

Brain Aging in Major Depressive Disorder: Results from the ENIGMA Major Depressive Disorder working group

Running title: Brain Aging in MDD: results from ENIGMA

Laura K M Han, MSc,^{1,*} Richard Dinga, MSc,¹ Tim Hahn, PhD,² Christopher R K Ching, BA,^{3,4} Lisa T Eyler, PhD,^{5,6} Lyubomir Aftanas, PhD,^{7,8} Moji Aghajani, PhD,¹ André Aleman, PhD,^{9,10} Bernhard T Baune, PhD,^{2,11,12} Klaus Berger, MD,¹³ Ivan Brak, PhD,^{7,14} Geraldo Busatto Filho, PhD,¹⁵ Angela Carballedo, MD,^{16,17} Colm G Connolly, PhD,¹⁸ Baptiste Couvy-Duchesne, PhD,¹⁹ Kathryn Cullen, MD,²⁰ Udo Dannlowski, PhD,² Christopher G Davey, PhD,^{21,22} Danai Dima, PhD,^{23,24} Fabio L S Duran, PhD,¹⁵ Verena Enneking, MSc,² Elena Filimonova, MD,⁷ Stefan Frenzel, MSc,²⁵ Thomas Frodl, PhD,^{16,26,27} Cynthia H Y Fu, PhD,^{28,29} Beata R Godlewska, MD,³⁰ Ian H Gotlib, PhD,³¹ Hans J Grabe, MD,^{25,32} Nynke A Groenewold, PhD,^{33,34} Dominik Grotegerd, PhD,² Oliver Gruber, MD,³⁵ Geoffrey B Hall, PhD,³⁶ Ben J Harrison, PhD,³⁷ Sean N Hatton, PhD,^{38,39} Marco Hermesdorf, PhD,¹³ Ian B Hickie, MD,³⁸ Tiffany C Ho, PhD,^{31,40} Norbert Hosten, MD,⁴¹ Andreas Jansen, PhD,⁴² Claas Kähler, MSc,² Tilo Kircher, MD,⁴² Bonnie Klimes-Dougan, PhD,⁴³ Bernd Krämer, PhD,³⁵ Axel Krug, PhD,⁴² Jim Lagopoulos, PhD,^{38,44} Ramona Leenings, MSc,² Frank P MacMaster, PhD,^{45,46} Glenda MacQueen, PhD,⁴⁷ Andrew McIntosh, MD,⁴⁸ Quinn McLellan, MSc,⁴⁵ Katie L McMahon, PhD,^{49,50} Sarah E Medland, PhD,⁵¹ Bryon A Mueller, PhD,²⁰ Benson Mwangi, PhD,⁵² Evgeny Osipov, MSc,¹⁴ Maria J Portella, PhD,^{53,54} Elena Pozzi, MSc,^{21,37} Liesbeth Reneman, PhD,⁵⁵ Jonathan Repple, MD,² Pedro G P Rosa, MD,¹⁵ Matthew D Sacchet, PhD,⁵⁶ Philipp G Sämann, MD,⁵⁷ Knut Schnell, PhD,^{58,59} Anouk Schranz, PhD,⁵⁵ Egle Simulionyte, MD,³⁵ Jair C Soares, PhD,⁵² Jens Sommer, PhD,⁴² Dan J Stein, PhD,^{34,60} Olaf Steinträter, PhD,⁴² Lachlan T Strike, PhD,⁶¹ Sophia I Thomopoulos, BA,³ Marie-José van Tol, PhD,⁶² Ilya M Veer, PhD,⁶³ Robert R J M Vermeiren, PhD,^{64,65} Henrik Walter, PhD,⁶³ Nic J A van der Wee, PhD,^{65,66} Steven J A van der Werff, PhD,^{65,66} Heather Whalley, PhD,⁴⁸ Nils R Winter, MSc,² Katharina Wittfeld, PhD,^{25,32} Margaret J Wright, PhD,^{61,67} Mon-Ju Wu, PhD,⁵² Henry Völzke, MD,⁶⁸ Tony T Yang, MD,⁶⁹ Vasileios Zannias, MSc,⁴⁸ Greig I de Zubicaray, PhD,^{50,70} Giovana B Zunta-Soares, MD,⁵² Christoph Abé, PhD,⁷¹ Martin Alda, MD,⁷² Ole A Andreassen, PhD,^{73,74} Erlend Bøen, PhD,⁷⁵ Caterina M Bonnin, PhD,⁷⁶ Erick J Canales-Rodriguez, PhD,⁷⁷ Dara Cannon, PhD,⁷⁸ Xavier Caseras, PhD,⁷⁹ Tiffany M Chaim-Avancini, MD,¹⁵ Torbjørn Elvsåshagen, PhD,^{80,81} Pauline Favre, PhD,⁸² Sonya F Foley, PhD,⁸³ Janice M Fullerton, PhD,^{84,85} Jose M Goikolea, PhD,⁷⁶ Bartholomeus C M Haarman, PhD,⁸⁶ Tomas Hajek, PhD,⁷² Chantal Henry, PhD,⁸⁷ Josselin Houenou, PhD,^{82,88} Fleur M Howells, PhD,^{34,89} Martin Ingvar, PhD,⁷¹ Rayus Kuplicki, PhD,⁹⁰ Beny Lafer, PhD,⁹¹ Mikael Landén, PhD,^{92,93} Rodrigo Machado-Vieira, PhD,⁹¹ Ulrik F Malt, MD,^{94,95} Colm McDonald, PhD,⁷⁸ Philip B Mitchell, MD,^{96,97} Leila Nabulsi, MPharm,⁷⁸ Maria Concepcion Garcia Otaduy, PhD,⁹⁸ Bronwyn J Overs, BPsych,⁷⁶ Mircea Polosan, PhD,^{99,100} Edith Pomarol-Clotet, PhD,⁷⁷ Joaquim Radua, PhD,⁷⁶ Maria M Rive, MD,¹⁰¹ Gloria Roberts, PhD,^{96,97} Henricus G Ruhe, MD,^{101,102,103} Raymond Salvador, PhD,⁷⁷ Salvador Sarró, PhD,⁷⁷ Theodore D Satterthwaite, MD,¹⁰⁴ Jonathan Savitz, PhD,^{90,105} Aart H Schene, PhD,^{102,103} Peter R Schofield, PhD,^{84,85} Mauricio H Serpa, MD,¹⁵ Kang Sim, MD,^{106,107} Marcio Gerhardt Soeiro-de-Souza, PhD,⁹¹ Ashley N Sutherland, MS,⁶ Henk S Temmingh, MD,^{34,108} Garrett M Timmons,⁶ Anne Uhlmann, PhD,³⁴ Eduard Vieta, PhD,⁷⁶ Daniel H Wolf, PhD,¹⁰⁴ Marcus V Zanetti, MD,^{15,109} Neda Jahanshad, PhD,³ Paul M Thompson, PhD,³ Dick J Veltman, PhD,¹ Brenda W J H Penninx, PhD,^{1,§} Andre F Marquand, PhD,^{103,110,§} James H Cole, PhD,^{24,§} Lianne Schmaal, PhD^{21,22,§}

§These authors jointly supervised this work.

