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Genetic Architecture of Subcortical Brain Structures in 38,851 Individuals

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1 Abstract

2 Subcortical brain structures are integral to motion, consciousness, emotions, and
3 learning. We identified common genetic variation related to the volumes of nucleus
4 accumbens, amygdala, brainstem, caudate nucleus, globus pallidus, putamen, and thalamus,
5 using genome-wide association analyses in almost 40,000 individuals from CHARGE,
6 ENIGMA and the UK-Biobank. We show that variability in subcortical volumes is heritable,
7 and identify 48 significantly associated loci (40 novel at the time of analysis). Annotation of
8 these loci utilizing gene expression, methylation, and neuropathological data identified 199
9 genes putatively implicated in neurodevelopment, synaptic signaling, axonal transport,
10 apoptosis, inflammation/infection, and susceptibility to neurological disorders. This set of
11 genes is significantly enriched for *Drosophila* orthologs associated with
12 neurodevelopmental phenotypes, suggesting evolutionarily conserved mechanisms. Our
13 findings uncover novel biology and potential drug targets underlying brain development
14 and disease.

15

16 Subcortical brain structures are essential for the control of autonomic and
17 sensorimotor functions^{1,2}, modulation of processes involved in learning, memory, and
18 decision-making^{3,4}, as well as in emotional reactivity^{5,6} and consciousness⁷. They often act
19 through networks influencing input to and output from the cerebral cortex^{8,9}. The
20 pathology of many cognitive, psychiatric, and movement disorders is restricted to, begins
21 in, or predominantly involves subcortical brain structures and related circuitries¹⁰. For
22 instance, tau pathology has shown to manifest itself early in the brainstem of individuals
23 with Alzheimer's disease before spreading to cortical areas through efferent networks¹¹.
24 Similarly, the formation of Lewy bodies and Lewy neurites in Parkinson's disease appears
25 early in the lower brainstem (and olfactory structures) before affecting the substantia
26 nigra¹².

27 Recent investigations have identified genetic loci influencing the volumes of the
28 putamen, caudate, and pallidum, which pointed to genes controlling neurodevelopment
29 and learning, apoptosis, and transport of metals^{13,14}. However, a larger study combining
30 these samples, which include individuals of a broad age-range across diverse studies,
31 would enable increased power to identify additional novel genetic variants contributing to
32 variability in subcortical structures, and further improve our understanding of brain
33 development and disease.

34 We sought to identify novel genetic variants influencing the volumes of seven subcortical
35 structures (nucleus accumbens, amygdala, caudate nucleus, putamen, globus pallidus,
36 thalamus, and brainstem – including mesencephalon, pons, and medulla oblongata),
37 through genome-wide association (GWA) analyses in almost 40,000 individuals from 53

38 study samples (Supplementary Table 1-3) from the Cohorts of Heart and Aging Research in
39 Genomic Epidemiology (CHARGE) consortium, the Enhancing Neuro Imaging Genetics
40 through Meta-Analysis (ENIGMA) consortium, and the United Kingdom Biobank (UKBB).

41

42 **RESULTS**

43

44 ***Heritability***

45 To examine the extent to which genetic variation accounts for variation in subcortical
46 brain volumes, we estimated their heritability in two family-based cohorts: the
47 Framingham Heart Study (FHS) and the Austrian Stroke Prevention Study (ASPS-Fam). Our
48 analyses are in line with previous studies conducted in twins¹⁵, suggesting that variability
49 in subcortical volumes is moderately to highly heritable. The structures with highest
50 heritability in the FHS and the ASPS-Fam are the brainstem (ranging from 79-86%),
51 caudate nucleus (71-85%), putamen (71-79%) and nucleus accumbens (66%); followed by
52 the globus pallidus (55-60%), thalamus (47-54%), and amygdala (34-59%) (Figure 1,
53 Supplementary Table 4). We additionally estimated SNP-based heritability using GCTA in
54 the Rotterdam Study, and LD score regression (LDSC) in the full European sample. As
55 expected, SNP-based heritability estimates were somewhat lower, ranging from 47% for
56 the thalamus to 17% for the amygdala using GCTA, and ranging from 33% for the
57 brainstem to 9% for the amygdala using LDSC. These values are consistent with heritability
58 estimates reported by the UKBB¹⁴.

