HHS Public Access

Author manuscript

J Psychiatr Res. Author manuscript; available in PMC 2022 August 02.

Published in final edited form as:

J Psychiatr Res. 2016 November ; 82: 1–7. doi:10.1016/j.jpsychires.2016.07.006.

Circulating biosignatures of late-life depression (LLD): Towards a comprehensive, data-driven approach to understanding LLD pathophysiology

Breno Satler Diniz[a], **Chien-Wei Lin**[b], **Etienne Sibille**[c], **George Tseng**[b], **Francis Lotrich**[d], **Howard J. Aizenstein**[d], **Charles F. Reynolds**[d], **Meryl A. Butters**[d,*]

[a]Department of Psychiatry & Behavioral Sciences, University of Texas Health Science Center at Houston, Houston, TX, USA

[b]Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA

[c]Campbell Family Mental Health Research Institute of CAMH, Department of Psychiatry, University of Toronto, Toronto, ON, Canada

[d]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Abstract

There is scarce information about the pathophysiological processes underlying Late-Life Depression (LLD). We aimed to determine the neurobiological abnormalities related to LLD through a multi-modal biomarker approach combining a large, unbiased peripheral proteomic panel and structural brain imaging. We examined data from 44 LLD and 31 control participants. Plasma proteomic analysis was performed using a multiplex immunoassay. We evaluated the differential protein expression between groups with random intercept models. We carried out enrichment pathway analyses (EPA) to uncover biological pathways and processes related to LLD. Machine learning analysis was applied to the combined dataset to determine the accuracy with which specific proteins could correctly discriminate LLD versus control participants. Sixty-one proteins were differentially expressed in LLD ($p < 0.05$ and FDR < 0.01). EPA showed that these proteins were related to abnormal immune-inflammatory control, cell survival and proliferation, proteostasis control, lipid metabolism, intracellular signaling. Machine learning analysis showed that a panel of three proteins (C-peptide, FABP-liver, ApoA-IV) discriminated LLD and control participants with 100% accuracy. The plasma proteomic profile in LLD revealed dysregulation in biological processes essential to the maintenance of homeostasis at cellular and systemic levels.

*Corresponding author. 3811 O'Hara Street, Pittsburgh, PA, 15213, USA. butterma@upmc.edu (M.A. Butters).

Contributors

Breno Satler Diniz, MD, PhD: Study concept, statistical analysis, interpretation of the results and writing the manuscript.
Chien-Wei Lin, PhD: statistical analysis and writing the manuscript.
Etienne Sibille, PhD: statistical analysis, interpretation of the results, and writing the manuscript.
George Tseng, PhD: statistical analysis and writing the manuscript.
Francis Lotrich, MD, PhD: Study concept and writing the manuscript.
Howard J. Aizenstein, MD, PhD: Study concept and writing the manuscript.
Charles F. Reynolds III, MD: Study concept, interpretation of the results and writing the manuscript.
Meryl A. Butters, PhD: Study concept, interpretation of the results and writing the manuscript.

Financial disclosure

The authors have no financial conflict of interest related to this work to disclose.

These abnormalities increase brain and systemic allostatic load leading to the downstream negative outcomes of LLD, including increased risk of medical comorbidities and dementia. The peripheral biosignature of LLD has predictive power and may suggest novel putative therapeutic targets for prevention, treatment, and neuroprotection in LLD.

Keywords

Late-life depression; Elderly; Neurobiology; Proteomic

1. Introduction

Late-life major depression (LLD) is a common psychiatric disorder in older adults, with one-year prevalence rates ranging from 4% to 12% in developed and developing countries (Byers et al., 2010; do Nascimento et al., 2015). It is a clinically heterogeneous disorder, associated with negative health outcomes, e.g., higher rates of medical comorbidities and mortality risk (including suicide), disability, and increased risk for dementia (Alexopoulos et al., 2002; Diniz et al., 2013a, 2014a).

Despite high public health burden and significance, there is still only sparse information about basic neurobiological abnormalities related to this disorder. Structural neuroimaging studies have consistently shown that individuals with LLD have higher cerebrovascular disease burden and higher rates of whole brain, caudate and hippocampal atrophy compared to non-depressed individuals (Culang-Reinlieb et al., 2011; Butters et al., 2009; Taylor et al., 2014). LLD is associated with significantly higher levels of pro-inflammatory and lower levels of anti-inflammatory markers, reduced neurotrophic support, and higher levels of oxidative stress markers and activity of glycogen synthase kinase 3β compared to non-depressed older adults (Alexopoulos and Morimoto, 2011; Diniz et al., 2011, 2012, 2014b; Pomara et al., 2012; Xiong et al., 2015).

Although these studies have increased our understanding of neurobiological abnormalities associated with LLD, our current knowledge is nonetheless fragmented. One potential reason is that most studies have investigated single or a few biomarkers in isolation, and thus their results do not provide an integrated view of related biological and molecular processes. The recent development of large biomarker panels analyzed by multiplex technology and other “omics” methods (e.g. metabolomics, genomics) now permits simultaneous measurement of most relevant biological pathways, helping overcome some of the current conceptual and methodological limitations of single biomarker studies (Arnold et al., 2012; Diniz et al., 2015; Wu et al., 2006; Paige et al., 2016).

