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Brain IGFBP-5 Modifies the Relation of Depressive Symptoms to Decline in Working Memory in Older Persons

Ana W. Capuano^{a,b,*}, Robert S. Wilson^{a,b,c}, William G. Honer^d, Vladislav A. Petyuk^e, Sue E. Leurgans^{a,b}, Lei Yu^{a,b}, Jennifer R. Gatchel^{f,g}, Steven Arnold^h, David A. Bennett^{a,b}, and Zoe Arvanitakis^{a,b}

^aRush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA

^bDepartment of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

^cDepartment of Behavioral Sciences, Rush University Medical Center, Chicago, IL, USA

^dDepartment of Psychiatry, University of British Columbia, Vancouver, BC Canada

^eBiological Sciences Division and Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, Richland, WA, USA

^fDepartment of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA

^gDivision of Geriatric Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA

^hDepartment of Neurology, Massachusetts General Hospital, Boston, MA, USA

Abstract

Background: Brain proteins, including Insulin-like Growth Factor Binding Protein 5 (IGFBP-5), have been associated with cognitive dysfunction in aging. Mechanisms linking depression with cognition are poorly understood. We hypothesize that the association of depressive symptoms with cognition is mediated or modified by brain proteins.

Methods: IGFBP-5, HSPB2, AK4, ITPK1 and PLXNB1 were measured in dorsolateral prefrontal cortex in 1057 deceased participants, who underwent annual assessments of depressive symptoms and cognition for a mean of 8.9 years. The average number of depressive symptoms per year before a dementia diagnosis was calculated for each person.

Results: A one standard deviation above the mean IGFBP-5 was associated with a 14% higher odds of having more depressive symptoms ($p < 0.031$). Higher IGFBP-5 was associated with faster decline in global cognition ($p < 0.001$) and five cognitive domains ($p < 0.008$), controlling for depressive symptoms. IGFBP-5 moderated the association of depressive symptoms with decline in

*Corresponding author: Ana W. Capuano, Rush Alzheimer's Disease Center, 1750 W Harrison, Suite 1009N Chicago, IL 60612
Phone: (312) 942-4823 Fax: (312) 942-2297.

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global cognition ($p=0.045$). IGFBP-5 mediated ten percent or less of the total effect of depressive symptoms on decline in global cognition and the cognitive domains ($p>0.070$).

Limitations: Participants were volunteers and self-selection bias limits the generalizability of our findings. In addition, we used self-reported data on depressive symptoms. However, we also used data on depression medications as sensitivity analyses to confirm findings.

Conclusions: In old age, brain IGFBP-5 is associated with depressive symptoms and cognition. The association of depressive symptoms with cognitive decline is conditional on IGFBP-5.

Keywords

Depression; dementia; cognition; IGFBP-5; protein

INTRODUCTION

Depressive symptoms are related to faster cognitive decline in late life (Kohler, et al, 2010). The biologic mechanisms underlying depression (Martins-de-Souza, et al, 2010) and its association with cognitive decline in later life are not well understood, and do not appear to be explained by common neuropathologies of dementia, such as Alzheimer's disease (Donovan, et al, 2015; Wilson, et al, 2014). Yet, depressive symptoms and cognitive dysfunction may share other common underlying pathophysiologic mechanisms. Indeed, many studies show disturbances in synaptic plasticity, spinodendritic density and morphology, and neurogenesis in the hippocampus, prefrontal cortex, and other brain regions, in both disorders (Levada and Troyan, 2017). Given established protein disturbances in depressive symptoms and cognition (Martins-de-Souza, et al, 2012; Martins-de-Souza, 2014; Ramsey, et al, 2016; Yu, et al, 2018), proteomics may be one useful tool to provide some insight into molecular mechanistic processes linking depression with cognition (Filiou, et al, 2012). To date, only a few small studies have examined human brain proteins of major depression patients and controls (Martins-de-Souza, et al, 2012; Martins-de-Souza, 2014; Young, et al, 2016). In a recent study, our group examined a total of 12 selected reaction monitoring (SRM) quantitative proteins that we identified in a gene coexpression network associated with cognitive decline called module 109 (m109) (Mostafavi, et al, 2018). We found five proteins associated with cognitive decline: Insulin-like Growth Factor Binding Protein 5 (IGFBP-5), Heat Shock Protein Family B (Small) Member 2 (HSPB2), Adenylate Kinase 4 (AK4) and Inositol-Tetrakisphosphate 1-Kinase (ITPK) and Plexin B1 (PLXNB1) (Yu, et al, 2017). In this follow-up study, we examined whether the level of depressive symptoms shares common protein disturbances with cognitive dysfunction in aging.

All participants were enrolled in Religious Order Study and Memory and Aging Project, and at death brain tissue was available for proteomic studies. Participants had annual clinical evaluations which included an assessment of depressive symptoms with the 10-item Center for Epidemiological Studies Depression scale (CESD) and testing for cognitive function using a range of individual neuropsychological tests. At death, brain autopsies were performed. Frozen dorsolateral prefrontal cortex tissue was used to quantify the 5 proteins of interest. In analyses adjusted for demographics, we tested whether proteins previously shown to be associated with cognitive dysfunction were also associated with higher levels of

depressive symptoms. We next tested whether proteins associated with depressive symptoms mediated or modified the association of depressive symptoms with cognitive decline, including measures of global cognition and of 5 cognitive domains.