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57
58 ¹ Department of Psychiatry, Amsterdam University Medical Centers, VU University Medical Center, GGZ
59 inGeest, Amsterdam Neuroscience, Amsterdam, The Netherlands.
60 ² Department of Psychiatry, University of Münster, Münster, Germany.
61 ³ Imaging Genetics Center, Mark & Mary Stevens Neuroimaging & Informatics Institute, Keck School of
62 Medicine, University of Southern California, Los Angeles, CA, USA.
63 ⁴ Graduate Interdepartmental Program in Neuroscience, UCLA School of Medicine.
64 ⁵ Desert-Pacific Mental Illness Research Education and Clinical Center, VA San Diego Healthcare.
65 ⁶ Department of Psychiatry, University of California San Diego.
66 ⁷ FSSBI “Scientific Research Institute of Physiology & Basic Medicine”, Lab. of Affective, Cognitive &
67 Translational Neuroscience, Novosibirsk, Russia.
68 ⁸ Novosibirsk State University, Department of Neuroscience.
69 ⁹ University of Groningen, University Medical Center Groningen, Department of Neuroscience, Groningen,
70 The Netherlands.
71 ¹⁰ University of Groningen, Department of Clinical and Developmental Neuropsychology, Groningen, The
72 Netherlands.
73 ¹¹ Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, VIC,
74 Australia.
75 ¹² The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, VIC,
76 Australia.
77 ¹³ Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany.
78 ¹⁴ Novosibirsk State University, Lab. of Experimental & Translational Neuroscience.
79 ¹⁵ Laboratory of Psychiatric Neuroimaging (LIM-21), Instituto de Psiquiatria, Hospital das Clinicas
80 HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.
81 ¹⁶ Department for Psychiatry, Trinity College Dublin, Dublin, Ireland.
82 ¹⁷ North Dublin Mental Health Services, Dublin, Ireland.
83 ¹⁸ Department of Biomedical Sciences, Florida State University, Tallahassee FL.
84 ¹⁹ Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia.
85 ²⁰ Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA.
86 ²¹ Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia.
87 ²² Centre for Youth Mental Health, The University of Melbourne.
88 ²³ Department of Psychology, School of Arts and Social Sciences, City University London, London, UK.
89 ²⁴ Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King’s College
90 London, UK.
91 ²⁵ Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Germany.
92 ²⁶ Department of Psychiatry and Psychotherapy, Otto von Guericke University (OVGU), Magdeburg,
93 Germany.
94 ²⁷ German Center for Neurodegenerative Diseases (DZNE), Germany.
95 ²⁸ Centre for Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience, King’s College
96 London, UK.
97 ²⁹ School of Psychology, University of East London, UK.
98 ³⁰ Department of Psychiatry, University of Oxford.
99 ³¹ Department of Psychology, Stanford University, Stanford, CA, USA.
100 ³² German Center of Neurodegenerative Diseases (DZNE) Site Rostock/Greifswald, Germany.
101 ³³ University of Groningen, University Medical Center Groningen, Interdisciplinary Center
102 Psychopathology and Emotion regulation (ICPE), Groningen, The Netherlands.
103 ³⁴ Department of Psychiatry and Mental Health, University of Cape Town, South Africa.
104 ³⁵ Section for Experimental Psychopathology and Neuroimaging, Department of Psychiatry, University of
105 Heidelberg, Heidelberg, Germany.
106 ³⁶ Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, Canada.
107 ³⁷ Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne &
108 Melbourne Health, Melbourne, Australia.
109 ³⁸ Youth Mental Health Team, Brain and Mind Centre, University of Sydney, Australia.
110 ³⁹ Department of Neuroscience, University of California San Diego, CA, USA.

- 111 ⁴⁰ Department of Psychiatry & Behavioral Sciences, Standord University, Stanford, CA, USA.
112 ⁴¹ Department of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Germany.
113 ⁴² Department of Psychiatry, Philipps-University Marburg, Germany.
114 ⁴³ Department of Psychology, University of Minnesota, Minneapolis, MN, USA.
115 ⁴⁴ Sunshine Coast Mind and Neuroscience Institute, University of the Sunshine Coast QLD, Australia.
116 ⁴⁵ Departments of Psychiatry and Pediatrics, University of Calgary, Calgary, AB, Canada.
117 ⁴⁶ Addictions and Mental Health Strategic Clinical Network.
118 ⁴⁷ Department of Psychiatry, University of Calgary, Calgary, AB, Canada.
119 ⁴⁸ Division of Psychiatry, University of Edinburgh, UK.
120 ⁴⁹ School of Clinical Sciences, Queensland University of Technology, Brisbane, Australia.
121 ⁵⁰ Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane,
122 Australia.
123 ⁵¹ QIMR Berghofer Medical Research Institute, Brisbane, Australia.
124 ⁵² Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at
125 Houston.
126 ⁵³ Institut d'Investigació Biomèdica Sant Pau, Barcelona, Catalonia.
127 ⁵⁴ Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Spain.
128 ⁵⁵ Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, AMC,
129 Amsterdam, The Netherlands.
130 ⁵⁶ Center for Depression, Anxiety, and Stress Research, McLean Hospital, Harvard Medical School,
131 Belmont, MA, USA.
132 ⁵⁷ Max Planck Institute of Psychiatry.
133 ⁵⁸ Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen,
134 Germany.
135 ⁵⁹ Department of Psychiatry and Psychotherapy, Asklepios Fachklinikum Göttingen, Göttingen, Germany.
136 ⁶⁰ MRC Unit on Risk and Resilience, University of Cape Town, Cape Town, South Africa.
137 ⁶¹ Queensland Brain Institute, University of Queensland, Brisbane, Australia.
138 ⁶² Cognitive Neuroscience Center, University Medical Center Groningen, University of Groningen,
139 Groningen, the Netherlands.
140 ⁶³ Division of Mind and Brain Research, Department of Psychiatry and Psychotherapy CCM, Charité -
141 Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu
142 Berlin, and Berlin Institute of Health, Berlin, Germany.
143 ⁶⁴ Department of Child Psychiatry, University Medical Center, Leiden, the Netherlands.
144 ⁶⁵ Leiden Institute for Brain and Cognition, Leiden University, Leiden, the Netherlands.
145 ⁶⁶ Department of Psychiatry, University Medical Center Leiden, Leiden, the Netherlands.
146 ⁶⁷ Centre for Advanced Imaging, University of Queensland, Brisbane, Australia.
147 ⁶⁸ Institute for Community Medicine, University Medicine Greifswald, Germany.
148 ⁶⁹ Department of Psychiatry, Division of Child and Adolescent Psychiatry, UCSF School of Medicine,
149 UCSF, San Francisco, CA, USA.
150 ⁷⁰ Faculty of Health, Queensland University of Technology, Brisbane, Australia.
151 ⁷¹ Department of Clinical Neuroscience, Osher Center, Karolinska Institutet, Stockholm, Sweden.
152 ⁷² Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada.
153 ⁷³ NORMENT Centre, Inst. of Clinical Medicine, University of Oslo, Oslo, Norway.
154 ⁷⁴ Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway.
155 ⁷⁵ Clinic for Mental Health and Dependency, C-L psychiatry and psychosomatic unit, Oslo University
156 Hospital, Oslo, Norway.
157 ⁷⁶ Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain.
158 ⁷⁷ FIDMAG Germanes Hospitalàries Research Foundation, CIBERSAM, Barcelona, Catalonia, Spain.
159 ⁷⁸ Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES
160 Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National
161 University of Ireland Galway, H91 TK33 Galway, Ireland.
162 ⁷⁹ MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, UK.
163 ⁸⁰ Norwegian Centre for Mental Disorders Research, Inst. of Clinical Medicine, University of Oslo, Oslo,
164 Norway.
165 ⁸¹ Department of Neurology, Oslo University Hospital, Oslo, Norway.
166 ⁸² UNIACT, Psychiatry Team, Neurospin, Atomic Energy Commission, Gif-Sur-Yvette, France.

- 167 ⁸³ Cardiff University Brain Research Imaging Centre, Cardiff University, UK.
168 ⁸⁴ Neuroscience Research Australia, Randwick, Sydney, Australia.
169 ⁸⁵ School of Medical Sciences, University of New South Wales, Kingsford, Sydney, Australia.
170 ⁸⁶ University of Groningen, University Medical Center Groningen, Department of Psychiatry, Groningen,
171 The Netherlands.
172 ⁸⁷ Unité Perception et Mémoire, Centre National de la Recherche Scientifique, Institut Pasteur, Paris,
173 France.
174 ⁸⁸ APHP, Hôpitaux Universitaires Mondor, INSERM, U955, Translational Psychiatry Team, Pôle de
175 psychiatrie, Faculté de médecine, Créteil, France.
176 ⁸⁹ Neuroscience Institute, University of Cape Town, Cape Town, South Africa.
177 ⁹⁰ Laureate Institute for Brain Research.
178 ⁹¹ Instituto de Psiquiatria, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao
179 Paulo, Sao Paulo, SP, BR.
180 ⁹² Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the
181 Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden.
182 ⁹³ Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.
183 ⁹⁴ Department of Clinical Neuroscience, University of Oslo, Norway.
184 ⁹⁵ Clinic for Psychiatry and Dependency, C-L psychiatry and psychosomatic unit, Oslo University Hospital,
185 Oslo, Norway.
186 ⁹⁶ School of Psychiatry, University of New South Wales, Kingsford, Sydney, Australia.
187 ⁹⁷ Black Dog Institute, Prince of Wales Hospital, Randwick, Sydney, Australia.
188 ⁹⁸ Instituto de Radiologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao
189 Paulo, Sao Paulo, SP, BR.
190 ⁹⁹ Department of Psychiatry and Neurology, CHU Grenoble Alpes, Univ. Grenoble Alpes, F-38000
191 Grenoble, France.
192 ¹⁰⁰ Inserm 1216, Grenoble Institut des Neurosciences, GIN, F-38000 Grenoble.
193 ¹⁰¹ Department of Psychiatry, Amsterdam University Medical Centers, AMC, Amsterdam, The
194 Netherlands.
195 ¹⁰² Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands.
196 ¹⁰³ Donders Institute for Brain, Cognition and Behavior, Radboud University, Nijmegen, The Netherlands.
197 ¹⁰⁴ Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia,
198 PA, USA.
199 ¹⁰⁵ Oxley College of Health Sciences, The University of Tulsa.
200 ¹⁰⁶ West Region and Research Division, Institute of Mental Health, Singapore.
201 ¹⁰⁷ Yong Loo Lin School of Medicine, National University of Singapore, Singapore.
202 ¹⁰⁸ Valkenberg Psychiatric Hospital, Cape Town, South Africa.
203 ¹⁰⁹ Instituto de Ensino e Pesquisa, Hospital Sírio-Libanês, Sao Paulo, SP, Brazil.
204 ¹¹⁰ Department of Cognitive Neuroscience, Radboud University Medical Centre, Nijmegen, The
205 Netherlands.
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216 *Correspondence to:

217 Laura Kim Mae Han, MSc
218 Amsterdam University Medical Centers, VU University Medical Center
219 The Netherlands
220 l.han@vumc.nl

221 **Abstract**
222

223 **Background:** Major depressive disorder (MDD) is associated with an increased risk of brain atrophy,
224 aging-related diseases, and mortality. We examined potential advanced brain aging in MDD patients, and
225 whether this process is associated with clinical characteristics in a large multi-center international dataset.

226 **Methods:** We performed a mega-analysis by pooling brain measures derived from T1-weighted MRI
227 scans from 29 samples worldwide. Normative brain aging was estimated by predicting chronological age
228 (10-75 years) from 7 subcortical volumes, 34 cortical thickness and 34 surface area, lateral ventricles and
229 total intracranial volume measures separately in 1,147 male and 1,386 female controls from the ENIGMA
230 MDD working group. The learned model parameters were applied to 1,089 male controls and 1,167
231 depressed males, and 1,326 female controls and 2,044 depressed females to obtain independent
232 unbiased brain-based age predictions. The difference between predicted “brain age” and chronological
233 age was calculated to indicate brain predicted age difference (brain-PAD).

234 **Findings:** On average, MDD patients showed a higher brain-PAD of +0.90 (SE 0.21) years (Cohen’s
235 $d=0.12$, 95% CI 0.06-0.17) compared to controls. Relative to controls, first-episode and currently
236 depressed patients showed higher brain-PAD (+1.2 [0.3] years), and the largest effect was observed in
237 those with late-onset depression (+1.7 [0.7] years). In addition, higher brain-PAD was associated with
238 higher self-reported depressive symptomatology ($b=0.05$, $p=0.004$).

239 **Interpretation:** This highly powered collaborative effort showed subtle patterns of abnormal structural
240 brain aging in MDD. Substantial within-group variance and overlap between groups were observed.
241 Longitudinal studies of MDD and somatic health outcomes are needed to further assess the predictive
242 value of these brain-PAD estimates.

243 **Funding:** This work was supported, in part, by NIH grants U54 EB020403 and R01 MH116147.
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249 **Research in context**

250 **Evidence before this study**

251 Accumulating evidence from studies suggests that, at the group level, MDD patients follow advanced
252 aging trajectories, as their functional (e.g. walking speed, hand grip strength) and biological state (e.g.
253 telomeres, epigenetics, mitochondria) reflects what is normally expected at an older age (i.e. biological
254 age “outpaces” chronological age). While subtle structural brain abnormalities have been identified in
255 MDD, it remains to be elucidated whether patients also deviate from the normal aging process at the
256 brain level (brain predicted age difference [brain-PAD]) and whether this deviation is associated with
257 clinical characteristics. We searched PubMed for relevant literature published in English [Language]
258 before January 25, 2019. In this search we used ((‘brain age’ OR ‘brainAGE’ OR ‘brain-PAD’ OR
259 ‘predicted brain ag*’) AND ‘depression’ [Title/Abstract]), which revealed only two papers. One study found
260 that MDD patients (N=104) were estimated to be +4.0 years older using brain-based age prediction
261 models. A second study reported a non-significant relationship between brain-PAD and a short self-report
262 scale of depressive symptoms in male veterans (N=359) who served in the United States military. Thus,
263 whether a diagnosis of MDD is associated with the multivariate metric of brain aging in a large dataset,
264 and which clinical characteristics further impact this metric, remains elusive.

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266 **Added value of this study**

267 To our knowledge, this is the first study to examine deviations of normative brain aging in MDD and
268 associated clinical heterogeneity in a large international and multi-center dataset, by pooling data from
269 >8,000 subjects from 29 research samples worldwide. The current study shows that chronological age
270 can be predicted from gray matter features in a large heterogeneous dataset with an age range covering
271 almost the entire lifespan (10-75 years). Moreover, we show that our brain age prediction model
272 generalizes to unseen hold-out samples, as well as to completely independent samples from different
273 scanning sites. We found that, at the group level, patients had, on average, a +0.90 years greater
274 discrepancy between their predicted and actual age compared to control participants and there was a
275 subtle relationship between self-reported symptom severity and advanced brain aging in the MDD group.
276 Finally, the strongest effects were observed in patients with a late onset of depression (>55 years old;

277 +1.7 years), currently depressed (+1.2 years), and in their first episode (+1.2 years), compared to
278 controls.

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280 **Implications of all the available evidence**

281 This study confirms previously observed advanced biological aging in MDD at the group and brain level of
282 analysis. However, it is important to mention the large within-group and small between-group variance,
283 demonstrating that many patients did not show advanced brain aging. Our work contributes to the
284 maturation of brain age models in terms of generalizability, deployability, and shareability, in pursuance of
285 a canonical brain age algorithm. Further, other research groups with deep clinical phenotyping and
286 longitudinal information on mental and somatic health outcomes may use our model to promote continued
287 growth of knowledge for greater clinical application.

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302 Introduction

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304 Major Depressive Disorder (MDD) is associated with an increased risk of cognitive decline,¹ brain
305 atrophy,² aging-related diseases,² and importantly, overall mortality.^{3,4} While normal aging is associated
306 with significant loss of gray matter,⁵ growing evidence suggests that neuropsychiatric disorders such as
307 depression may have an accelerating effect on age-related brain atrophy.⁶ Simultaneously, the aging
308 population is increasing, and both depression and aging have been linked to poor somatic health and
309 quality of life, and increased costs for society and healthcare.^{7,8} This underscores the importance of
310 identifying brain aging patterns in MDD patients to determine whether and how they deviate from healthy
311 patterns of aging.

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313 Emerging evidence indicates that chronological age and biological age may be distinct processes that
314 can diverge. Current multivariate pattern methods can predict chronological age from biological data (i.e.,
315 epigenetics, transcriptomics, proteomics, metabolomics, see Jylhava, Pedersen, and Hagg for a review)⁹
316 with high accuracy. Similarly, chronological age can be predicted from brain images, resulting in an
317 estimate known as “brain age”.¹⁰ Importantly, by calculating the difference between a person’s estimated
318 brain age and their chronological age, one can translate a complex aging pattern across the brain into a
319 single outcome:¹¹ brain-predicted age difference (brain-PAD).¹² A positive brain-PAD represents having
320 an ‘older’ brain than expected for a person of their chronological age, whereas a negative brain-PAD
321 signals a ‘younger’ brain than expected at the given chronological age. Higher brain-PAD scores have
322 been associated with greater cognitive impairment,¹³ increased morbidity,¹⁰ and exposure to cumulative
323 negative fateful life events (e.g., death of a close family member, financial hardship, or divorce).¹⁴

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325 Prior studies from the Enhancing NeuroImaging Genetics through Meta-analysis (ENIGMA)-MDD
326 consortium with sample sizes over 9,000 participants have shown subtle reductions in subcortical
327 structure volumes in major depression that were robustly detected across many samples worldwide.
328 Specifically, smaller hippocampal volumes were found in individuals with earlier age of onset and
329 recurrent episode status.¹⁵ In addition, different patterns of cortical alterations were found in adolescents

330 versus adults with MDD, suggesting that MDD may affect brain morphology (or vice versa) in a way that
331 depends on the developmental stage of the individual.¹⁶ Likewise, brain development and aging likely
332 differ by sex.¹⁷ The different neural and clinical presentations of depression and aging across sex
333 emphasize the need to stratify populations studied into groups of females and males to better understand
334 sex-dependent or sex-specific effects.