No study thus far has attempted to identify a circulating proteomic signature for LLD. Within this context, the current study sought to evaluate blood-based biomarker abnormalities related to LLD, using a plasma-based, unbiased, data-driven, comprehensive multiplex proteomic analysis. We also sought to elucidate biological pathways and molecular processes related to these peripheral biomarkers. Although we had no a *priori* hypotheses, given the intentionally data-driven design of the study, we expected to confirm the association of LLD with markers of inflammation and vascular disease, and, mainly to

uncover novel circulating peripheral biomarkers related to major depression. We anticipate that observations from such an approach will inform subsequent confirmatory studies. Finally, we applied a machine learning approach to identify putative predictive biomarkers for LLD.

2. Methods

2.1. Subject recruitment and cognitive assessment

Forty-four older adults age ≥65 years with remitted LLD and 31 older adults with no history of major depression or other major psychiatric disorder (control group) were included in this analysis. All of the participants were enrolled in a research clinic based at the University of Pittsburgh's NIMH-sponsored Advanced Center for Intervention and Services Research for Late-Life Mood Disorders (P30 MH90333). All LLD participants had previously met DSM-IV criteria for current unipolar Major Depressive Disorder without psychotic features. They were enrolled in a longitudinal observational study aiming to evaluate the biological mechanisms of cognitive impairment in LLD (The Pathways Study, R01 MH072947). All of the assessments were completed after full remission of the depressive episode (i.e., Hamilton Depression Rating Scale-17 of 10 or less for two consecutive weeks) with pharmacotherapy alone or in combination with interpersonal psychotherapy. The participants then remained on stable maintenance doses of antidepressant medication.

Exclusion criteria for all participants encompassed substance abuse within the past year, unstable medical illness (precluding participation in clinical trials for depression), history of psychosis, bipolar disorder, neurologic disorder (including dementia) or significant head trauma (defined as loss of consciousness > 30 min). The study was approved by the University of Pittsburgh Institutional Review Board.

The LLD and control participants' evaluation included administration of the SCID-IV, the 17-item Hamilton Depression Rating Scale (HDRS17), neurologic examination, the Clinical Dementia Rating, the Informant Questionnaire on Cognitive Decline in the Elderly, medical history, the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and medication review. After study recruitment (and following successful treatment to remission of mood symptoms for patients), participants underwent blood collection.

2.2. Proteomic analysis

Whole blood samples were withdrawn with EDTA tubes by antecubital venous puncture. Plasma samples were separated, aliquoted, and stored at −80 °C. Plasma samples (750 μL) were sent to the Myriad Rules Based Medicine® (Myriad RBM®; www.myriadrbm.com) laboratory (Austin, TX, USA) for biomarker measurements. We used the Human DiscoveryMAP® 250 + v2.0 assay from Myriad RBM®. Details of the laboratory analysis methods can be found in a previous publication from our group (Diniz et al., 2015).

We ran the laboratory analyses at two different points in time, approximately 12 months apart. Due to batch-to-batch differences for some analytes, we ran a third batch including a random sample of participants from the first and second batches for reliability analysis (see).

2.3. Laboratory quality assessment

Before statistical analysis, we carried out a quality assessment of the protein multiplex assay. Due to assay design changes between the two time points, (LLD participants were processed in the first batch and control participants were processed in the second batch, about a year later) we first identified 232 proteins that were measured in both batches. Among the 232 matched proteins, 15 proteins had 100% of samples below preset detection level (different proteins have different detection levels, provided by Myriad RBM®) and were removed from the analysis, resulting in 217 remaining proteins. Within these remaining proteins, values below the preset detection level were treated as missing values. Missing values were imputed with half of the geometric mean of the lower limit of quantitation in the two batches. Data were transformed to log2 scale and normalized by quantile normalization. After reliability analysis, 195 proteins showed reliable and consistent measures over assays and were included in the differential expression analyses (see).

2.4. Statistical analysis

Differences (LLD vs. control participants) in socio-demographic, cognitive and neuroimaging data were evaluated by t-tests (for continuous variables) or chi-square test (for dichotomous variables).

2.5. Differential expression analysis

A random intercept model (RIM) with variable selection was applied to detect main effects of diagnosis status (LLD vs. controls). Several variables can significantly influence the levels of the biomarkers and confound their relationship with depression. Based on previous literature, sex, age, antidepressant use (yes or no), burden of medical comorbidities (measured by CIRS-G), depressive symptoms (measured with the HDRS-17), and length of depressive illness (measured by the number of years since the first episode depressive episode) were included as covariates in the RIM analyses.

Linear models were fitted using the selected confounding variables combined with the main factor. Variable selection was achieved through Bayesian Information Criterion. The obtained p-values were adjusted by random permutation of sample labels (B = 1000 times), and the false discovery rate (FDR) was controlled by the Benjamini-Hochberg procedure (see additional details of statistical methods in). For the main factors, diagnosis (LLD vs. control) was coded as a binary variable. The FDR cutoff was set at 0.01 to select differentially expressed biomarkers in this analysis, thus minimizing the risk of false-positive results.