METHODS

Participants

Participants were enrolled in one of 2 ongoing longitudinal clinical-pathologic studies (ROSMAP), one involving older Catholic clergy recruited from multiple sites across the United States (ROS) that began in 1994, and the other involving older lay individuals from the Chicago area (MAP) that began in 1997 (Bennett, et al, 2018). At baseline, all participants agreed to yearly clinical assessments and to brain donation at death, and were not known to have been diagnosed with dementia. In each study, individuals signed an informed consent form after a detailed conversation with study staff. Each project was approved by Rush University Medical Center's institutional Review Board.

At time the brain tissue was sent for the additional round of proteomic profiling, a total of 1661 individuals had died during follow-up; a brain autopsy was performed on 1433 (86.3%). At the time of these analyses, the SRM proteomics analyses had been completed on 1207 participants. Among these, 1057 had at least one Center for Epidemiological Studies Depression scale (CESD) administered before a clinical diagnosis of dementia and two measures of global cognition at time of death, allowing assessing for cognitive decline. They died at an average age of 89.6 years (SD=6.5) with an average of 16.3 years of schooling (SD=3.6); 31% were men. They completed an average of 8.9 years of follow-up (SD=4.6). Compared to the participants who died without autopsy (n=228), these participants were on average about 2.1 years older ($t[327.35] = -4.46, p < 0.001$) and had 1.3 more years of education ($t[309.73] = -4.43, p < 0.001$). The percentages of men ($\chi^2(1) = 0.16, p = 0.686$) and the number of depressive symptoms (Mann-Whitney U test=136576, $p = 0.307$) were similar to the participants who died without autopsy.

Cognitive Function

A total of 17 cognitive performance tests were common in both cohorts and summarized to yield five cognitive domains, for each annual evaluation. Domains are episodic memory (7 tests), semantic memory (3 tests), working memory (3 tests), perceptual speed (2 tests), and visuospatial ability (2 tests), as described in many prior publications (Bennett, et al, 2018). To construct a global cognitive outcome measure, we converted the 17 raw test scores to z scores (based on the mean and SD from the initial evaluation of the combined cohorts) and computed the mean of these z scores. Further information on the individual tests and composite measures is published elsewhere (Wilson, et al, 2003; Wilson, et al, 2005). A clinical diagnosis of dementia was rendered at each annual evaluation based on historical evidence of declining cognition and evidence of impairment in at least 2 cognitive domain based on neuropsychological data (McKhann, et al, 1984). After death, a summary cognitive diagnosis, taking all years of data into account, was established by a neurologist with expertise in dementia.

Depressive Symptoms

A short form (Kohout, et al, 1993) of the CESD (Radloff, 1977) was administered at each annual evaluation. Briefly, participants were asked “Have you felt this way much of the past week?” for a total of 10 items relevant to depression. At each annual visit, the score is calculated as the number of depressive symptoms recorded as occurring “much of the time” over the past week (a score between 0 and 10). For analyses, the average number of depressive symptoms over the years was calculated for each person, excluding measures at or after the first visit (if any) at which a clinical diagnosis of dementia since symptoms were self-reported (Wilson, et al, 2014; Wilson, et al, 2016).

During each visit, participants supplied all medications prescribed by a clinician and over-the-counter agents (including vitamins, supplements, and biologic agents) taken in the 2 weeks before the evaluation. A list of medication names and dosages were documented directly on laptop computers after direct visual inspection of all containers. Medications were subsequently coded using the Medi-Span Drug Data Base system (Medi-Span, 1995). A dummy variable indicating use of antidepressants at any time during the study was created.

Proteomics

Quantitative proteomics was performed on co-expressed cortical genes in a network associated with cognitive decline in older adults ((Gaiteri, et al, 2014; Zhang, et al, 2013), as described in detail elsewhere (Yu, et al, 2018). Briefly, using a standard protocol (Petyuk, et al, 2010) (Andreev, et al, 2012), frozen tissue samples from the dorsolateral prefrontal cortex were prepared and analyzed with LC-SRM (combination of liquid chromatography (LC) selected reaction monitoring (SRM)). Relative abundances of the IGFBP-5, HSPB2, AK4, ITPK1 and PLXNB1 proteins were quantified using proteotypic peptides. Endogenous (light) peptide abundances were measured relative to the spiked-in stable isotope labeled synthetic peptide standards (heavy). Peptide ratios (light/heavy) were log2-transformed and centered at the median. The z score of the transformed ratios of the proteins IGFBP-5, HSPB2, AK4, ITPK1 and PLXNB1 were used in analyses. In these analyses we included proteins from an additional 223 persons on whom protein data was generated since our prior manuscript (total n=1057) (Yu, et al, 2018).