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336 Given that prior studies suggest advanced biological aging in MDD (e.g., shorter telomere length,¹⁸
337 greater epigenetic aging,^{19,20} and advanced brain aging),⁶ it is important to examine whether biological
338 aging findings in depression can be confirmed in a large heterogeneous dataset consisting of many
339 independent samples worldwide, based on commonly derived gray matter measures. Only a handful of
340 studies have investigated brain-PAD in people with psychiatric disorders,²¹ showing older brain-PAD in
341 schizophrenia,^{6,22,23} borderline personality disorder, and first-episode and at-risk mental state for
342 psychosis,^{6,24} yet findings were less consistent in bipolar disorder.^{23,25}

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344 Only two studies to date specifically investigated premature brain aging in MDD - using relatively small
345 samples of 104 and 211 patients, respectively, with inconsistent findings of a brain-PAD of +4.0 years
346 versus no significant difference.^{6,26} The current study is the first to examine brain aging in over 8,000
347 individuals from the ENIGMA MDD consortium (29 cohorts, 11 countries worldwide), covering almost the
348 entire lifespan (10-75 years). We hypothesized higher brain-PAD in MDD patients compared to controls.
349 We also conducted exploratory analyses to investigate whether higher brain-PAD in MDD patients was
350 associated with demographic (age, sex) and clinical characteristics such as disease recurrence,
351 antidepressant use, remission status, depression severity, and age of onset of depression.

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353 **Methods**

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355 **Samples**

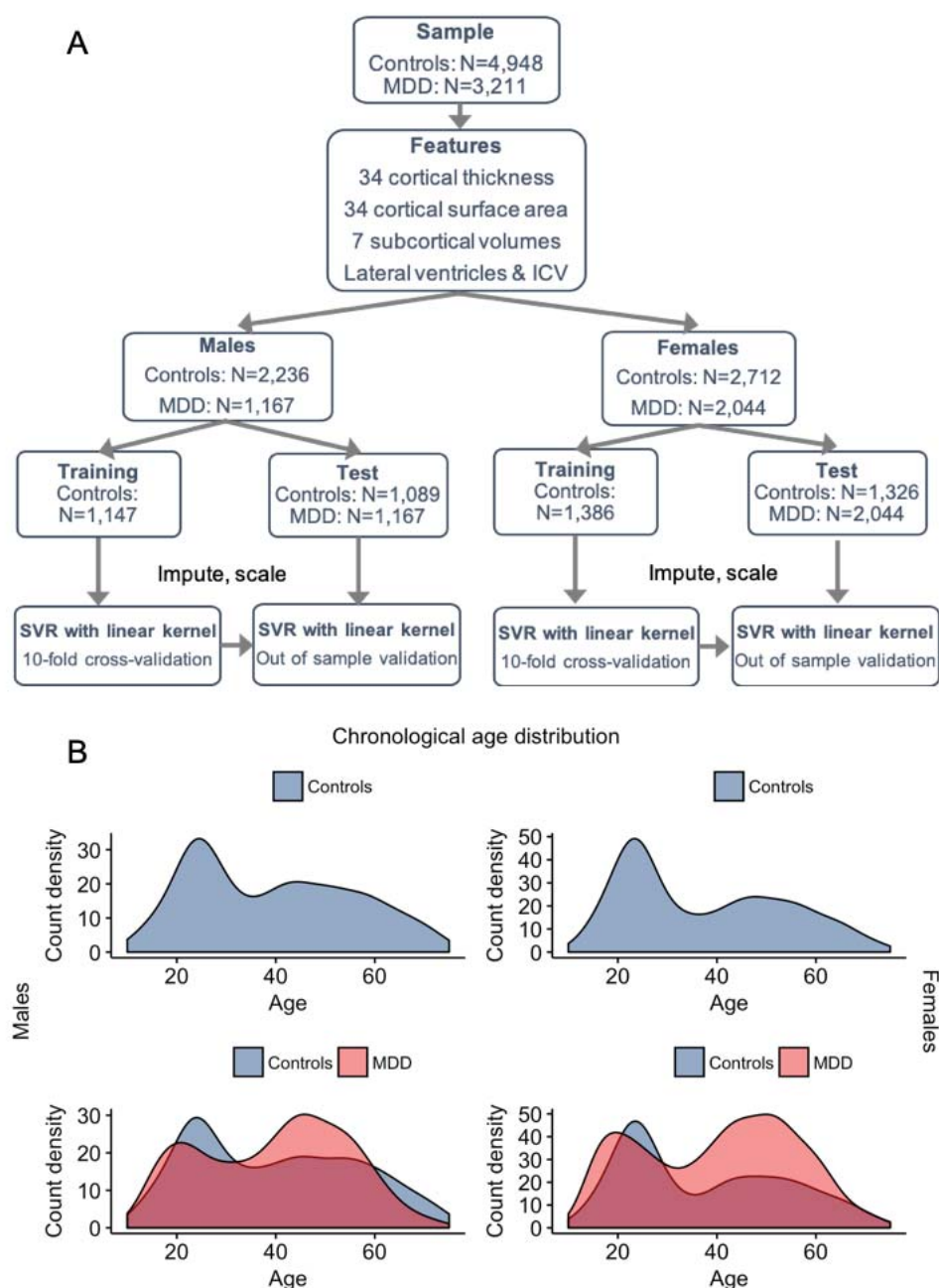
356 Twenty-nine cohorts from the ENIGMA-MDD working group with neuroimaging and clinical data from
357 MDD patients and controls participated in this study (**appendix**). The combined sample covered almost

358 the entire lifespan (10-75 years of age). Details regarding demographics, clinical characteristics, and
359 exclusion criteria for each cohort may be found in the **appendix**. Because the literature suggests
360 differential brain development and maturation by sex,¹⁷ we estimated brain age models separately for
361 male and female samples. Sites with less than ten healthy males or females were excluded from the
362 training dataset and subsequent analyses (for exclusions see **appendix**). In total, we included data from
363 N=8,159 (93.5%) participants, including N=4,948 (56.7%) control individuals (N=2,236 [45.2%] males;
364 N=2,712 [54.8%] females) and N=3,211 (36.8%) individuals with MDD (N=1,167 [36.3%] males; N=2,044
365 [63.7%] females). All participating sites obtained approval from the appropriate local institutional review
366 boards and ethics committees, and all study participants or their parents/guardians provided written
367 informed consent.

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369 **Training and test samples**

370 An overview of the data partition is shown in **figure 1A** and described in more detail in the **appendix**.
371 Structural brain measures from 1,147 male obtained from 28 scanners and 1,386 female controls
372 obtained from 34 scanners were included in the training sample. The top panel in **figure 1B** shows the
373 chronological age distribution in the training sample. A hold-out dataset comprised of controls served as
374 test sample to validate the accuracy of brain age prediction model; 1,089 male and 1,326 female controls
375 from the same scanning sites were included. Likewise, 1,167 male and 2,044 female MDD patients from
376 the corresponding neuroimaging sites were included in the MDD test sample. The bottom panel in **figure**
377 **1B** shows the chronological age distributions across the test samples. More details on data partitioning
378 are shown in the **appendix**.



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Figure 1: (A) Schematic illustration of features used and data partition into training and test samples, separately for males and females. (B) Data from control groups (blue) were partitioned within scanning sites preserving chronological age distribution. Major depressive disorder (MDD) groups are shown in red. The top panel illustrates the male and female training samples. The bottom panels show the male (controls: mean [SD] in years, 40.0 [16.5]; MDD: 39.6 [14.8]) and female test samples (controls: 37.6 [16.2]; MDD: 40.0 [15.5]). ICV, intracranial volume; SVR, support vector regression.