2.6. Pathway enrichment analysis

We applied pathway enrichment analysis to identify enriched functional annotation of differentially expressed proteins. Any differentially expressed (DE) proteins with detection rate less than 0.8 in the two groups (LLD and control) were excluded from pathway enrichment analysis. Two thousand one hundred eleven pathways were downloaded and parsed from the MsigDB database from GO, KEGG, BIOCARTA and REACTOME. Pathways associated with more than 200 genes were excluded to avoid general terms. The pathway enrichment analysis was applied on the differentially expressed proteins associated

with the main factors LLD, whole brain gray matter volume and WMH, respectively. A detailed description of the pathway enrichment analysis is available in the.

2.7. Predicting LLD with machine learning technique

We constructed a predictive model with a machine learning method using support vector machines (with linear kernel) to predict the classification of LLD versus control participants. Proteins to be included in the model were selected based on statistical significance (p-value < 0.05) with effect sizes (log2-scale fold change average group expression difference greater than 0.2) (Wang et al., 2012). The stability of the predictive model was evaluated by a left-out test sample procedure. The analysis is repeated until all samples are left out once. In this manner, the left-out test sample is independent of the model selection stage, including the selection of model with the minimum error rate, and the procedure guarantees an unbiased error estimate (See additional details of machine learning methods in).

3. Results

Table 1 shows the socio-demographic, clinical, and cognitive characteristics of the LLD and control participants. Participants with LLD had a lower frequency of males and higher scores on the HDRS-17 and CIRS-G scales (for medical comorbidity) compared to control participants.

Sixty-one proteins were significantly associated with LLD (p-value < 0.05 and q-value < 0.01) (Table 2). Pathway enrichment analysis showed that these proteins were related to known biological processes associated with depression, in particular, immune-inflammatory control, HPA axis dysfunction, neurotrophic support, and cell survival and proliferation (Table 3). We uncovered further abnormalities related to depression, including abnormal proteostasis control, impaired nutrient sensing and insulin signaling cascades, lipid metabolism, intracellular signaling, control of gene transcription, and hemostasis.

Machine learning analysis showed that three proteins (C-peptide, fatty acid-binding protein - liver, and ApoA-IV) correctly discriminated subjects with LLD from control participants with an accuracy of 100% (sensitivity = 100%, specificity = 100%).

4. Discussion

In the present study, an unbiased, multi-modal, data-driven analysis of peripheral circulating proteins showed that LLD was associated with abnormal expression of a large set of circulating proteins spanning distinct biological pathways, e.g., immuneinflammatory control, proteostasis, lipid metabolism, cell survival and apoptosis, and nutrient sensing. Our results provide evidence that the neurobiological abnormalities in LLD are extensive and involve several distinct, but interrelated biological processes. Future studies are necessary to understand how these cascades interact with each other and importantly, to identify the temporal pattern of evolution of these abnormalities, preferably using a lifespan perspective.

In addition to confirming the relationship of LLD with well-known biological processes like immune-inflammatory control or vascular processes, the current data also provides

evidence of the involvement of other biological processes less well studied in depression, namely, proteostasis and nutrient sensing. In fact, proteostasis was the most robust abnormally regulated biological process in LLD (e.g. protein homo- and heterodimerization, the establishment of protein localization) (Table 3). Proteostatic control is essential for maintenance of normal cellular functioning. Loss of proteostasis is linked to increased endoplasmic reticulum (ER) stress and mitochondrial dysfunction (Lin and Sibille, 2015). A growing body of evidence suggests that ER stress and mitochondrial dysfunction play important roles in the pathophysiology of mood disorders in adults, and may be therapeutic targets for these conditions (Pfaffenseller et al., 2014; Machado-Vieira et al., 2014). In fact, some agents, like lithium, peroxisome proliferator-activated receptor inhibitors, anti-inflammatory agents, rapamycin, and others can modulate several biological processes abnormally regulated in the present study (Eissa Ahmed et al., 2009; Köhler et al., 2014; Dwyer and Duman, 2013; Diniz et al., 2013b). These agents can be tested as long-term neuroprotective agents to prevent the negative outcomes (especially cognitive) related to depression, in addition to the antidepressant effect *per se*. Future studies should address the extent to which these abnormalities represent permanent “damage” or may be partly or completely reversible by treatment with antidepressants or other medications. Finally, our results provide a set of circulating biomarkers that can be useful for monitoring the progression of neurobiological abnormalities, and to evaluate the long-term effect of neuroprotective and restorative interventions in older depressed patients.

It should be noted that the LLD participants had blood drawn after remission of a major depressive episode and were in current treatment with antidepressants. The effect of antidepressants on these identified neurobiological processes is not known. A recent study in adult individuals with major depressive disorder (MDD) showed no major differences in peripheral biomarker expression between those with or with antidepressant treatment (Bot et al., 2015). The authors of this study concluded that the abnormal protein expression was mainly due the depressive state and was not affected by the use of antidepressants. Our results expand previous observations and the pattern of protein abnormalities that we uncovered can be viewed as an ongoing pathological change in LLD that persists or continues even after improvement in depressive symptoms and the ongoing use of antidepressants.