Statistical Analyses

Descriptive analyses were performed. The Pearson correlations of the five proteins were examined. In the first set of models, we examined number of depressive symptoms (ordinal from 0 to 10) as the outcome, using constrained ordinal regression models assuming proportional odds (POM) (Agresti, 2010; Capuano, et al, 2007) and trend odds (TOM) (Capuano and Dawson, 2013) with terms for one protein at time. The distributions of average depressive symptoms was skewed and inflated at an average of about zero symptoms (range of 0-10, median= 0.90, IQR=0.31-1.88), so in these analyses, sparse levels were grouped: less than one (0 to <1), one (1 to <2), two (2 to <3), three (3 to <4) and four or more symptoms. The proportionality assumption, assessed with the score test for proportional odds and the trend odds model, was found to be adequately met (trend effect= -0.014 SE= 0.042, p= 0.739). All models controlled for demographic factors: age at death,

years of education, sex and years in study. Models used a conservative Bonferroni adjusted 2-tailed significance level of 0.01 (0.05/5 proteins) to evaluate of the effects of the five proteins, and 0.05 otherwise.

In the second set of models, we examined longitudinal global cognition and cognitive domain data, via mixed effects regression models with our updated protein dataset. First, we ran the models with a term for the protein found to be associated with depressive symptoms. We ran the same model replacing the protein by the depressive symptom variable. Then we repeated the analysis, but with a term for the protein and a term for depressive symptoms. We then estimated the indirect effect of depressive symptoms on cognitive decline over time mediated through the protein based on the described linear mixed model with cognition as outcome, as well as a linear regression model with protein as the outcome and a term for depressive symptoms (to meet normality assumptions required for the test), and tested with the multivariate delta method based on a first order Taylor series approximation (MacKinnon, et al, 2002). Finally, to test for moderation, we augmented each model with an interaction term between the protein and depressive symptoms. All models controlled for demographic factors: age at death, years of education and sex. Models used a 2-tailed significance level of 0.05. Analyses were performed in SAS software, Version 9.4, of the SAS(R) system for Linux.

RESULTS

Proteins and depressive symptoms

A total of 1057 participants were included in these analyses, 43.2% developed dementia over the course of the study, and 20.8% (of all participants) took an Alzheimer's disease medication at some point during the study period. Over the entire study period before a diagnosis of dementia, 540 (51.1%) reported less than one symptom, 261 (24.7%) reported about one (1 to <2), 119 (11.3%) reported two (2 to <3), and 137 (12.9%) reported three or more symptoms. Table 1 shows that participants with one or more depressive symptoms were similar to other participants in age at baseline and at death, and in the percentage of women, but they had about one year less education. About half of participants with one or more depressive symptoms took an antidepressant medication during the study period. The decline in global cognitive decline was -0.099 ($SE=0.0039$, $p<0.001$), and the decline in each of the five cognitive domains was between -0.063 and -0.099 ($SE=0.0035$ to 0.0045 , $p<0.001$) per year, with time measured as negative years from death (i.e. death as zero and one year from death as -1).

The absolute correlations among the relative protein abundances were between 0.03 and 0.27. The weakest correlations were the negative correlations between HSPB2 and ITPK1 ($r=-0.05$, $p=0.081$) and between AK4 and PBXNB1 ($r=-0.03$, $p=0.3714$). The strongest correlations were the positive correlation between PLXNB1 and ITPK1 ($r=0.26$, $p<0.001$) and the negative correlation between AK4 and ITPK1 ($r=-0.27$, $p<0.001$). There was a negative correlation between IGFBP-5 and ITPK1 ($r=-0.19$, $p<0.001$), and a negative correlation between IGFBP-5 and all other proteins ($r=0.14$ to 0.16 , $p<0.001$). The mean IGFBP-5 for participants with one or more depressive symptoms was higher than for other

participants (Table 1). The means of the other four proteins were similar between the two groups.

In separate constrained adjusted ordinal models, we tested if each protein was associated with depressive symptoms. Participants with a one standard deviation higher abundance of IGFBP-5 had a 14% higher odds ($p=0.031$) of having more depressive symptoms (Table 2). The figure represents the effect of abundance of IGFBP-5 on the predicted probability of different numbers of depressive symptoms for a woman (69% of participants were women) with the mean age at death (89 years) and the mean education (16 years) in this study. The figure shows that a higher abundance of IGFBP-5 was associated with a higher probability of having more depressive symptoms. No other protein was associated with depressive symptoms (Table 2). In sensitivity analyses, we replaced the depressive symptoms outcome variable with use of antidepressant medications before the diagnosis of dementia, and found that a one standard deviation higher abundance of IGFBP-5 was also associated with a 29% higher odds (odds ratio= 1.289; estimate=0.254, SE= 0.073, $p<0.001$) of antidepressant medication use.