389 **Image processing and analysis**

390 Structural T1-weighted scans of each subject were acquired at each site and analyzed locally using
391 standardized protocols to facilitate harmonized image analysis across multiple sites
392 (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>). Briefly, the fully automated and validated
393 segmentation software, FreeSurfer 5.1 or 5.3 was used to segment seven subcortical gray matter regions
394 (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus), lateral
395 ventricles, 34 cortical thickness and 34 surface area measures, and total intracranial volume (ICV).
396 Segmentations were visually inspected and statistically examined for outliers. Further details on cohort
397 type, image acquisition parameters, software descriptions, and quality control may be found in the
398 **appendix**. Individual-level structural brain measures and clinical and demographic measures from each
399 cohort were pooled at a central site to perform the mega-analysis.

400

401 **Brain age prediction model**

402 To estimate the normative brain age models, we combined the FreeSurfer measures from the left and
403 right hemispheres by calculating the mean $((\text{left}+\text{right})/2)$ of volumes for subcortical regions and lateral
404 ventricles, and thickness and surface area for cortical regions. Using a mega-analytic approach, we first
405 estimated normative models of the association between the 77 average structural brain measures and
406 chronological age in the training sample of controls (separately for males and females) using a support
407 vector regression (SVR) with a linear kernel, from the python-based *sklearn* package.²⁷ All measures
408 were combined as predictors in a single multivariate model.

409

410 To assess model performance and optimize the regularization parameter, C , we performed 10-fold cross-
411 validation. To quantify model performance, we calculated the mean absolute error (MAE) between
412 predicted brain age and chronological age. Both male and female brain age models will be made public
413 upon publication (<https://www.photon-ai.com/>); for guidelines and instructions, see **appendix**. Of note, we
414 also estimated a model including left and right hemisphere measures, that did not result in significantly
415 superior prediction accuracy, which allowed us to reduce the feature space to average left/right values as
416 described (data not shown). We also compared the SVR to other machine learning methods, including

417 ridge regression, Gaussian process regression, and generalized additive models. Results of these
418 comparisons are provided in the **appendix**; briefly, the different approaches all showed similar
419 performance to the model presented here.

420

421 **Model validation**

422 Model performance was further validated in the test sample of controls. The parameters learned from the
423 trained model in controls were applied to the test sample of controls and to the MDD test samples to
424 obtain brain-based age estimates for these individuals. To assess model performance in these test
425 samples, we calculated: a) MAE; b) Pearson correlation coefficients between predicted brain age and
426 chronological age; and c) the proportion of the variance explained by the model (R^2). To evaluate
427 generalization power to completely independent test samples, we also applied the training model
428 parameters to healthy control subjects (males, N=646; females, N=757) from the ENIGMA Bipolar
429 Disorder (BD) working group (**appendix**).

430

431 **Statistical analyses**

432 All statistical analyses were conducted in the test samples only. Brain-PAD (predicted brain-based age -
433 chronological age) was calculated for each individual and used as the outcome variable. While different
434 prediction models were built for males and females separately, the generated brain-PAD estimates were
435 pooled for statistical analyses. For our main analysis, we investigated three linear mixed models (LMM) of
436 brain-PAD: a) main effects of age, sex, and diagnosis, b) all main effects and all second order interactions
437 of age, sex, and diagnosis, and c) main effects and all second and third order interactions of age, sex,
438 and diagnosis. To calculate the association between each FreeSurfer feature and brain-PAD, we used
439 univariate regressions corrected for multiple comparisons (false discovery rate; FDR). Surface area and
440 subcortical measures were additionally corrected for ICV.

441

442 Within MDD patients, we also used LMM to examine associations of brain-PAD with clinical
443 characteristics, including recurrence status (first vs. recurrent episode), antidepressant use at time of
444 scanning (yes/no), remission status (currently depressed vs. remitted), depression severity at study

445 inclusion (the 17-item Hamilton Depression Rating Scale (HDRS-17) and the Beck Depression Inventory
446 (BDI-II)), and age of onset of depression (categorized as: early, <26 years; adult, >25 & <56 years; and
447 late onset, >55 years). All analyses included scanning site as a random intercept to account for scanner
448 and FreeSurfer version differences and were corrected for chronological age, age², age³, and sex, tested
449 two-sided. Findings were considered statistically significant at $p < 0.05$.

450

451 **Role of the funding source**

452 The study design, data collection, analysis, interpretation, writing, and submission of this report were
453 performed independently from any funding source. The corresponding author had full access to the
454 complete dataset in the study. All authors had the final responsibility for the decision to submit for
455 publication.

456

457 **Results**

458

459 **Brain age can be predicted from regional brain measures**

460 Within the training set of controls, under cross-validation the structural brain measures predicted
461 chronological age with a MAE of 6.86 (SD 5.32) years in males and 6.91 (5.34) years in females.
462 Correlations between chronological and predicted brain age were $r=0.85$, $p < 0.001$ in males, and $r=0.84$,
463 $p < 0.001$ in females, with $R^2=0.72$ and $R^2=0.71$, respectively. When applying the model parameters to the
464 test samples of controls, the MAE was 6.35 (4.92) and 6.63 (5.08) years for males and females,
465 respectively. Similarly, within the MDD group, the MAE was 6.86 (5.58) and 7.22 (5.42) years for males
466 and females, respectively. **Figure 2** shows the correlation between chronological age (y-axis) and
467 predicted brain age (x-axis)²⁸ in the out-of-sample control (males $r=0.87$, $p < 0.001$; $R^2=0.76$ and females
468 $r=0.86$, $p < 0.001$; $R^2=0.74$), and MDD test samples (males $r=0.81$, $p < 0.001$; $R^2=0.66$ and females $r=0.82$,
469 $p < 0.001$; $R^2=0.68$). The model also showed relatively good generalization to completely independent
470 healthy control samples of the ENIGMA Bipolar Disorder working group (MAE=7.24 [SD 5.82]; $r=0.76$,
471 $p < 0.001$; $R^2=0.57$ for males and MAE=7.45 [5.44]; $r=0.75$, $p < 0.001$; $R^2=0.56$, for females), **appendix**.

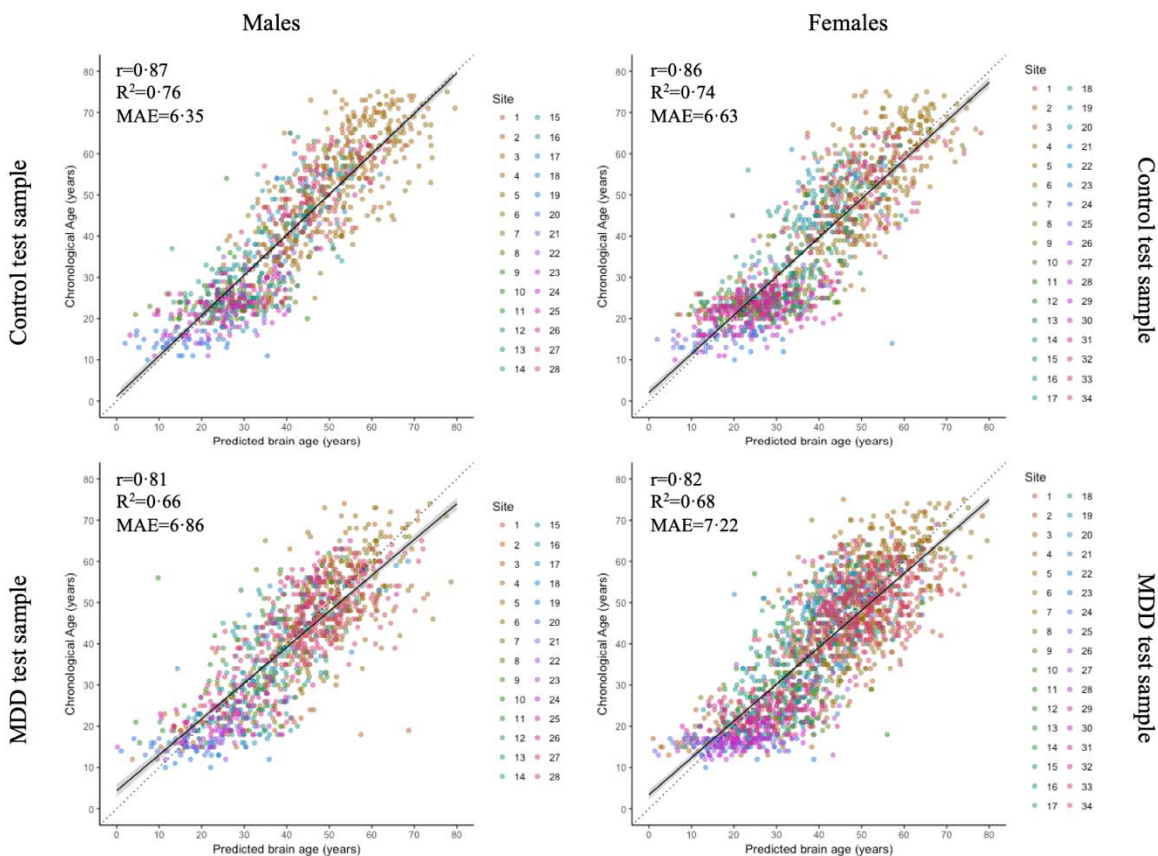
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479 **Figure 2: Brain age prediction based on 7 FreeSurfer subcortical volumes, lateral ventricles, 34**