It is worth noting that some biomarkers found in the present study are common to different data-driven studies, including different types of patients (younger, first-episode, unmedicated MDD patients, medicated recurrent MDD patients, or MDD patients from population-based studies) (Diniz et al., 2015; Bot et al., 2015; Stelzhammer et al., 2014; Domenici et al., 2010). The most common biomarkers found are generally related to the regulation of lipid metabolism, control of immunoinflammatory response, control of vascular function, inter and intra-cellular communication. We additionally found that biomarkers related to nutrient sensing and proteostasis are related to LLD. Altogether, these studies suggest that there are core abnormalities, which are present in the first depressive episode, continue over mid-life and late-life, and are persistent even after successful antidepressant treatment. This view is consistent with the presence of biological “scars” in depression that render individuals with major depression, at any age, more vulnerable to systemic illness, disability, cognitive

impairment and other negative health outcomes, which are not fully ameliorated despite successful antidepressant treatment (Wichers et al., 2010).

Robust machine learning techniques showed that three proteins (C-peptide, fatty acid-binding protein, and ApoA-IV) have a very high accuracy at discriminating individuals with remitted LLD compared to never depressed control participants. In fact, our study showed the highest discriminatory power of any previous studies, including those for schizophrenia, bipolar disorder or other common mental illnesses (Wu et al., 2016; Clementz et al., 2016; Villar Bergua et al., 2016). This set of proteins may be useful in aiding the identification of individuals with LLD, identifying specific targets for intervention, and monitoring the effects of intervention in these patients. Our results could be due to the small sample size and the inclusion of very well characterized depressed individuals and healthy older adults. This could lead to significant a *priori* classification advantage for the biomarkers that could not be appropriately addressed by the machine learning models. Also, due to the small sample size, we could not split the sample into training and validation sets, nor we had an independent sample available to validate the current results. Therefore, the current machine learning results should be viewed as exploratory and needs to be replicated in independent and larger samples of LLD individuals.

The present results should be viewed in light of several limitations. Because the sample size is relatively small and we conducted a large number of analyses related to peripheral biomarkers, the risk of both false positive and false negative results should be noted. To manage this risk, we used a conservative FDR rate (q-value < 0.01) for evaluating differences in expression of circulating biomarkers between depressed and control participants. We did not evaluate specific depression phenotypes, like psychotic depression or melancholic depression. These phenotypes may have specific neurobiological changes and involve different types of pathways, like dysfunction of hypothalamus-pituitary-adrenal and the endocannabinoid system (Penninx et al., 2013; Hill and Gorzalka, 2005). Moreover, our sample was enriched with patients with early-onset depression (EOD, 82%) compared to late-onset depression (LOD, 18%). Given the clinical and, possibly, neurobiological, differences between these subgroups of patients the current results may be more biased to reflect the changes observed in EOD. Our analysis is further limited by the biological pathways covered in the multiplex assay, and our results might have overlooked other relevant biological processes that may related to LLD, like neurotransmitter function and cellular metabolites changes. Furthermore, the annotated functional pathway analysis relies on databases that, despite providing comprehensive coverage of known biological processes and molecular functions, are under continuous updating as novel biological processes and molecular functions of proteins are identified and reported. Finally, the proteins were measured in the plasma, and it is not clear to what extent the changes observed in the periphery reflect central nervous system biological changes. Since this is an exploratory study, the present observations need to be replicated in other independent and larger samples.

The present study provides a step toward a comprehensive and integrated view of the neurobiological changes related to LLD. Our results indicate biological processes that can be targeted for intervention (e.g., proteostasis control, nutrient sensing). Future trials should

aim to test the modulation of these biological processes for their potential relevance not only to depression prevention and treatment but also for mitigating depression's downstream negative outcomes, including the higher risk of cognitive impairment and functional disability.

Acknowledgment

This work was support by NIH grants P30MH90333 (Reynolds), MH080240, MH080240-S1 & S2(Butters), P50 AG05133 (Butters, Aizenstein); MH093723 (Sibille), the UPMC Endowment in Geriatric Psychiatry (Reynolds), The John A. Hartford Foundation Center of Excellence in Geriatric Psychiatry (Reynolds); CNPq 472138/2013-8 and 466623/2014-3(Diniz). We thank Drs. James Becker and Oscar Lopez for participating in the cognitive adjudication of the study participants.

Role of funding sources

The funding sources did not have any role in the conception of the study, data collection and analysis, interpretation of the results, writing of the manuscript and in the final decision to publish the present study.

References

Alexopoulos GS, Morimoto SS, 2011. The inflammation hypothesis in geriatric depression. Int. J. Geriatr. Psychiatry 26, 1109e1118. 10.1002/gps.2672.