IGFBP-5, cognition and depressive symptoms

We next tested whether IGFBP-5 mediated or modified the effect of depressive symptoms on cognitive decline. To assess mediation, first we fit separate mixed-effects model with longitudinal cognition (global cognition and five domains) as outcomes, including terms for depressive symptoms and for demographics. A higher number of depressive symptoms was associated with a faster decline in global cognition and all cognitive domains (all $p < 0.01$, table 3). Second, we repeated the models but adding a term for IGFBP-5. Higher IGFBP-5 was associated with a faster decline in global cognition and in all five cognitive domains (all $p<0.01$, table 3). We repeated the models with terms for both depressive symptoms and IGFBP-5, and tested if there was a partial mediation of depressive symptoms on decline in cognition. IGFBP-5 mediated ten percent or less of the total effect of depressive symptoms on decline in global cognition and the cognitive domains ($z=-1.813$, $p>0.070$).

To assess moderation by the protein, the models were rerun with an interaction term between IGFBP-5 and depressive symptoms. There was weak evidence that the association of depressive symptoms with decline in global cognition was conditional on the abundance of IGFBP-5. Analyses showed that a one standard deviation higher abundance of IGFBP-5 was associated with an increased effect of depressive symptoms on the decline in global cognition of -0.0031 ($p=0.045$, table 3), and borderline on the decline in working memory of -0.0033 ($p=0.082$, table 3). IGFBP-5 did not modify the association of depressive symptoms with any other cognitive domain ($p>0.163$, table 3).

LIMITATIONS AND STRENGTHS

This study has several limitations. First, participants were volunteers in research involving brain donation, and self-selection bias limits the generalizability of our findings. For example, given healthy volunteer effects, community volunteers tend to have lower levels of depressive symptoms for a variety of reasons including lower levels of physical illness that increases the risk of developing depression (Goodwin, 2006; Moussavi, et al, 2007; Roose,

et al, 2001). Also the Religious Order Study participants tended to report less depressive symptoms (Mann-Whitney U test=244723, $p<0.001$) in average over the study period before a clinical diagnosis of dementia (56.6% reported less than one symptom), although the percentages of antidepressant medication ($\chi^2(1)=0.160$, $p=0.686$) were similar to other participants. Second, we used self-reported data on depressive symptoms, rather than a clinical diagnosis of depression. However, we also used data on antidepressant medications taken in the 2 weeks prior each annual visit, with drug labels being visually inspected by the research team, and detailed medication data documented directly into an electronic platform. Although antidepressants are sometimes prescribed for other off-label indications, this approach allows us to capture participants who have clinical depression but whose symptoms are controlled with antidepressant medications. The sensitivity analyses taking medication into account were consistent and indeed confirm our findings. The study also has several strengths. In both cohorts, of the cumulative number of persons who have withdrawn from the study are small, 9% or less, minimizing attrition related bias. We used quantitative measures of several proteins derived from human brain tissue in a very large sample of persons who were well-characterized before death. Also, participants were evaluated annually over an average of 9 years, enhancing our confidence in the classification of clinical characteristics such as depressive symptoms and performance-based cognitive function. Furthermore, cognitive data included a global measure as well as five cognitive domain measures, with potential to provide additional insights into brain pathways involved in linking depressive symptoms, proteins, and cognition.

CONCLUSIONS

In this study of relative abundance of select brain proteins in more than 1000 older adults, we found that a higher IGFBP-5 abundance was associated with more depressive symptoms. In additional analyses adjusting for depressive symptoms, abundance of IGFBP-5 remained associated with decline in global cognition and five cognitive domains. Although IGFBP-5 is significantly associated with both depressive symptoms and cognitive decline, only a small part of the association of depressive symptoms with decline in cognition was mediated by IGFBP-5. However, IGFBP-5 modified the relation of depressive symptoms with cognitive decline, such that persons with higher IGFBP-5 and more depressive symptoms had faster decline in cognition. More specifically, results suggest that older adults with higher levels of depressive symptoms and higher IGFBP-5 are more likely decline more rapidly in cognition, compared to older adults with similar levels of depressive symptoms but lower IGFBP-5. Furthermore, these results suggest that, in addition to IGFBP-5, other factors also play a role in the association of depressive symptoms with cognition. Indeed, the literature suggests that inflammation, immunity, oxidative stress, and other putative factors are likely involved (Hermida, et al, 2012; Maes, et al, 2011). For example, aberrations in oxidative stress pathways, also involved in Alzheimer's disease, are found in depression (Maes, et al, 2011).

These data provide novel insights into potential biologic mechanisms linking depression and cognitive decline in aging. Altered protein abundance and function, in particular of proteins associated with neurodegenerative, vascular, and metabolic processes, have long been known to be involved in the pathophysiologic pathways of cognitive dysfunction and mood

disorders, including those in the family of insulin-like growth factor-binding proteins (IGFBPs) (Bezchlibnyk, et al, 2007). In particular, IGFBP-5 is one of the six IGFBPs that regulate the activity of Insulin Growth Factor IGF-1 (Emeny, et al, 2014). Specifically, IGFBP-5 sequesters IGF-1, resulting in reduced signaling through the IGF1R receptor (Kalus, et al, 1998). IGFBP-5 and IGF-1 gene expression demonstrate a temporally coordinated laminar expression in the developing cerebellar cortex and hippocampal formation. IGFBP-5 has known roles in differentiation, proliferation, and apoptosis in the developing brain (Bibollet-Bahena, et al, 2017). In rats, IGFBP-5 gene expression was found in the developing cortex and hippocampus as well as many components of the limbic system during postnatal brain development (Bondy and Lee, 1993; Ye and D'Ercole, 1998). It is also detected in forebrain white matter tracts and the olfactory nerve from the second week after birth into maturity (Bondy and Lee, 1993). Thus, most data on IGFBP-5 protein in brain tissue was derived from non-human research studies, with the exception of studies of brain cancers such as glioblastoma multiforme (Santosh, et al, 2010), and much work remains to replicate and expand our findings of the understanding of IGFBP-5 in human brain.