480 **cortical thickness and 34 surface area measures, and total intracranial volume.** The plots show the

481 correlation between chronological age and predicted brain age in the test samples, derived from the 10-

482 fold cross-validation of the Support Vector Regression model in the training samples, separately for males

483 (left) and females (right). The colors indicate scanning sites and each circle represents an individual

484 subject: the upper panels display controls and the lower panels MDD patients. Diagonal dashed line

485 reflects the line of identity ($x=y$).

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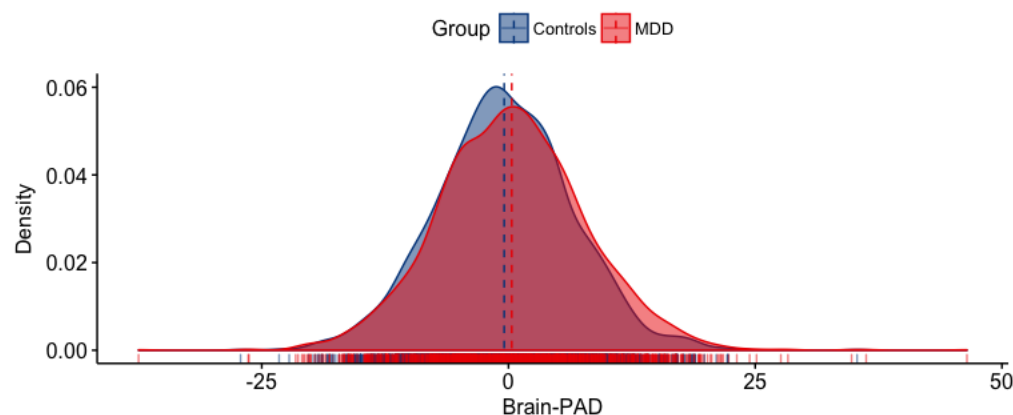
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491 **MDD patients show increased brain-PAD compared to controls**

492 There was a main effect of diagnostic group. Specifically, individuals with MDD showed +0.90 (SE 0.21)
493 years higher brain-PAD than controls ($p < 0.0001$, Cohen's $d = 0.12$, 95% CI 0.06-0.17), **figure 3**.
494 Additionally, we found significant main effects for age, age^2 , and age^3 ($b = -0.02$ - 0.72 , all p 's < 0.0001), and
495 a trend for a main effect of sex, with higher brain-PAD in females ($b = 0.39$, $p = 0.0501$). Our analyses
496 revealed no significant three-way interaction between diagnosis-by-age-by-sex, nor significant two-way
497 interactions. Of note, there were no significant interactions with age, age^2 , or age^3 and MDD status; thus,
498 the residual age effects in the brain-PAD estimates did not influence the case-control difference. Further,
499 all nonlinear age effects were accounted for in analyses. All FreeSurfer features, except the entorhinal
500 and temporal pole average thickness, showed a significant ($P_{FDR} < 0.05$) association with brain-PAD. All
501 features, except the mean lateral ventricles, yielded negative associations, and are visualized in **figure 4**.

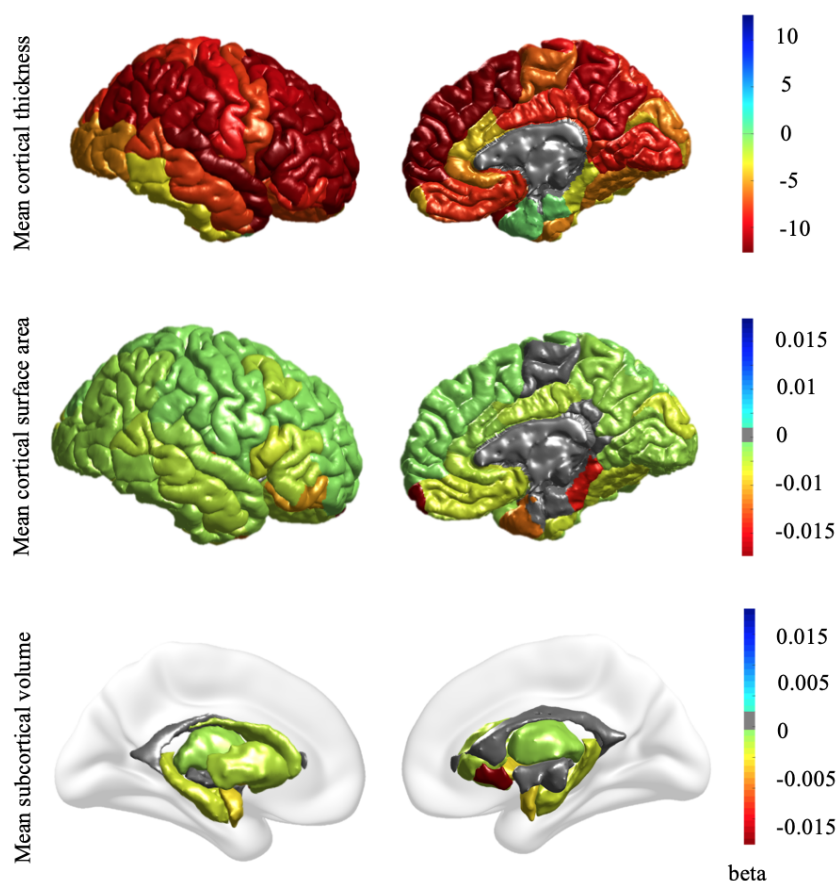
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507 **Figure 3: Case-control differences in brain aging.** Brain-PAD (predicted brain age - chronological age)
508 in patients with major depressive disorder (MDD) and controls. Group level analyses showed that MDD
509 patients exhibited significantly higher brain-PAD than controls ($b = 0.90$, $p < 0.0001$), although large within-
510 group variation and between-group overlap is observed. The brain-PAD estimates are adjusted for
511 chronological age, age^2 , age^3 , sex and scanning site.

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Figure 4: Univariate associations between brain predicted age difference (predicted brain age - chronological age; brain-PAD) and FreeSurfer measures across controls and major depressive disorder (MDD) groups. Effect sizes (regression coefficients) are shown for regions with a significant ($P_{FDR} < 0.05$) negative association with brain-PAD, only the mean lateral ventricles yielded a significant positive association. The figure shows associations with cortical thickness measures (*top row*), cortical surface areas (*middle row*), and subcortical volumes (*bottom row*). The brain-PAD estimates are adjusted for chronological age, age^2 , age^3 , sex and scanning site. The significant negative association with ICV was excluded from this figure for display purposes.

547
548 **Clinical characteristics and brain-PAD**

549 Strongest effects of higher brain-PAD were observed in patients with late age of onset of depression (>55
550 years; +1.7 years, $p=0.009$, Cohen's $d=0.17$), currently depressed (+1.2y, $p<0.0001$, $d=0.13$), and first
551 episode (+1.2y, $p=0.0001$, $d=0.12$) MDD patients, compared to controls. However, we observed relatively
552 similar effects in remitted (+1.2y, $p=0.01$, $d=0.11$), both antidepressant users and antidepressant
553 medication-free (both +0.9y, $p's<0.002$, $d=0.09$), early age of onset of depression (<26 years; +0.8y,
554 $p=0.0005$, $d=0.10$), and recurrent depressed patients (+0.7y, $p=0.003$, $d=0.08$), as well as in those with
555 an adult age of onset of MDD (+0.5y, $p=0.02$, $d=0.06$), compared to controls (**table 1**). Post-hoc
556 comparisons between the MDD subgroups did not show any significant differences (i.e., first vs. recurrent
557 episode, antidepressant medication-free vs. antidepressant users, remitted vs. currently depressed
558 patients, or early vs. adult vs. late age of onset of depression). Brain-PAD was positive in all MDD
559 subgroups, and there were no negative associations with any clinical characteristics.