Alexopoulos GS, Buckwalter K, Olin J, Martinez R, Wainscott C, Krishnan KR, 2002. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. Biol. Psychiatry 52, 543–558. [PubMed: 12361668]

Arnold SE, Xie SX, Leung YY, Wang LS, Kling MA, Han X, et al. , 2012. Plasma biomarkers of depressive symptoms in older adults. Transl. Psychiatry 2, e65. 10.1038/tp.2011.63. [PubMed: 22832727]

Bot M, Chan MK, Jansen R, Lamers F, Vogelzangs N, Steiner J, et al. , 2015. Serum proteomic profiling of major depressive disorder. Transl. Psychiatry 5, e599. 10.1038/tp.2015.88. [PubMed: 26171980]

Butters MA, Aizenstein HJ, Hayashi KM, Meltzer CC, Seaman J, Reynolds CF, et al. , 2009. Three-dimensional surface mapping of the caudate nucleus in late-life depression. Am. J. Geriatr. Psychiatry 17, 4–12. [PubMed: 18790876]

Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML, 2010. High occurrence of mood and anxiety disorders among older adults: the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 67 (5), 489–496. 10.1001/archgenpsychiatry.2010.35. [PubMed: 20439830]

Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, et al. , 2016. Identification of distinct psychosis biotypes using brain-based biomarkers. Am. J. Psychiatry 173, 373–384. 10.1176/appi.ajp.2015.14091200. Epub 2015. [PubMed: 26651391]

Culang-Reinlieb ME, Johnert LC, Brickman AM, Steffens DC, Garcon E, Sneed JR, 2011. MRI-defined vascular depression: a review of the construct. Int. J. Geriatr. Psychiatry 26, 1101–1108. [PubMed: 21192018]

Diniz BS, Talib LL, Joaquim HP, de Paula VR, Gattaz WF, Forlenza OV, 2011. Platelet GSK3B activity in patients with late-life depression: marker of depressive episode severity and cognitive impairment? World J. Biol. Psychiatry 12, 216–222. [PubMed: 21314327]

Diniz BS, Teixeira AL, Campos AC, Miranda AS, Rocha NP, Talib LL, et al. , 2012. Reduced serum levels of adiponectin in elderly patients with major depression. J. Psychiatr. Res. 46, 1081–1085. 10.1016/j.jpsychires.2012.04.028. [PubMed: 22633396]

Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3rd, 2013a. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br. J. Psychiatry 202, 329–335. 10.1192/bjp.bp.112.118307. [PubMed: 23637108]

Diniz BS, Machado-Vieira R, Forlenza OV, 2013b. Lithium and neuroprotection: translational evidence and implications for the treatment of neuropsychiatric disorders. Neuropsychiatr. Dis. Treat. 9, 493–500. 10.2147/NDT.S33086. [PubMed: 23596350]

Diniz BS, Reynolds CF 3rd, Butters MA, Dew MA, Firmo JO, Lima-Costa MF, et al. , 2014a. The effect of gender, age, and symptom severity in late-life depression on the risk of all-cause mortality: the Bambuí Cohort Study of Aging. Depress Anxiety 31, 787–795. 10.1002/da.22226. [PubMed: 24353128]

Diniz BS, Teixeira AL, Machado-Vieira R, Talib LL, Radanovic M, Gattaz WF, Forlenza OV, 2014b. Reduced cerebrospinal fluid levels of brain-derived neurotrophic factor is associated with cognitive impairment in late-life major depression. J. Gerontol. B. Psychol. Sci. Soc. Sci. 69, 845–851. 10.1093/geronb/gbu096. [PubMed: 25149921]

Diniz BS, Sibille E, Ding Y, Tseng G, Aizenstein HJ, Lotrich F, et al. , 2015. Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. Mol. Psychiatry 20, 594–601. 10.1038/mp.2014.76. [PubMed: 25092249]

do Nascimento KK, Pereira KS, Firmo JO, Lima-Costa MF, Diniz BS, Castro-Costa E, 2015. Predictors of incidence of clinically significant depressive symptoms in the elderly: 10-year follow-up study of the Bambui cohort study of aging. Int. J. Geriatr. Psychiatry 30, 1171–1176. 10.1002/gps.4271. [PubMed: 25703304]

Domenici E, Wille DR, Tozzi F, Prokopenko I, Miller S, McKeown A, et al. , 2010. Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections. PLoS One 5, e9166. 10.1371/journal.pone.0009166. [PubMed: 20161799]

Dwyer JM, Duman RS, 2013. Activation of mammalian target of rapamycin and synaptogenesis: role in the actions of rapid-acting antidepressants. Biol. Psychiatry 73, 1189–1198. 10.1016/j.biopsych.2012.11.011. [PubMed: 23295207]

Eissa Ahmed AA, Al-Rasheed NM, Al-Rasheed NM, 2009. Antidepressant-like effects rosiglitazone, a PPARg agonist, in the rat forced swim and mouse tail suspension tests. Behav. Pharmacol. 20, 635–642. 10.1097/FBP.0b013e328331b9bf. [PubMed: 19745723]

Hill MN, Gorzalka BB, 2005. Is there a role for the endocannabinoid system in the etiology and treatment of melancholic depression? Behav. Pharmacol. 16, 333–352. [PubMed: 16148438]

Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, et al. , 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 71, 1381–1391. 10.1001/jamapsychiatry.2014.1611. [PubMed: 25322082]

Lin LC, Sibille E, 2015. Somatostatin, neuronal vulnerability and behavioral emotionality. Mol. Psychiatry 20, 377–387. 10.1038/mp.2014.184. [PubMed: 25600109]

Machado-Vieira R, Soeiro-De-Souza MG, Richards EM, Teixeira AL, Zarate CA Jr., 2014. Multiple levels of impaired neural plasticity and cellular resilience in bipolar disorder: developing treatments using an integrated translational approach. World J. Biol. Psychiatry 15, 84–95. 10.3109/15622975.2013.830775.