59

60 ***Genome-wide associations***

61 We undertook a GWA analysis on the MRI-derived volumes of subcortical structures
62 using the 1000 Genomes Project¹⁶ reference panel (phase 1 v.3) for imputation of missing
63 variants in CHARGE and ENIGMA. The UKBB performed imputation of variants using the
64 HRC reference panel¹⁷ (see details on image acquisition and genotyping in Supplementary
65 Table 5 and Supplementary Table 6, respectively). Our sample comprised up to $n = 37,741$
66 individuals of European ancestry from 48 study samples across CHARGE, ENIGMA and the
67 UKBB. Additionally, we included three samples for generalization in African-Americans (up
68 to $n = 769$), and two for generalization in Asians ($n = 341$). Details on the population
69 characteristics, definition of the outcome and genotyping can be found in the supplement
70 (Supplementary Tables 2-5). Each study examined the association of genetic variants with
71 minor allele frequency (MAF) $\geq 1\%$ to the volumes of subcortical structures (average
72 volume for bilateral structures) using additive genetic models adjusted for sex, age, total
73 intracranial volume (or total brain volume in the UKBB); as well as age², population
74 structure, psychiatric diagnosis (ENIGMA cohorts), and study site when applicable. After
75 quality control, we conducted meta-analyses per ethnicity combining all samples using
76 sample-size-weighted fixed effects methods in METAL¹⁸. An analysis of genetic correlations
77 showed consistency of associations across the CHARGE-ENIGMA and the UKBB ($r_g > 0.94$; P
78 $< 1.46 \times 10^{-15}$), demonstrating the similar genetic architecture of subcortical volumes in
79 these two datasets.

80 We identified 48 independent genome-wide significant single nucleotide
81 polymorphisms (SNPs) across all seven subcortical structures, 40 of which are novel at the

82 time of analysis (Table 1). Among these, 26 SNPs were located within genes (one missense,
83 25 intronic), and 22 in intergenic regions. Most of the inflation observed in the quantile
84 plots (Supplementary Figure 1) is due to polygenic effects. We carried forward these 48
85 SNPs for *in-silico* generalization in African-American and Asian samples, and performed a
86 combined meta-analysis of all samples (Supplementary Table 7). Of the 46 SNPs present in
87 the generalization samples, the direction of association was the same for 13 across all
88 ethnicities and for an additional 6 SNPs in either the African-American or the Asian
89 samples. In the combined meta-analysis, 43 of the 48 associations remained significant, and
90 for 21 SNPs, the strength of association increased when all samples were combined.
91 Although we did not find significant associations for most SNPs at the generalization
92 sample level, likely due to their limited sample size, the sign test for the direction of effect
93 suggested that a large proportion of the SNPs associated with subcortical volumes in the
94 European sample are also associated in the African-American and Asian samples at the
95 polygenic level ($P < 1 \times 10^{-4}$; Supplementary Table 8).

96 To functionally annotate the 48 SNPs identified in the European sample, we used Locus
97 Zoom¹⁹, investigated expression quantitative trait loci (eQTL) and methylation QTL
98 (meQTL) in post-mortem brains from the Religious Order Study and the Rush Memory and
99 Aging Project (ROSMAP), and also queried *cis*- and *trans*-eQTL datasets in brain and non-
100 brain tissues for the top 48 SNPs or their proxies ($r^2 > 0.8$), using the European population
101 reference (Supplementary Tables 9-12). Lead variants and their proxies were annotated to
102 genes based on the combination of physical proximity, eQTL and meQTL, which in some
103 instances assigned more than one gene to a single SNP. Most of our index SNPs had genes

104 assigned based on more than one functional source. This strategy allowed us to identify
105 199 putatively associated genes (Supplementary Table 13). More details can be found in
106 the Supplementary note.