To our knowledge, no other study has examined the association of the abundance of IGFBP-5 in human brain to depression in older age, and the association of depressive symptoms with cognitive decline taking this protein into account. Most work available in the literature is on proteins assessed in biofluids (i.e. blood or cerebrospinal fluid), using mRNA expression in brain tissue (Bezchlibnyk, et al, 2007), or in animal models (Basta-Kaim, et al, 2014). Basta-Kaim et al. studied IGFBP-5 in brain tissue of pre-natally stressed mice and found alterations in various IGFBPs, including IGFBP-5, along with IGF-1. Using serum samples in humans, IGFBP-5 protein was found to be associated with major depression in some studies (Diniz, et al, 2016; Lamers, et al, 2016; Ramsey, et al, 2016) but not in others (Wang, et al, 2016). In humans with cerebrospinal fluid samples, higher *in vivo* concentrations of IGFBPs were found in 20 Alzheimer's disease patients, compared to 20 controls (Barucker, et al, 2015).

We recently reported that higher relative abundance of IGFBP-5 peptides in brain tissue was associated with faster decline in global cognitive function (Yu, et al, 2018), an association that was mediated in part by the presence of Alzheimer's disease pathology. The present study adds to the literature by showing that, in more than 1000 older deceased and autopsied persons, human brain IGFBP-5 is associated with depressive symptoms and that IGFBP-5 modifies the association of depressive symptoms with decline in cognition.

Further research to examine mechanistic links between depressive symptoms and cognition is needed to advance our understanding of these common and disabling conditions. While we studied a set of predetermined brain proteins as informed by our prior work, other proteins in brain and other tissues are likely to have a role in the relation of depression and cognitive decline. For example, in the IGFBP family of proteins, plasma levels of IGFBP-2 have been associated with Alzheimer's disease and brain atrophy, important factors in cognitive decline in aging (Lane, et al, 2017). Furthermore, serum IGFBP-3 abundance was associated with depression in patients with brain gliomas (Wang, et al, 2014). Specific details of the pathways involved in IGFBP-5 and other proteins need further elucidation, and additional brain and other factors need to be evaluated. Research on other psychological

markers is likely to contribute to our understanding. Indeed, prenatal stress leads to changes in the network of IGF-1 binding proteins in the hippocampus and frontal cortex of the adult male rat (Basta-Kaim, et al, 2014), with IGFBP-5 concentration in particular found to be decreased in the hippocampus of prenatally stressed animals (Basta-Kaim, et al, 2014).

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References

- Agresti A, 2010 Analysis of Ordinal Categorical Data. Wiley, Hoboken, N.J.
- Andreev VP, Petyuk VA, Brewer HM, Karpievitch YV, Xie F, Clarke J, Camp D, Smith RD, Lieberman AP, Albin RL, Nawaz Z, El Hokayem J, Myers AJ, 2012 Label-free quantitative LC-MS proteomics of Alzheimer's disease and normally aged human brains. *J. Proteome Res* 11, 3053–3067. [PubMed: 22559202]
- Barucker C, Sommer A, Beckmann G, Eravci M, Harmeier A, Schipke CG, Brockschneider D, Dyrks T, Althoff V, Fraser PE, Hazrati LN, George-Hyslop PS, Breitner JC, Peters O, Multhaup G, 2015 Alzheimer amyloid peptide abeta42 regulates gene expression of transcription and growth factors. *J. Alzheimers Dis* 44, 613–624. [PubMed: 25318543]
- Basta-Kaim A, Szczesny E, Glombik K, Slusarczyk J, Trojan E, Tomaszewski KA, Budziszewska B, Kubera M, Lason W, 2014 Prenatal stress leads to changes in IGF-1 binding proteins network in the hippocampus and frontal cortex of adult male rat. *Neuroscience*. 274, 59–68. [PubMed: 24857711]
- Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA, 2018 Religious Orders Study and Rush Memory and Aging Project. *J. Alzheimers Dis* 64, S161–S189. [PubMed: 29865057]
- Bezchlibnyk YB, Xu L, Wang JF, Young LT, 2007 Decreased expression of insulin-like growth factor binding protein 2 in the prefrontal cortex of subjects with bipolar disorder and its regulation by lithium treatment. *Brain Res*. 1147, 213–217. [PubMed: 17395163]
- Bibollet-Bahena O, Okafuji T, Hokamp K, Tear G, Mitchell KJ, 2017 A dual-strategy expression screen for candidate connectivity labels in the developing thalamus. *PLoS One*. 12, e0177977. [PubMed: 28558017]
- Bondy C and Lee WH, 1993 Correlation between insulin-like growth factor (IGF)-binding protein 5 and IGF-I gene expression during brain development. *J. Neurosci* 13, 5092–5104. [PubMed: 7504720]
- Capuano AW, Dawson JD, Gray GC, 2007 Maximizing power in seroepidemiological studies through the use of the proportional odds model. *Influenza Other Respir. Viruses* 1, 87–93. [PubMed: 18176626]
- Capuano AW and Dawson JD, 2013 The trend odds model for ordinal data. *Stat. Med.* 32, 2250–2261. [PubMed: 23225520]
- Diniz BS, Lin CW, Sibille E, Tseng G, Lotrich F, Aizenstein HJ, Reynolds CF, Butters MA, 2016 Circulating biosignatures of late-life depression (LLD): Towards a comprehensive, data-driven approach to understanding LLD pathophysiology. *J. Psychiatr. Res* 82, 1–7. [PubMed: 27447786]
- Donovan NJ, Hsu DC, Dagley AS, Schultz AP, Amariglio RE, Mormino EC, Okereke OI, Rentz DM, Johnson KA, Sperling RA, Marshall GA, 2015 Depressive Symptoms and Biomarkers of Alzheimer's Disease in Cognitively Normal Older Adults. *J. Alzheimers Dis* 46, 63–73. [PubMed: 25697700]
- Emeny RT, Bidlingmaier M, Lacruz ME, Linkohr B, Peters A, Reincke M, Ladwig KH, 2014 Mind over hormones: sex differences in associations of well-being with IGF-I, IGFBP-3 and physical activity in the KORA-Age study. *Exp. Gerontol* 59, 58–64. [PubMed: 25106099]