Paige LA, Mitchell MW, Krishnan KR, Kaddurah-Daouk R, Steffens DC, 2016. A preliminary metabolomic analysis of older adults with and without depression. Int. J. Geriatr. Psychiatry 22, 418–423.

Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N, 2013. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med. 11, 129. 10.1186/1741-7015-11-129. [PubMed: 23672628]

Pfaffenseller B, Wollenhaupt-Aguiar B, Fries GR, Colpo GD, Burque RK, Bristot G, et al. , 2014. Impaired endoplasmic reticulum stress response in bipolar disorder: cellular evidence of illness progression. Int. J. Neuropsychopharmacol. 17, 1453–1463. 10.1017/S1461145714000443. [PubMed: 24800824]

Pomara N, Bruno D, Sarreal AS, Hernando RT, Nierenberg J, Petkova E, et al. , 2012. Lower CSF amyloid beta peptides and higher F2-isoprostanes in cognitively intact elderly individuals with major depressive disorder. Am. J. Psychiatry 169, 523–530. [PubMed: 22764362]

Stelzhammer V, Haenisch F, Chan MK, Cooper JD, Steiner J, Steeb H, et al. , 2014. Proteomic changes in serum of first onset, antidepressant drug-naïve major depression patients. Int. J. Neuropsychopharmacol. 17, 1599–1608. 10.1017/S1461145714000819. [PubMed: 24901538]

Taylor WD, McQuoid DR, Payne ME, Zannas AS, MacFall JR, Steffens DC, 2014. Hippocampus atrophy and the longitudinal course of late-life depression. Am. J. Geriatr. Psychiatry 22, 1504e1512. 10.1016/j.jagp.2013.11.004.

Vilar-Bergua A, Riba-Llena I, Nafría C, Bustamante A, Llombart V, Delgado P, et al. , 2016. Blood and CSF biomarkers in brain subcortical ischemic vascular disease: involved pathways and clinical applicability, 2015 Apr 22 J. Cereb. Blood Flow Metab. 36, 55–71.

Wang X, Lin Y, Song C, Sibille E, Tseng GC, 2012. Detecting disease-associated genes with confounding variable adjustment and the impact on genomic meta-analysis: with application to major depressive disorder. BMC Bioinforma. 13, 52. 10.1186/1471-2105-13-52.

Wichers M, Geschwind N, van Os J, Peeters F, 2010. Scars in depression: is a conceptual shift necessary to solve the puzzle? Psychol. Med. 40, 359–365. [PubMed: 20120516]

Wu M, Rosano C, Butters M, Whyte E, Nable M, Crooks R, et al. , 2006. A fully automated method for quantifying and localizing white matter hyperintensities on MR images. Psychiatry Res. 148, 133–142. [PubMed: 17097277]

Wu MJ, Mwangi B, Bauer IE, Passos IC, Sanches M, Zunta-Soares GB, et al., 2016. Identification and individualized prediction of clinical phenotypes in bipolar disorders using neurocognitive data, neuroimaging scans and machine learning, 2016 Feb 13 Neuroimage. 10.1016/j.neuroimage.2016.02.016 (Epub ahead of print).

Xiong GL, Prybol K, Boyle SH, Hall R, Streilein RD, Steffens DC, et al. , 2015. Inflammation markers and major depressive disorder in patients with chronic heart failure: results from the sertraline against depression and heart disease in chronic heart failure study. Psychosom. Med. 77, 808e815. 10.1097/PSY.0000000000000216.

Table 1

Demographic and clinical data for late-life major depression and control participants (means and standard deviations).

		Group			
		LLD	**Control**	**Statistics**	**p-value**
Age (years)		72.4 ± 6.0	72.7 ± 6.2	t = 0.22	0.8
Gender	F	86%	45%	14.5	<0.001
	M	14%	55%		
Education (years)		14.9 ± 2.6	14.9 ± 3.1	t = 0.01	0.9
HDRS17 (at remission)		4.4 ± 3.0	2.6 ± 2.5	t = 2.62	0.01
CIRS-G		11.6 ± 3.8	8.0 ± 3.3	t = 4.12	<0.001
Antidepressant drug					
Venlafaxine		36%	-		
Duloxetine		18%	-		
Escitalopram		16%	-		
Fluoxetine		2%	-		
Citalopram		5%	-		
		Venlafaxine + bupropion		2%	-
		Mirtazapine + nortriptyline		2%	-
None		19%	-		
EOD/LOD		82%/18%	-		
Single/Recurrent episode		29%/71%	-		
Duration of depressive disorder[a]		32.4 ± 19.1 years	-		

F: female; M: male; HDRS17: Hamilton Depression Rating Scale 17 items; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; WMH: White matter hyperintensities; GMV: Gray matter volume; EOD: early-onset depression (age of first depressive episode before 60 years-old); LOD: late-onset depression (age of first depressive episode after 60 years-old).