107

108 ***Associations with cognition and neuropathology***

109 Although individual SNPs were not related to neuro-pathological traits or cognitive
110 function in ROSMAP (Supplementary Table 14), we found that cortical mRNA expression of
111 12 of our putatively associated genes was associated with neuropathological alterations
112 typically observed in Alzheimer's Disease (Supplementary Table 15). These included β -
113 amyloid load / presence of neuritic plaques (*APOBR*, *FAM65C*, *KTN1*, *NUPR1*, *OPA1*) and tau
114 density / neurofibrillary tangles (*FAM65C*, *MEPCE*, *OPA1*, *STAT1*). Many of these genes,
115 together with *ANKRD42*, *BCL2L1*, *RAET1G*, *SGTB*, and *ZCCHC14*, were also related to
116 cognitive function.

117

118 ***Phenotypic and genetic correlations***

119 We explored both phenotypic (Supplementary Table 16) and genetic (Supplementary
120 Table 17) correlations among subcortical volumes. We also investigated genetic
121 correlations of subcortical volumes with traits previously examined in the CHARGE and
122 ENIGMA consortia, including MRI-defined brain volumes^{20,21,22}, stroke subtypes²³,
123 anthropometric traits²⁴, general cognitive function²⁵, Alzheimer's disease²⁶, Parkinson's
124 Disease²⁷, bipolar disorder and schizophrenia²⁸, and attention deficit/hyperactivity
125 disorder (ADHD)²⁹. We observed strong phenotypic and genetic overlap among most

126 subcortical structures using LDSC methods, consistent with our finding that many of the
127 loci identified have pleiotropic effects on the volumes of several subcortical structures.

128 As expected, we found strong genetic correlations among the nuclei composing the
129 striatum, particularly for nucleus accumbens with caudate nucleus ($P = 9.83 \times 10^{-19}$), and
130 with putamen ($P = 1.02 \times 10^{-17}$). The genetic architecture of thalamic volume highly
131 overlapped with that of most subcortical volumes, except for the caudate nucleus. In
132 contrast, there were no significant genetic correlations for the volume of the brainstem
133 with that of most structures, with the exception of very strong correlations with volumes of
134 the thalamus ($P = 1.56 \times 10^{-22}$) and the globus pallidus ($P = 1.52 \times 10^{-21}$). Individual level
135 analyses using GCTA in the Rotterdam Study ($n = 3,486$) showed similar correlations
136 despite the smaller sample.

137 We also observed strong genetic correlations for hippocampal volumes with amygdalar
138 and thalamic volumes. Height correlated with thalamic volumes and volume of the
139 brainstem was inversely correlated with ADHD. Notably, caudate nucleus volumes
140 correlated with white matter hyperintensity burden.

141

142 ***Cross-species analysis***

143 To investigate for potential evolutionarily conserved requirements of our gene-set in
144 neurodevelopment, neuronal maintenance, or both, we examined available genetic and
145 phenotypic data from the fruit fly, *Drosophila melanogaster*. Importantly, compared to
146 mammalian models, the fly genome has been more comprehensively interrogated for roles
147 in the nervous system. We found that a large proportion of candidate genes for human

148 subcortical volumes are strongly conserved in the *Drosophila* genome (59%), and many of
149 these genes appear to have conserved nervous system requirements (Supplementary Table
150 18). To examine if this degree of conservation was greater than that expected by chance,
151 we leveraged systematic, standardized phenotype data based on FlyBase annotations using
152 controlled vocabulary terms. Indeed, 22% of the conserved fly homologs are documented
153 to cause “neuroanatomy defective” phenotypes in flies, representing a significant ($P = 7.3 \times$
154 10^{-4}), nearly two-fold enrichment compared to 12.9% representing all *Drosophila* genes
155 associated with such phenotypes (Supplementary Table 19).

