent depression scored lower on average on the digit symbol substitution test (β= -1.89 (-3.21 to -0.57), p=0.005) with the model explaining a good amount of the variance. They scored higher on average on the Mill Hill vocabulary test (β=0.75 (0.34 to 1.15) p<0.001), which is primarily a measure of pre-morbid functioning and on the verbal fluency task (β= 1.97 (0.82 to 3.11) p=0.001) which measures both verbal ability and executive control. (Raven, 1958; Shao et al., 2014) The final model for the verbal fluency task only explained 7.7% of the variance. Again, as shown in supplementary Table 30 we found that chronic inflammation itself has a detrimental effect on cognition.

Table 2

Table 3

Discussion

In this study we have used two large population cohorts (UK Biobank and Generation Scotland) to examine the effect of recurrent depression on later performance in cognitive tasks in middle age, and to assess whether the use of anti-inflammatory medications modifies this relationship. In UK Biobank, which was the bigger of the two studies we found robust evidence of a difference in cognitive task performance in individuals with previous recurrent depression, but no evidence that this was affected by anti-inflammatory medications. In Generation Scotland, which was much smaller and used more precise cognitive phenotyping, we found that recurrent depression was associated with worse performance on the digit symbol substitution task (a task which covers multiple cognitive domains) but better performance on the verbal fluency and Mill Hill vocabulary tasks. (Jaeger, 2018) Taken together this suggests that recurrent depression does have a persistent effect on cognitive performance even when controlling for current low mood. We found no evidence that this effect was mitigated by taking anti-inflammatory medication suggesting that the effect of previous recurrent depression on cognition is probably not mediated by neuroinflammation. We replicated the finding of Lyall et al that chronic inflammation itself has a detrimental effect on cognition (see supplementary Tables 16 &30). (Lyall et al., 2019)

The majority of the current evidence on neuroinflammation and depression comes from younger adults. Few studies have examined directly whether inflammatory markers differ between later life and earlier onset depression. One such study, the NESDO study, looked at whether onset of depression before the age of 60 compared to afterwards led to such differences. It should be noted that the average age of the earlier onset group was 67, suggesting that they had either been depressed for a considerable period of time or suffered from recurrent depression. They found relatively weak evidence that CRP and IL-6 had more effect in individuals with later onset depression compared to those whose depression had an onset earlier in life. (Rozing et al., 2019)

In studies examining later life depression without comparison to younger adults there is somewhat more compelling evidence that neuroinflammation may be involved in later life depression. A small (n=60) cross-sectional study of older adults, with robust phenotypes for depression but a limited range of cytokines measured, found that IL-1β was elevated in those with depression and that levels of IL-1β correlated strongly with the severity of depression. (Alan J. Thomas et al., 2005) Another small study (n with depression=64, control n=18) of psychiatric in-patients with depression found, using multiplex assays, that multiple pro-inflammatory cytokines were elevated in depression. (Gaarden et al., 2018) A much larger, well-performed study from the Netherlands (n=1285) found that IL-6 but not CRP was elevated in older adults with depression. (Bremmer et al., 2008) Finally a very small PET study (n=5 with depression) suggested that there was increased microglial activation in older adults with depression in several brains areas that have been associated with mood regulation (e.g. anterior cingulate). (Su et al., 2016) It appears, from the existing evidence base, that there is no evidence that levels of inflammation differ in older adults between different subtypes of depression. (Veltman et al., 2018)

Strengths of this study include the large number of participants in UK Biobank, the precision of information available on prescriptions and other medical conditions within UK Biobank, the use of the SCID in Generation Scotland to define depression and the detailed cognitive phenotyping performed in the Generation Scotland study. Limitations include the cross-sectional characteristic of both UK Biobank and Generation Scotland, the less detailed cognitive phenotyping in UK Biobank, the much lower numbers in phase 2 of UK Biobank, the lower numbers of individuals who completed some of the cognitive tests in phase 1 of UK Biobank, the use of self-reported information on mood in UK Biobank instead of validated rating scales, the relative lack of information on other medical conditions in Generation Scotland and the lower numbers in Generation Scotland.

In summary we report that recurrent depression appears to have persistent effects on performance in cognitive tasks which does not appear to differ in those taking anti-inflammatory medications. This suggests that either neuroinflammation might not be not the mechanism by which depression affects cognition or that the medications taken by individuals in this study did not affect central neuroinflammation. Further studies should address the longitudinal effect of depression and anti-inflammatory medications on cognition.

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Declarations of Interest

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Author Contribution

LS had the original idea and wrote the application for funding with BB-A and HB. SB and JG were involved in obtaining the data and in further developing the research question. LS, BB-A and HB cleaned the data and designed the analysis strategy. LS performed the analysis and wrote the first draft of the paper which all authors contributed to. All authors have approved the final version of the manuscript.

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