560
561

MDD patients vs. Controls	N	b (p value)	SE	Cohen's d	SE	95% CI
First episode MDD	1,080	1.15 (0.0001)	0.28	0.12	0.04	0.05-0.19
Recurrent episode MDD	1,940	0.73 (0.0027)	0.24	0.08	0.03	0.02-0.14
Current MDD	2,179	1.23 (<0.0001)	0.26	0.13	0.03	0.07-0.19
Remitted MDD	344	1.24 (0.0146)	0.51	0.11	0.06	-0.006-0.22
AD medication-free	1,753	0.84 (0.0006)	0.25	0.09	0.03	0.03-0.15
AD user	1,366	0.85 (0.0020)	0.28	0.09	0.03	0.02-0.15
All MDD patients	3,211	0.90 (<0.0001)	0.21	0.12	0.03	0.06-0.17
Early onset MDD	1,400	0.85 (0.0005)	0.24	0.10	0.03	0.03-0.16
Adult onset MDD	1,420	0.54 (0.0244)	0.24	0.06	0.03	-0.002-0.13
Late onset MDD	125	1.73 (0.0091)	0.66	0.17	0.09	-0.01-0.35

562 **Table 1: Clinical characteristics and brain aging.** Positive brain-PAD scores (predicted brain age -
563 chronological age) were found for all subgroups of patients with major depressive disorder (MDD)
564 compared to controls (N=2,256). b=regression coefficient; this indicates the average brain-PAD difference
565 between MDD patients and controls in years. AD, Antidepressant.
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569

570 **Increased brain-PAD is associated with greater depressive symptom severity**

571 There was an association with depression severity at the time of scanning within the MDD sample,
572 illustrated by higher brain-PAD in individuals with more severe self-reported depressive symptomatology
573 ($b=0.05$, $p=0.004$) as measured in $N=1,538$ patients who completed the BDI-II. We were not able to
574 confirm this, however, in $N=1,905$ depressed individuals who were assessed using the HDRS-17
575 clinician-based questionnaire ($b=0.003$, $p=0.90$).

576

577 **Discussion**

578

579 Using a brain age algorithm based on commonly used brain measures derived from T1-weighted scans
580 from over 3,500 males and 4,900 females, we found subtle age-associated gray matter differences in
581 major depressive disorder (MDD). At the group level, the brain age model predicted chronological age in
582 controls and MDD patients from 77 brain morphometric features, and patients had, on average, a 0.90
583 years greater discrepancy between their predicted and actual age compared to control participants.
584 Strongest effects were observed in late-life onset of depression ($+1.7y$, $d=0.17$), currently depressed
585 ($+1.2y$, $d=0.13$), and first episode MDD ($+1.2y$, $d=0.12$) patients, compared to controls. Finally, each one-
586 point increase in self-reported symptom severity score at study inclusion added, on average, 18 days of
587 brain aging, potentially underscoring the importance of reducing the number of symptoms in the treatment
588 of depression.

589

590 The positive association between brain aging and symptom severity, measured with the self-report BDI-II
591 questionnaire, was not confirmed using the clinician-based HDRS-17. Post-hoc analyses in overlapping
592 samples with both scores ($N=1,302$) yielded a significant correlation between them ($r=0.67$, $p<0.0001$),
593 yet the same discrepant association with brain-PAD. This could perhaps be explained by the differential
594 proportion of items emphasizing cognitive and affective (BDI-II) or somatic and behavioral dimensions
595 (HDRS-17).²⁹ Alternatively, brain age may be more sensitive to subjective (BDI) than to objectively
596 (HDRS-17) rated experiences, consistent with the finding of Kwak and colleagues (2018) that the
597 subjective experience of aging was closely related to predicted brain age.³⁰ However, it is important to

598 bear in mind the small effect size ($b=0.05$). Nonetheless, positive associations with current depressive
599 symptom severity have been previously reported with more advanced levels of biological aging, as
600 indicated by shorter telomere length³¹ and increased epigenetic aging.¹⁹

601
602 This study showed relatively largest effect size of advanced brain aging in patients with a late-life onset of
603 depression (>55 years old) compared to controls. However, we did not find significant differences
604 between early vs. adult vs. late onset of depression groups. Additionally, no differences between remitted
605 ($N=344$) and acute patients ($N=2,179$) were found, leading to the speculation that an initial brain insult
606 during a first episode of depression or preceding clinical disease onset may leave a lasting impact even
607 after remission. To date, the reversibility of gray matter alterations in MDD over time remains rather
608 elusive due to the lack of reliable longitudinal studies.³² Yet, cross-sectional studies show that “younger”
609 appearing brains are seen in groups of individuals with greater physical activity,³³ long-term meditation
610 practitioners,¹¹ and amateur musicians,³⁴ suggesting that brain age might be a modifiable metric.
611 Moreover, one study suggests dynamic potential by showing that in healthy individuals brain-PAD was
612 temporarily reduced by 1.1 years due to the probable acute anti-inflammatory effects of ibuprofen.³⁵ In
613 this study, there was no detectable effect of antidepressant use on brain aging within MDD individuals. As
614 antidepressants are suggested to exert a neuroprotective effect, for example by promoting brain-derived
615 neurotrophic factor (BDNF),³⁶ it remains to be elucidated how adaptable brain age is in response to
616 pharmacotherapy. However, the cross-sectional nature of the current study and the lack of detailed
617 information on lifetime use, dosage and duration of use of antidepressants, do not allow us to draw any
618 conclusions regarding direct effects of antidepressants on brain aging. Thus, longitudinal research and
619 randomized controlled intervention studies are needed to develop an understanding of how reversible
620 brain aging is after remission of MDD and how modifiable in response to pharmacology, but also to non-
621 pharmacological strategies (e.g., psychological, exercise and/or nutritional interventions), as seen in other
622 biological age indicators.³⁷⁻³⁹

623
624 Further, the currently observed effect size of Cohen's $d=0.12$ with regard to brain aging is consistent with
625 previously seen modest structural brain differences in MDD. Earlier work from the ENIGMA MDD working

626 group also showed small subcortical (hippocampus; $d=-0.14$), and small to moderate cortical reductions
627 (e.g. left medial orbitofrontal cortex thickness in adults, $d=-0.13$ and right lingual gyrus surface area in
628 adolescents, $d=-0.42$) in patients compared to controls.^{15,16} Here, we particularly find strong widespread
629 significant negative associations between brain aging and cortical thickness, and comparably weaker
630 associations with surface area and subcortical volume measures (**figure 4**), consistent with literature on
631 age-related structural brain changes in adolescents⁴⁰ and adults.⁴¹ We also visualized these associations
632 separately for controls and MDD patients, but findings were similar and suggest comparable spatial brain
633 aging patterns in both groups (**appendix**). Notably, we did not include a spatial weight map of our brain
634 age model, as the weights (although linear) are obtained from a multivariable model, and do not allow for
635 a straightforward interpretation of the importance of the brain regions contributing to the aging pattern.