156

157 ***Partitioning heritability***

158 We further investigated enrichment for functional categories of the genome using
159 stratified LDSC methods³⁰ (Figure 2). Super enhancers were significantly enriched in most
160 subcortical structures, with 17% of SNPs explaining 43% of SNP-heritability in the
161 brainstem, 39% in the caudate, 44% in the pallidum, 37% in the putamen, and 38% in the
162 thalamus. Similarly, strong enrichment was observed for regular enhancers (H3K27ac
163 annotations from Hnisz³¹) in several subcortical structures, explaining over 60% of their
164 SNP-heritability. Conserved regions were enriched in the nucleus accumbens and the
165 brainstem, with 2.6% of SNPs explaining 53% and 35% of their SNP heritability,
166 respectively. Finally, only the brainstem showed enrichment for transcription start sites
167 (TSS), with 1.8% of SNPs explaining 26% of this structure SNP-heritability. Full results are
168 presented in Supplementary Table 20.

169

170 ***Protein-protein interactions***

171 To explore potential functional relationships between proteins encoded by our set of genes,
172 we conducted protein-protein interaction analyses in STRING³². Our results showed
173 enrichment of genes involved in brain-specific pathways (i.e. regulation of neuronal death
174 and neuronal apoptosis), as well as immune-related (i.e. antigen processing, Epstein-Barr
175 virus infection) and housekeeping processes (i.e. proteasome, cell differentiation,
176 signaling). Figure 3 shows these protein networks, and the detailed pathways are
177 presented in Supplementary Table 21.

178 **DISCUSSION**

179 We undertook the largest GWA meta-analysis of variants associated with MRI-derived
180 volumes of the nucleus accumbens, amygdala, brainstem, caudate nucleus, globus pallidus,
181 putamen, and thalamus; in almost 40,000 individuals from 53 study samples worldwide.
182 Our analyses identified a set of 199 candidate genes influencing the volume of these
183 subcortical brain structures, most of which have relevant roles in the nervous system.

184 Our results show wide overlap of genetic variants determining the volume of
185 subcortical structures as elucidated from genetic correlations and individual look-ups
186 among structures. We find that 26 candidate genes may influence more than one structure.
187 For instance, significant SNPs near *KTN1*, are also associated with the volume of the
188 nucleus accumbens, caudate nucleus, and globus pallidus, suggesting that this genomic
189 region may have an important role in determining multiple subcortical brain volumes
190 during development. Furthermore, 14 of the candidate genes were associated with the
191 caudate, globus pallidus and putamen, supporting the shared genetic architecture of the
192 functionally defined corpus striatum.

193 We identified genes implicated in **neurodevelopment**. We confirm the 11q14.3 genomic
194 region near the *FAT3* gene, previously associated with the caudate nucleus¹³, additionally
195 associated with the putamen in our analysis. This gene encodes a conserved cellular
196 adhesion molecule implicated in neuronal morphogenesis and cell migration based on
197 mouse genetic studies³³. SNPs near *PBX3* were associated with caudate volume. *PBX3* is
198 robustly expressed in the developing caudate nucleus of the non-human primate, *Macaca*
199 *fuscata*, consistent with a role in striatal neurogenesis³⁴.

200 We found several genes involved in insulin/IGF1 signaling, including *IGF1*, *PAPPA*,
201 *GRB10*, *SH2B1* and *TXNDC5* across the amygdala, brainstem, caudate, and putamen. *PAPPA*
202 encodes a secreted metalloproteinase that cleaves IGFBPs, thereby releasing bound IGF.
203 Although IGF may be beneficial in early- and midlife, its effects may be detrimental during
204 aging. Studies of *PAPPA* similarly support antagonistic pleiotropy. Low circulating *PAPPA*
205 levels are a marker for adverse outcomes in human embryonic development³⁵, but in later
206 life, higher levels have been associated with acute coronary syndromes and heart
207 failure^{36,37}. Further, *Grb10* and *SH2B1* act as regulators of insulin/IGF1 signaling through
208 their SH2 domains³⁸. Finally, *TXNDC5* has been suggested to increase IGF1 activity by
209 inhibiting the expression IGFBP1 in the context of rheumatoid arthritis³⁹.