- Filiou MD, Martins-de-Souza D, Guest PC, Bahn S, Turck CW, 2012 To label or not to label: applications of quantitative proteomics in neuroscience research. *Proteomics*. 12, 736–747. [PubMed: 22247077]
- Gaiteri C, Ding Y, French B, Tseng GC, Sibille E, 2014 Beyond modules and hubs: the potential of gene coexpression networks for investigating molecular mechanisms of complex brain disorders. *Genes Brain Behav*. 13, 13–24. [PubMed: 24320616]
- Goodwin GM, 2006 Depression and associated physical diseases and symptoms. *Dialogues Clin. Neurosci* 8, 259–265. [PubMed: 16889110]
- Hermida AP, McDonald WM, Steenland K, Levey A, 2012 The association between late-life depression, mild cognitive impairment and dementia: is inflammation the missing link? *Expert Rev. Neurother* 12, 1339–1350. [PubMed: 23234395]
- Kalus W, Zweckstetter M, Renner C, Sanchez Y, Georgescu J, Grol M, Demuth D, Schumacher R, Dony C, Lang K, Holak TA, 1998 Structure of the IGF-binding domain of the insulin-like growth factor-binding protein-5 (IGFBP-5): implications for IGF and IGF-I receptor interactions. *EMBO J*. 17, 6558–6572. [PubMed: 9822601]
- Kohler S, van Boxtel MP, van Os J, Thomas AJ, O'Brien JT, Jolles J, Verhey FR, Allardyce J, 2010 Depressive symptoms and cognitive decline in community-dwelling older adults. *J. Am. Geriatr. Soc* 58, 873–879. [PubMed: 20374396]
- Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J, 1993 Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J. Aging Health* 5, 179–193. [PubMed: 10125443]
- Lamers F, Bot M, Jansen R, Chan MK, Cooper JD, Bahn S, Penninx BW, 2016 Serum proteomic profiles of depressive subtypes. *Transl. Psychiatry* 6, e851. [PubMed: 27404283]
- Lane EM, Hohman TJ, Jefferson AL, Alzheimer's Disease Neuroimaging Initiative, 2017 Insulin-like growth factor binding protein-2 interactions with Alzheimer's disease biomarkers. *Brain Imaging Behav*. 11, 1779–1786. [PubMed: 27817134]
- Levada OA and Troyan AS, 2017 Insulin-like growth factor-1: a possible marker for emotional and cognitive disturbances, and treatment effectiveness in major depressive disorder. *Ann. Gen. Psychiatry* 16, 38-017-0161-3. eCollection 2017.
- MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V, 2002 A comparison of methods to test mediation and other intervening variable effects. *Psychol. Methods* 7, 83–104. [PubMed: 11928892]
- Maes M, Galecki P, Chang YS, Berk M, 2011 A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 676–692. [PubMed: 20471444]
- Martins-de-Souza D, Harris LW, Guest PC, Turck CW, Bahn S, 2010 The role of proteomics in depression research. *Eur. Arch. Psychiatry Clin. Neurosci* 260, 499–506. [PubMed: 19997739]
- Martins-de-Souza D, Guest PC, Harris LW, Vanattou-Saifoudine N, Webster MJ, Rahmoune H, Bahn S, 2012 Identification of proteomic signatures associated with depression and psychotic depression in post-mortem brains from major depression patients. *Transl. Psychiatry* 2, e87. [PubMed: 22832852]
- Martins-de-Souza D, 2014 Proteomics, metabolomics, and protein interactomics in the characterization of the molecular features of major depressive disorder. *Dialogues Clin. Neurosci* 16, 63–73. [PubMed: 24733971]
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM, 1984 Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 34, 939–944. [PubMed: 6610841]
- Medi-Span I, 1995 Master drug database documentation manual.
- Mostafavi S, Gaiteri C, Sullivan SE, White CC, Tasaki S, Xu J, Taga M, Klein HU, Patrick E, Komashko V, McCabe C, Smith R, Bradshaw EM, Root DE, Regev A, Yu L, Chibnik LB, Schneider JA, Young-Pearse TL, Bennett DA, De Jager PL, 2018 A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease. *Nat. Neurosci* 21, 811–819. [PubMed: 29802388]

- Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B, 2007 Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 370, 851–858. [PubMed: 17826170]
- Petyuk VA, Qian WJ, Smith RD, Smith DJ, 2010 Mapping protein abundance patterns in the brain using voxelation combined with liquid chromatography and mass spectrometry. *Methods*. 50, 77–84. [PubMed: 19654045]
- Radloff LS, 1977 The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*. 1, 385–401.
- Ramsey JM, Cooper JD, Bot M, Guest PC, Lamers F, Weickert CS, Penninx BW, Bahn S, 2016 Sex Differences in Serum Markers of Major Depressive Disorder in the Netherlands Study of Depression and Anxiety (NESDA). *PLoS One*. 11, e0156624. [PubMed: 27232630]
- Roose SP, Glassman AH, Seidman SN, 2001 Relationship between depression and other medical illnesses. *JAMA*. 286, 1687–1690. [PubMed: 11594878]
- Santosh V, Arivazhagan A, Sreekanthreddy P, Srinivasan H, Thota B, Srividya MR, Vrinda M, Sridevi S, Shailaja BC, Samuel C, Prasanna KV, Thennarasu K, Balasubramaniam A, Chandramouli BA, Hegde AS, Somasundaram K, Kondaiah P, Rao MR, 2010 Grade-specific expression of insulin-like growth factor-binding proteins-2, -3, and -5 in astrocytomas: IGFBP-3 emerges as a strong predictor of survival in patients with newly diagnosed glioblastoma. *Cancer Epidemiol. Biomarkers Prev* 19, 1399–1408. [PubMed: 20501753]
- Wang Q, Su X, Jiang X, Dong X, Fan Y, Zhang J, Yu C, Gao W, Shi S, Jiang J, Jiang W, Wei T, 2016 iTRAQ technology-based identification of human peripheral serum proteins associated with depression. *Neuroscience*. 330, 291–325. [PubMed: 27268281]
- Wang Y, Huang M, Jiao JT, Wu YL, Ouyang TH, Huang J, Liu SS, Li CL, 2014 Relationship between concentrations of IGF-1 and IGFBP-3 and preoperative depression risk, and effect of psychological intervention on outcomes of high-grade glioma patients with preoperative depression in a 2-year prospective study. *Med. Oncol* 31, 921-014-0921-8. Epub 2014 Mar 26.
- Wilson R, Barnes L, Bennett D, 2003 Assessment of lifetime participation in cognitively stimulating activities. *J. Clin. Exp. Neuropsychol* 25, 634–642. [PubMed: 12815501]
- Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA, 2005 Early and late life cognitive activity and cognitive systems in old age. *J. Int. Neuropsychol. Soc* 11, 400–407. [PubMed: 16209420]
- Wilson RS, Capuano AW, Boyle PA, Hoganson GM, Hizez LP, Shah RC, Nag S, Schneider JA, Arnold SE, Bennett DA, 2014 Clinical-pathologic study of depressive symptoms and cognitive decline in old age. *Neurology*. 83, 702–709. [PubMed: 25080520]
- Wilson RS, Boyle PA, Capuano AW, Shah RC, Hoganson GM, Nag S, Bennett DA, 2016 Late-life depression is not associated with dementia-related pathology. *Neuropsychology*. 30, 135–142. [PubMed: 26237627]
- Ye P and D'Ercole J, 1998 Insulin-like growth factor I (IGF-I) regulates IGF binding protein-5 gene expression in the brain. *Endocrinology*. 139, 65–71. [PubMed: 9421399]
- Young JJ, Silber T, Bruno D, Galatzer-Levy IR, Pomara N, Marmar CR, 2016 Is there Progress? An Overview of Selecting Biomarker Candidates for Major Depressive Disorder. *Front. Psychiatry* 7, 72. [PubMed: 27199779]
- Yu L, Petyuk VA, Gaiteri C, Mostafavi S, Young-Pearse T, Shah RC, Buchman AS, Schneider JA, Piehowski PD, Sontag RL, Fillmore TL, Shi T, Smith RD, Jager PL, Bennett DA, 2018 Targeted brain proteomics uncover multiple pathways to Alzheimer's dementia. *Ann. Neurol* 0.
- Zhang B, Gaiteri C, Bodea LG, Wang Z, McElwee J, Podtelezhnikov AA, Zhang C, Xie T, Tran L, Dobrin R, Fluder E, Clurman B, Melquist S, Narayanan M, Suver C, Shah H, Mahajan M, Gillis T, Mysore J, MacDonald ME, Lamb JR, Bennett DA, Molony C, Stone DJ, Gudnason V, Myers AJ, Schadt EE, Neumann H, Zhu J, Emilsson V, 2013 Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell*. 153, 707–720. [PubMed: 23622250]