636
637 Our findings were in contrast to earlier work showing a +4.0 years of brain aging in a smaller sample of
638 MDD patients (N=104; 18-65 years).⁶ However, a recent preliminary study in 211 MDD patients (18-71
639 years) found a similar effect size to ours, albeit non-significant ($d=0.10$, $p=0.33$).²⁶ In the latter study,
640 brain-PAD was derived using a brain age model trained on >12,000 healthy individuals (vs. the 800 in the
641 Koutsouleris study⁶ vs. >1,100 in this study), emphasizing the relevance of sample size for both training
642 and test samples for sensitivity to detect reliable, yet subtle, effects. Similarly, with respect to reaching
643 statistical significance, large sample sizes are needed to detect small effect sizes commonly found with
644 biological age indicators,^{18,19,31} but also other markers (e.g. BDNF, cortisol, oxidative stress)⁴²⁻⁴⁴ in
645 depression research. A major strength of this study is, therefore, the mega-analytic approach of pooling
646 harmonized data from many heterogeneous sites, making predictive models less susceptible to
647 overfitting⁴⁵ and more generalizable to other populations.⁴⁶

648
649 Inflammation may be a common biological mechanism between MDD and brain aging. Neuroimmune
650 mechanisms (e.g. pro-inflammatory cytokines) influence biological processes (e.g. synaptic plasticity),
651 and inflammatory biomarkers are commonly dysregulated in depression.⁴⁷ Both cerebrospinal fluid and
652 peripheral blood interleukin (IL)-6 levels are elevated in MDD,⁴⁸ and increased IL-6 expression may affect
653 brain morphology through neurodegenerative processes.⁴⁹ Moreover, work by Kakeda and colleagues

654 (2018) demonstrated a significant inverse relationship between IL-6 levels and surface-based cortical
655 thickness and hippocampal subfields in medication-free, first-episode MDD patients.⁵⁰ This accords with
656 the current observation of increased brain-PAD in medication-free and first-episode patients, compared to
657 controls, perhaps suggesting that neuroimmune mechanisms may be chief candidates involved in the
658 brain morphology alterations, also in the early stage of illness. Further, the age-related structural
659 alterations in MDD may also be explained by shared underlying (epi)genetic mechanisms involved in
660 brain development and plasticity (thereby influencing brain structure) and psychiatric illness.⁵¹ For
661 instance, Aberg and colleagues (2018) showed that a significant portion of the genes represented in
662 overlapping blood-brain methylome-wide association findings for MDD were important for brain
663 development, such as induction of synaptic plasticity by BDNF.⁵²

664
665 Our current findings in MDD show lower brain aging than previously observed in schizophrenia (SCZ)
666 (brain-PAD ranges from +2.6 - +5.5y, $d=0.64$)^{6,22}, even in early stages of first episode SCZ.²⁵ Inconsistent
667 findings are reported in bipolar disorder (BD), with “younger” brain age²³ or no differences compared to
668 controls.²⁵ However, more studies with larger sample sizes are needed to confirm brain aging in these
669 psychiatric disorders - endeavors currently pursued by other ENIGMA psychiatric disease working groups
670 using the same brain age models, which will allow future cross-disorder comparisons between brain-PAD
671 in e.g. MDD, BD and SCZ.

672
673 While our results are generally consistent with existing literature on advanced or premature biological
674 aging and major depression using other biological indicators,¹⁸ it is important to critically consider the
675 current findings and note their limitations. First, limited information was available on clinical
676 characterization and brain-PAD could not be compared against somatic health outcomes here. Second,
677 given the relatively crude and limited number of gray matter features, the best MAE that could be
678 achieved was 6.9 years, compared to ~4.9 years accomplished by other brain age predictors (e.g., those
679 based on spatial images with high dimensional features that may also include white matter).¹² However,
680 an advantage to using FreeSurfer data over voxelwise methods is that the fewer dimensions render our
681 models less prone to overfitting and more flexible in exploring the use of different machines and kernels

682 **(appendix)**. Furthermore, pooling data from many scanning sites comes at the cost of increasing
683 heterogeneity of MRI data and other sample specifics. However, withstanding the latter limitation, models
684 are therefore consequently tested on “ecologically valid” samples, bolstering confidence in their
685 deployability and shareability.⁵³ Finally, the large within-group variance regarding the brain-PAD outcome
686 in both controls and MDD (**figure 3**), compared to the small between-group variance, renders the use of
687 this brain aging indicator for discriminating patients and controls at the individual level difficult. As many of
688 the MDD patients do not show advanced brain aging compared to controls, the clinical significance of the
689 observed higher brain-PAD in MDD patients in this study may be limited. Yet, interindividual differences
690 highlight the importance of studying the individual, rather than the average patient⁵⁴ and provide the
691 opportunity to elucidate whether a subgroup of patients with high brain-PAD may be at risk for worse
692 psychiatric, neurologic, and somatic health outcomes. Local sites that participated in this study with
693 clinical phenotyping and longitudinal information on mental and somatic health outcomes (e.g., genomic
694 variation, omics profiles, comorbidities, lifestyle, inflammation, oxidative stress, chronic diseases) will
695 allow further evaluation of the predictive value of the brain-PAD estimates. This is expected to promote
696 continued growth of knowledge in pursuance of useful clinical applications.

697
698 In conclusion, compared to controls, both male and female MDD patients show advanced brain aging,
699 with a subtle association with current symptom severity. This is consistent with other studies of biological
700 aging indicators in MDD at cellular and molecular levels of analysis (i.e., telomere length and epigenetic
701 age). The deviation of brain metrics from normative aging trajectories in MDD may contribute to increased
702 risk for mortality and aging-related diseases commonly seen in MDD. However, the substantial within-
703 group variance and overlap between groups signify that more (longitudinal) work including in-depth
704 clinical characterization and more precise biological age predictor systems are needed to elucidate
705 whether brain age indicators can be clinically useful in MDD. Future studies may use our current ENIGMA
706 brain age prediction model to associate brain-PAD with treatment response and other available
707 information on longitudinal mental and somatic health outcomes, other aging indicators, and incidence
708 and/or prevalence of other chronic diseases in their local samples in pursuance of greater clinical
709 application.

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714 **Authors contributions**

715

716 *Concept and design:* AFM, BP, JHC, LKM, LS, LTE, NJ, PMT.

717

718 *Acquisition, analysis or interpretation of data:* AA, AC, AFM, AHS, AJ, AK, AMM, ANS, AS, AU, BAM,
719 BCD, BG, BH, BJH, BJO, BK, BKD, BL, BP, BTB, CA, CC, CF, CGC, CGD, CH, CK, CM, CMB, CMD,
720 DD, DG, DHW, DJS, DMC, EB, ECR, EF, EO,EPC, ES, EV, FLSD, FMH, FPM, GBF, GBH, GdZ, GM,
721 GR, GT, GZ, HCW, HGR, HJG, HST, HV,HW, IB, IBH,IHG, IMV, JH, JHC,JL, JMF, JMG, JR, JR, JS, JS,
722 JS, KB, KC, KLM, KS, KS, KW, LA, LKM, LN, LR, LS, LTE, LTS, MA, MA, MA, MCGO,MDS, MGSS,
723 MH, MHS, MI, MJP, MJvT, MJW, ML, MMR, MP, MVZ, NG, NH, NRW, NW, OAA, OG, OS, PBM, PF,
724 PGPR, PGS, PMT, PRS, RD, RK, RL, RM, RS, RV, SF, SF, SIT, SNH, SSM, SW, TCH, TDS, TE, TF,
725 TH, TH, TK, TMC, TTY, UD, UFM, VE, VZ, XC.

726

727 *Drafting of the manuscript:* LKM, LS.

728

729 *Critical revision of the manuscript for important intellectual content:* AA, AC, AFM, AHS, AMM, AS, AU,
730 BAM, BCD, BH, BJH, BK, BKD, BM, BP, BTB, CA, CC, CF, CGC, CGD, CK, CMB, DG, DJS, EB, EP, ES,
731 EV, FLSD, FPM, GBF, GBH, GZ, HCW, HGR, HJG, HST, HV, HW, IHG, IMV, JHC, JMG, JR, JR, JS, JS,
732 KB,KC, KLM, KS, KW, LA, LKM, LR, LS, LTE, LTS, MA, MA, MA, MDS, MH, MJP, MJW, ML, MMR,
733 MW, NG, NH, NJ, NRW, NW, OAA, OG, PGS, PMT, RD, RK, RV, SEM, SF, SF, SW, TCH, TE, TF, TH,
734 TH, TTY, UD, UFM, VE, XC.

735

736 *Statistical analysis:* AFM, JHC, LKM, LS, RD.

737

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739 FPM, GBF, GZ, HJG, HV, IBH, IMV, JH, JMF, JS, KB, KLM, KS, KS, LR, LS, MA, MCGO, MGSS, MI,
740 MJW, ML, MP, NG, NH, NJ, OAA, OG, PBM, PMT, PRS, RM, RS, TE, TF, TH, TK, UD, UFM, XC.

741

742 *Administrative, technical or material support:* AA, AHS, AS, AU, BCD, BH, BL, BM, BP, CA, CMB, CMD,
743 DJS, DMC, ECR, EP, EPC, EV, FMH, GR, GZ, HGR, HJG, HST, HV, IMV, JMF, JMG, JR, JS, KLM, KS,
744 LN, LR, LTS, MA, MCGO, MGSS, MJW, MMR, MW, NG, NH, NJ, OAA, PBM, PGS, PMT, PRS, RM, RS,
745 SEM, SF, SSM, TH, XC.

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