210 Additional genes related to neurodevelopment include *PTPN1* (brainstem), *ALPL* and
211 *NBPF3*, (both related to the globus pallidus), and *SLC20A2* (nucleus accumbens). In studies
212 of both human and mouse embryonic stem cells, *PTPN1* was implicated as a critical
213 regulator of neural differentiation⁴⁰. In addition, *PTPN1* encodes a target for the
214 transcriptional regulator encoded by *MECP2*, which causes the neurodevelopmental
215 disorder Rett Syndrome, and inhibition of *PTPB1* is being explored as a therapeutic
216 strategy in mouse Rett models⁴¹. *ALPL* mediates neuronal differentiation early during
217 development and post-natal synaptogenesis in transgenic mouse models⁴². *ALPL* may also
218 help propagate the neurotoxicity induced by tau⁴³, and its activity increases in Alzheimer's
219 disease⁴⁴ and cognitive impairment⁴⁵. *NBPF3* belongs to the neuroblastoma breakpoint
220 family, which encodes domains of the autism- and schizophrenia-related DUF1220
221 protein⁴⁶. *SLC20A2*, related to the globus pallidus and the thalamus, encodes an inorganic

222 phosphate transporter for which more than 40 mutations have been described in
223 association with familial idiopathic basal ganglia calcification (Fahr's Syndrome)^{47,48}. It is
224 interesting to note that other three solute carrier genes were identified in this GWA
225 (*SLC12A9*, *SLC25A29*, *SLC39A8*), suggesting that the molecular transport of metals, amino
226 acids, and other solutes across the cellular membrane could play an important role in the
227 development of subcortical brain structures.

228 Several genes were related to ***synaptic signaling pathways***. We found a SNP in *NPTX1*
229 related to the thalamus, a gene expressed in the nervous system which restricts synapse
230 plasticity⁴⁹, and induces β -amyloid neurodegeneration in human and mouse brain tissues⁵⁰.
231 Additionally, we identified an intronic SNP in *SGTB* for the brainstem, which was an eQTL
232 for the expression of *SGTB* in dorsolateral prefrontal cortex. Experimental rat models
233 showed that β SGT, highly expressed in brain, forms a complex with the cysteine string
234 protein and heat-shock protein cognate (CSP/Hsc70) complex to function as a chaperone
235 guiding the refolding of misfolded proteins near synaptic vesicles⁵¹. Other experimental
236 studies in *C. elegans*, showed that the genetic manipulation of the ortholog, *sgt-1*,
237 suppresses toxicity associated with expression of the human β -amyloid peptide⁵². Other
238 genes involved in synaptic signaling are *CHPT1* (brainstem), involved in
239 phosphatidylcholine metabolism in the brain; *KATNA1* (brainstem), a conserved regulator
240 of neuronal process formation, outgrowth, and synaptogenesis^{53,54}; and *DLG2* (putamen),
241 encoding an evolutionarily conserved scaffolding protein involved in glutamatergic-
242 mediated synaptic signaling and cell polarity⁵⁵ that has been associated with
243 schizophrenia⁵⁶, cognitive impairment⁵⁷, and Parkinson's disease⁵⁸.

244 Another set of SNPs point to genes involved in **autophagy and apoptotic processes**,
245 such as *DRAM1* and *FOXO3*, both related to brainstem volumes. *DRAM1* encodes a
246 lysosomal membrane protein involved in activating TP53-mediated autophagy and
247 apoptosis,⁵⁹ and mouse models mimicking cerebral ischemia and reperfusion have found
248 that inhibiting the expression of *DRAM1* worsens cell injury⁶⁰. The top SNP was also
249 associated with a CpG site proximate to active TSS upstream of *DRAM1* in several mature
250 brain tissues (S3.6). *FOXO3* has been recently identified as pivotal in an astrocyte network
251 conserved across humans and mice involved in stress, sleep, and Huntington's disease⁶¹,
252 and has been related to longevity⁶². In *Drosophila*, a *FOXO3* ortholog regulates dendrite
253 number and length in the peripheral nervous system⁶³, and in the zebrafish, *Danio rario*,
254 *Foxo3a* knockdown led to apoptosis and mispatterning of the embryonic CNS⁶⁴. Additional
255 genes involved in apoptotic processes are *BCL2L1* (globus pallidus and putamen), *BIRC6*
256 (globus pallidus) and *OPA1* (brainstem).