[a]Calculate by difference of current age and the age of the first depressive episode.

Table 2

Circulating biomarkers related to late life major depression.

Protein	Disease effect	SD	p-value permute	q-value permute
Alpha-1-Antichymotrypsin (AACT)	0.55	0.07	5.13E-07	5.26E-06
Apolipoprotein A-IV (Apo A-IV)	−3.44	0.22	5.13E-07	5.26E-06
Apolipoprotein B (Apo B)	0.97	0.15	5.13E-07	5.26E-06
Beta-2-Microglobulin (B2M)	0.53	0.08	5.13E-07	5.26E-06
C-Peptide	5.88	0.44	5.13E-07	5.26E-06
Fatty Acid-Binding Protein, liver (FABP, liver)	−5.53	0.34	5.13E-07	5.26E-06
Fibrinogen	−1.83	0.16	5.13E-07	5.26E-06
Fibulin-1C (Fib-1C)	0.70	0.10	5.13E-07	5.26E-06
Interferon-inducible T-cell alpha chemoattractant (ITAC)	−1.21	0.20	5.13E-07	5.26E-06
Interleukin-6 receptor subunit beta (IL-6R beta)	0.44	0.07	5.13E-07	5.26E-06
Mesothelin (MSLN)	−1.82	0.13	5.13E-07	5.26E-06
Neutrophil Gelatinase-Associated Lipocalin (NGAL)	1.26	0.23	5.13E-07	5.26E-06
Progesterone	1.32	0.15	5.13E-07	5.26E-06
Prolactin (PRL)	−1.48	0.16	5.13E-07	5.26E-06
Resistin	−1.49	0.13	5.13E-07	5.26E-06
Tamm-Horsfall Urinary Glycoprotein (THP)	0.95	0.17	5.13E-07	5.26E-06
Endostatin	0.52	0.10	3.08E-06	2.86E-05
Galectin-3	−0.42	0.08	3.08E-06	2.86E-05
Insulin-like Growth Factor Binding Protein 5 (IGFBP5)	0.45	0.09	5.13E-06	4.35E-05
Interleukin-23 (IL-23)	−0.81	0.16	5.13E-06	4.35E-05
Cortisol (Cortisol)	0.70	0.15	7.69E-06	6.25E-05
Stem Cell Factor (SCF)	−0.54	0.12	1.49E-05	1.12E-04
Cathepsin D	0.43	0.10	2.31E-05	1.67E-04
Alpha-1-Microglobulin (A1Micro)	−0.31	0.07	3.49E-05	2.43E-04
Epidermal Growth Factor Receptor (EGFR)	0.44	0.11	7.59E-05	4.93E-04
Neuron-Specific Enolase (NSE)	−0.84	0.20	7.44E-05	4.93E-04
Angiogenin	0.36	0.09	8.00E-05	5.03E-04
Human Epidermal Growth Factor Receptor 2 (HER-2)	−0.37	0.09	8.82E-05	5.37E-04

Protein	Disease effect	SD	p-value permute	q-value permute
Chemokine CC-4 (HCC-4)	0.55	0.13	9.85E-05	5.71E-04
Macrophage Migration Inhibitory Factor (MIF)	1.38	0.34	9.95E-05	5.71E-04
Immunoglobulin E (IgE)	−1.80	0.45	1.28E-04	7.11E-04
CD 40 antigen (CD40)	−0.36	0.09	1.54E-04	8.33E-04
Apolipoprotein E (Apo E)	1.31	0.33	1.77E-04	9.35E-04
Apolipoprotein A-II (Apo A-II)	−0.38	0.10	2.54E-04	1.31E-03
Interleukin-12 Subunit p40 (IL-12p40)	−0.42	0.11	3.88E-04	1.89E-03
Kidney Injury Molecule-1 (KIM-1)	−0.90	0.24	3.87E-04	1.89E-03
Myeloid Progenitor Inhibitory Factor 1 (MPIF-1)	0.41	0.11	4.54E-04	2.11E-03
Tyrosine kinase with Ig and EGF homology domains 2 (TIE-2)	−0.36	0.10	4.55E-04	2.11E-03
Macrophage inflammatory protein 3 beta (MIP-3 beta)	−0.50	0.14	7.13E-04	3.17E-03
Creatine Kinase-MB (CK-MB)	−0.66	0.19	7.37E-04	3.20E-03
Apolipoprotein(a) (Lp(a))	1.48	0.43	7.99E-04	3.39E-03
Cystatin-C	−0.20	0.06	8.29E-04	3.44E-03
Stromal cell-derived factor-1 (SDF-1)	−0.29	0.09	1.02E-03	4.14E-03
Urokinase-type Plasminogen Activator (uPA)	−0.52	0.16	1.39E-03	5.54E-03
Tetranectin	0.26	0.08	1.53E-03	5.96E-03
Pancreatic Polypeptide (PPP)	0.92	0.29	1.79E-03	6.73E-03
von Willebrand Factor (vWF)	0.42	0.13	2.01E-03	7.40E-03
Transthyretin (TTR)	0.25	0.08	2.45E-03	8.67E-03
Tumor necrosis factor receptor 2 (TNFR2)	−0.26	0.08	2.41E-03	8.67E-03
Prostasin	−0.39	0.13	2.52E-03	8.78E-03
Apolipoprotein A-I (Apo A-I)	−0.25	0.08	2.57E-03	8.79E-03

Table 3

Biological processes and pathways related to the differentially expressed proteins in late life major depression.