HIGHLIGHTS

- Most data on IGFBP-5 protein in brain tissue were derived from non-human research studies, with the exception of studies of brain cancers such as glioblastoma multiforme.
- In old age, higher abundances of brain IGFBP-5 protein at death are associated with both depressive symptoms and cognitive decline.
- Higher abundance of IGFBP-5 is associated with an increased effect of depressive symptoms on the cognitive decline.
- Much work remains to replicate and expand our findings of the understanding of IGFBP-5 in human brain.

Figure. Estimated probability of having different numbers of depressive symptoms (CESD) depending on the abundance of IGFBP-5 in brain, from model adjusted for age at death, sex, education and years in study. Blue represents less than one depressive symptom in average over the study period, while red are the four of more depressive symptoms. Other colors are intermediate number of depressive symptoms as per heatmap column on the right.

Table 1

Descriptive characteristic of the study participants (n = 1057)

Variables	Number of depressive symptoms** $\bar{T}$	
	<1 n=540	1 n=517
Age at baseline (years), mean (SD)	79.86 (6.78)	80.35 (6.94)
Age at death (years), mean (SD) *	90.07 (6.33)	89.04 (6.63)
Education (years), mean (SD) *	16.79 (3.65)	15.72 (3.73)
Women, n (%)	359 (66.48%)	374 (72.34%)
Antidepressant use, n (%) * $\bar{T}$	115 (21.30%)	219 (42.36%)
Proteins, mean (SD)		
IGFBP-5 *	-0.09 (1.00)	0.04 (0.97)
HSPB2	-0.07 (1.06)	0.01 (0.97)
AK4	-0.06 (0.95)	0.02 (1.06)
ITPK1	0.01 (0.96)	0.03 (1.03)
PLXNB1	-0.06 (1.00)	0.03 (1.00)

Proteins are z-scores.

* Statistically significant group differences: age at death -t[1055]= 2.57 p=0.010, education - t[1032.8]= 4.91 p<0.001, women - χ^2 [1] =4.27 p=0.039, antidepressant use - χ^2 [1] =54.21 p<0.001 and IGFBP-5 - t[1055]=-2.17 p=0.030.

** Based on the Center for Epidemiological Studies Depression scale (CESD), with a range of 0-10, and median value in these participants of 0.90 (IQR=0.31-1.88)

$\bar{T}$ Over the entire study period before a diagnosis of dementia.

Table 2

Association of proteins with depressive symptoms

Term for Protein	Higher depressive symptoms			
	Odds Ratio	Estimate	SE	<i>p</i>
IGFBP-5	1.14	0.131	0.061	0.031
HSPB2	1.06	0.058	0.059	0.319
AK4	1.04	0.043	0.059	0.468
ITPK1	1.00	−0.002	0.059	0.973
PLXNB1	1.05	0.046	0.059	0.435

In separate ordinal logistic regression models adjusted for age at death, sex, education and years in study.

Table 3

Association of IGFBP-5 and depressive symptoms with change in global cognition and cognitive domains

Outcome	Estimate (SE, <i>p</i>)				
	Models I	Models II	Models III		Models IV
	Depressive symptoms x time from death	IGFB-5 x time from death	Depressive symptoms x time from death	IGFB-5 x time from death	Depressive symptoms x IGFB-5 x time from death
Global cognition	-.0111 (0.0028,<0.001)	-.0235 (0.0030,<0.001)	-.0103 (0.0027,<0.001)	-.0230 (0.0030,<0.001)	-.0031 (0.0015,0.0446)
Domains					
Episodic memory	-.0079 (0.0033,0.016)	-.0251 (0.0036,<0.001)	-.0071 (0.0032,0.027)	-.0248 (0.0036,<0.001)	-.0025 (0.0018,0.1630)
Semantic memory	-.0096 (0.0032,0.002)	-.0196 (0.0035,<0.001)	-.0089 (0.0031,0.005)	-.0192 (0.0035,<0.001)	-.0014 (0.0017,0.4162)
Perceptual speed	-.0142 (0.0033,<0.001)	-.0208 (0.0035,<0.001)	-.0136 (0.0032,<0.001)	-.0202 (0.0035,<0.001)	-.0020 (0.0023,0.3839)
Working memory	-.0121 (0.0026,<0.001)	-.0165 (0.0028,<0.001)	-.0117 (0.0026,<0.001)	-.0162 (0.0027,<0.001)	-.0033 (0.0019,0.0817)
Visuospatial ability	-.0108 (0.0026,<0.001)	-.0074 (0.0026,0.006)	-.0106 (0.0026,<0.001)	-.0070 (0.0026,0.008)	-.0002 (0.0019,0.9140)

Separate mixed effect models adjusted for age at death, sex and education.