257 Other genes have been implicated in **axonal transport**. We confirm the association
258 between the 13q22 locus near *KTN1* with putamen volume¹³ and expand by showing that
259 this region is also associated with the nucleus accumbens, caudate and the globus pallidus .
260 The most significant SNP (rs945270) is a robust eQTL for *KTN1* in peripheral blood cells.
261 This gene encodes a kinesin-binding protein involved in the transport of cellular
262 components along microtubules⁶⁵, and impairment of these molecular motors has been
263 increasingly recognized in neurological diseases with a subcortical component⁶⁶. The 5q12
264 locus upstream from *MAST4* was associated with nucleus accumbens volume. *MAST4*
265 encodes a member of the microtubule-associated serine/threonine kinases. This gene has

266 been associated with hippocampal volumes²⁰ and juvenile myoclonic epilepsy⁶⁷, and it
267 appears to be differentially expressed in the prefrontal cortex of atypical cases of
268 frontotemporal lobar degeneration⁶⁸. In *Drosophila*, the knockdown of a conserved *MAST4*
269 homolog enhanced the neurotoxicity of human tau⁶⁹, which aggregates to form
270 neurofibrillary tangle pathology in Alzheimer's disease. Further, we identified SNPs near
271 *NEFL* and *NEFM* (globus pallidus), where the top SNP was an eQTL for these genes in
272 subcortical brain tissue and esophagus mucosa. *NEFL* encodes the light chain, and *NEFM*
273 the medium chain of the neurofilament. These proteins determine neuronal caliber and
274 conduction velocity⁷⁰. Mutations in *NEFL/M* genes have been related to neuropsychiatric
275 disorders and both proteins are increasingly recognized as powerful biomarkers of
276 neurodegeneration⁷¹.

277 Finally, several of our candidate genes are also involved in ***inflammation, immunity***
278 ***and infection*** (*ANKRD42, DEFB124, IL27, NLRC4, PILRA/B, TRIM23, TRIM4*), in line with the
279 PPI analysis highlighting the KEGG-Epstein-Barr virus infection pathway. This suggests that
280 immune-related processes may be an important determinant influencing subcortical
281 volumes, as has been shown by other GWAS of neurologic traits^{72,73}.

282

283 Overall, the loci identified by our study pinpoint candidate genes not only associated
284 with human subcortical brain volumes, but also reported to disrupt invertebrate
285 neuroanatomy when manipulated in *Drosophila* and many other animal models. Thus, our
286 results are in line with the knowledge that the genomic architecture of central nervous
287 system development has been strongly conserved during evolution. Partitioning

288 heritability results suggest the nucleus accumbens and the brainstem are particularly
289 enriched in conserved regions.

290

291 One of the main limitations of our study was the small size of our generalization
292 samples, which limits the generalizability of our results to non-European ethnicities.
293 However, our analyses suggest significant concordance for the direction of effect across all
294 ethnicities at the polygenic level. We hope diverse samples become increasingly available
295 to further confirm our findings and make new discoveries. Additionally, we have focused
296 on the discovery of common and less frequent variants. Further efforts to also reveal rare
297 variants and epigenetic signatures associated with subcortical structures will provide an
298 even more refined understanding of the underlying mechanisms involved.

299

300 In conclusion, we describe multiple genes associated with the volumes of MRI-derived
301 subcortical structures in a large sample, leveraging diverse bioinformatic resources to
302 validation and follow-up our findings. Our analyses indicate that the variability of
303 evolutionarily old subcortical volumes of humans is moderately to strongly heritable, and
304 that their genetic variation is also strongly conserved across different species. The majority
305 of the variants identified in this analysis point to genes involved in neurodevelopment,
306 regulation of neuronal apoptotic processes, synaptic signaling, axonal transport,
307 inflammation/immunity, and susceptibility to neurological disorders. We show that the
308 genetic architecture of subcortical volumes overlaps with that of anthropometric measures
309 and neuropsychiatric disorders. In summary, our findings greatly expand current

- 310 understanding of the genetic variation related to subcortical structures, which can help
- 311 identify novel biological pathways of relevance to human brain development and disease.