Biological pathways and processes	DE in set	DE not in set	NonDE in set	NonDE not in set	Match gene	p-value-permute	q-value-permute
Go MF protein dimerization activity	10	39	171	10 134	AMBP/APOA2/APOA4/APOB/ APOE/CST3/EGFR/ERBB2/ IL12B/VWF	0.000999001	0.0834165834
Go MF protein homodimerization activity	6	43	114	10 191	AMBP/APOA2/APOA4/APOE/ CST3/VWF	0.000999001	0.0834165834
Go BP protein secretion	5	44	27	10 278	ANG/APOA1/APOA2/INS/PPY	0.002997003	0.1251248751
Go MF protein heterodimerization activity	6	43	71	10 234	APOA2/APOB/APOE/EGFR/ ERBB2/IL12B	0.002997003	0.1251248751
Go BP lipid homeostasis	4	45	12	10,293	APOA1/APOA2/APOA4/APOE	0.004995005	0.1429998573
Reactome chylomicron mediated lipid transport	5	44	12	10,293	APOA1/APOA2/APOA4/APOB/ APOE	0.005994006	0.1429998573
Go BP regulation of hydrolase activity	3	46	72	10,233	ANG/APOA2/EGFR	0.005994006	0.1429998573
Go BP establishment of protein localization	6	43	178	10,127	ANG/APOA1/APOA2/INS/ EGFR/PPY	0.006993007	0.145979021
Reactome lipoprotein metabolism	5	44	22	10,283	APOA1/APOA2/APOA4/APOB/ APOE	0.008991009	0.1668331668
Go MF phospholipid binding	3	46	38	10,267	APOA1/APOA4/APOE	0.011988012	0.1787498216
Go BP regulation of protein secretion	4	45	18	10,287	ANG/APOA1/APOA2/INS	0.012987013	0.1787498216
Go BP regulation of secretion	4	45	36	10,269	ANG/APOA1/APOA2/INS	0.012987013	0.1787498216
Go BP lipoprotein metabolic process	3	46	30	10,275	APOA1/APOA2/APOA4	0.013986014	0.1787498216
Go BP lipid transport	4	45	24	10,281	APOA1/APOA2/APOA4/APOE	0.014985015	0.1787498216
Go MF peptide binding	2	47	80	10,225	ANG/MSLN	0.021978022	0.2446886447
Go BP Secretion by cell	5	44	109	10,196	ANG/APOA1/APOA2/INS/PPY	0.035964036	0.2678111362
Go BP cytokine secretion	3	46	15	10,290	APOA1/APOA2/INS	0.036963037	0.2678111362
Biocarta ppara pathway	4	45	54	10,251	APOA1/APOA2/INS/FABP1	0.037962038	0.2678111362
Go CC cytoplasmic membrane bound vesicle	3	46	109	10,196	APOA1/EGFR/VWF	0.037962038	0.2678111362
Go CC membrane bound vesicle	3	46	111	10,194	APOA1/EGFR/VWF	0.037962038	0.2678111362
Go BP phospholipase c activation	2	47	9	10,296	ANG/EGFR	0.038961039	0.2678111362
Go BP Positive regulation of hydrolase activity	2	47	49	10,256	ANG/EGFR	0.038961039	0.2678111362
Go BP G protein signaling coupled to IP3 second messenger/PLC activating	2	47	39	10,266	ANG/EGFR	0.040959041	0.2678111362

Biological pathways and processes	DE in set	DE not in set	NonDE in set	NonDE not in set	Match gene	p-value-permute	q-value-permute
Go BP phosphoinositide mediated signaling	2	47	42	10,263	ANG/EGFR	0.040959041	0.2678111362
Go BP regulation of cytokine secretion	3	46	13	10,292	APOA1/APOA2/INS	0.041958042	0.2678111362
Go BP regulation of protein stability	2	47	17	10,288	APOA1/APOA2	0.041958042	0.2678111362
Go BP lipid biosynthetic process	3	46	94	10,211	ANG/APOA1/MIF	0.044955045	0.2678111362
Go BP lipoprotein biosynthetic process	2	47	24	10,281	APOA1/APOA2	0.047952048	0.2678111362
Go MF protein complex binding	3	46	51	10,254	AMBP/INS/VWF	0.048951049	0.2678111362
Go BP negative regulation of secretion	2	47	11	10,294	APOA1/APOA2	0.04995005	0.2678111362
Go CC extracellular matrix part	2	47	55	10,250	ANG/COL18A1	0.04995005	0.2678111362