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315 **AUTHOR CONTRIBUTIONS**

316 CLS drafted the manuscript with contributions from HHHA, DPH, CCW, TVL, AAV, SE,
317 AKH, MWV, DJ, TGMVE, CDW, MJW, SEF, KAM, PJH, BF, HJG, ADJ, OLL, SDe, SEM, JMS, PMT,
318 SS, and MAI.

319 MS, NJ, LRY, TVL, GC, LA, MER, ADB, IK, MA, SA, SE, RRS, AKH, HJJ, AS, JB, MWV, AVW,
320 KW, NA, SH, ALG, PHL, SG, SLH, DK, LS, SML, IA, EW, DTG, JCI, LNV, RB, FC, DJ, OC, UKH, BSA,
321 CYC, AAA, MPB, AFM, SKM, PA, AJS, DCML, TYW, LSh, PGS, EJCdG, MT, KRVE, NJAVd, AMM,
322 JSR, NR, WH, MCVH, JBJK, LMOL, AHo, GH, MBa, SR, JJHo, ASi, NH, PRS, TWM, PMa, OGru,
323 NAG, JES, HLe, BM, DVR, IJD, RMB, IM, RK, HV, MJW, DvtE, MMN, SEF, ASB, KAM, NRS, DJH,
324 HJG, CMvD, JMW, CDe, PLDJ, and VG contributed to the preparation of data; CLS, HHHA,
325 DPH, MJK, JLS, MS, MSa, NJ, GVR, AVS, JCB, XJ, ML, EH, AT, SjvdL, JY, LRY, SL, KJY, GC, MER,
326 NJA, HJJ, AVW, SH, NMS, SG, DTG, JS, CYC, LMOL, QY, ATh, IOF, DvtE, CDe, and PLDJ
327 performed statistical analyses; and CLS, HHHA, CCW, MJK, TVL, SL, YH, KJY, JDE, QY, and
328 ADJ carried out downstream analyses.

329 SEM, JMS, PMT, SS, and MAI jointly supervised this work.

330 All authors reviewed the manuscript for intellectual content.

331 **COMPETING INTERESTS**

332 DPH is currently an employee at Genentech, Inc. DJ has received travel and speaker's
333 honoraria from Janssen-Cilag and research funding from DFG. RLB is a consultant for
334 Pfizer, Roche. PA is a scientific adviser for Genoscreen. TYW is a consultant & advisory
335 board member for Allergan, Bayer, Boehringer-Ingelheim, Genentech, Merck, Novartis,
336 Oxurion (formerly ThromboGenics), Roche; and is a co-founder of Plano and EyRis. AMM
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341 Association for the Advancement of Science and Elsevier; is a faculty member of the
342 Lundbeck International Neuroscience Foundation; and is a consultant for Boehringer
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518 **Figure 1. Heritability and Manhattan plot of genetic variants associated with subcortical brain volumes in the**
519 **European sample.**

520

521 **a.** Family-based heritability (h^2) estimates were performed with SOLAR in the Framingham Heart Study ($n = 895$) and the
522 Austrian Stroke Prevention-Family Study ($n = 370$). **b.** Combined Manhattan plot highlighting the most significant SNPs across
523 all subcortical structures (nucleus accumbens = 32,562; amygdala = 34,431; brainstem = 28,809; caudate = 37,741; pallidum =
524 34,413; putamen = 37,571; thalamus = 34,464). Variants are colored differently for each structure (see legend in a). Linear
525 regression models were adjusted for sex, age, age², total intracranial volume (CHARGE) or total brain volume (UKBB), and
526 population stratification. The solid horizontal line denotes genome-wide significance as set in this study after additional
527 Bonferroni correction for six independent traits ($P < 5 \times 10^{-8}/6 = 8.3 \times 10^{-9}$ for two-sided tests), the dashed horizontal line
528 denotes the classic genome-wide threshold of $P < 5 \times 10^{-8}$. Individual Manhattan plots can be found in the Supplementary note.

529 **Figure 2. Partitioning heritability by functional annotation categories.**

530

531 Analyses performed in the European sample (nucleus accumbens = 32,562; amygdala = 34,431; brainstem = 28,809; caudate =
532 37,741; pallidum = 34,413; putamen = 37,571; thalamus = 34,464). Plotted ellipses represent enrichment (proportion of h^2_g
533 explained / proportion of SNPs in a given functional category) for subcortical structures (y-axis) across 28 functional
534 categories (x-axis). The color bar indicates the magnitude and direction of enrichment. Starred pairs denote significant over-
535 representation after Bonferroni correction for 168 tests (28 annotation categories and 6 independent traits, $P < 3 \times 10^{-4}$).
536 DHS, DNase I hypersensitivity site; TSS, transcription start site.

537 **Figure 3. Protein-protein interaction network of 158 genes enriched for common variants influencing the volume of**
538 **subcortical structures.**

539

540 The edges represent protein-protein associations, where the edge color indicates the predicted mode of action (bright green,
541 activation; pink, posttranslational modification; red, inhibition; dark blue, binding, purple, catalysis; light blue, phenotype;
542 black, reaction; yellow, transcriptional regulation) and the edge shape the predicted action effects (arrow, positive, flat arrow,
543 negative; oval arrow, unspecified). Colored nodes represent the queried proteins and first shell of interactors (5 maximum),
544 whereas white nodes represent the second shell of interactors (5 maximum).

545 **Table 1.** Genome-wide association^a results for subcortical brain volumes in Europeans from CHARGE, ENIGMA, and the UKBB

SNP	Chr	Position	Function	A1/A2	A1 Freq.	Weight	Z-score	P ^b	Direction	I ²
Nucleus accumbens (n=32,562)										
rs9818981 ^c	3	190602087	intergenic	A/G	0.09	32,282	-6.23	4.70E-10	---	63.2
rs13107325	4	103188709	missense	T/C	0.06	32,283	6.15	7.74E-10	+++	76.2
rs11747514 ^c	5	65839259	intronic	T/G	0.22	32,562	-5.99	2.11E-09	---	0.0
rs868202 ^c	14	56195762	intergenic	T/C	0.56	32,562	5.90	3.55E-09	+++	0.0
Amygdala (n=34,431)										
rs11111293 ^c	12	102921296	intergenic	T/C	0.78	34,313	6.25	4.16E-10	+++	0.0
Brainstem (n=28,809)										
rs11111090	12	102326461	intergenic	A/C	0.52	28,809	10.79	3.70E-27	+++	0.0
rs10217651 ^c	9	118923652	intronic	A/G	0.39	28,809	9.78	1.40E-22	+++	0.0
rs869640 ^c	5	65015128	intronic	A/C	0.72	28,809	-8.40	4.36E-17	---	9.5
rs9398173 ^c	6	109000316	intronic	T/C	0.33	28,809	-7.95	1.80E-15	---	19.0
rs10792032 ^c	11	68984602	intergenic	A/G	0.49	28,648	7.75	9.08E-15	+++	39.4
rs4396983 ^c	4	15132604	intergenic	A/G	0.44	28,809	-7.02	2.27E-12	---	73.6
rs9322194 ^c	6	149920249	intronic	T/C	0.34	28,156	6.91	4.94E-12	+++	0.0
rs7972561 ^c	12	107139983	intronic	A/T	0.33	28,809	6.90	5.05E-12	+++	0.0

rs2206656 ^c	20	49130119	intronic	C/G	0.61	28,809	6.83	8.26E-12	+++	0.0
rs12479469 ^c	20	61145196	intergenic	A/G	0.33	25,822	-6.80	1.08E-11	---	65.6
rs4784256 ^c	16	52814559	intergenic	A/G	0.40	28,809	6.76	1.41E-11	+++	0.0
rs555925 ^c	3	193544359	intergenic	T/G	0.41	27,934	6.37	1.88E-10	+++	62.9
rs12313279 ^c	12	102846504	intronic	A/G	0.29	28,809	6.21	5.39E-10	+++	24.9
rs9505301 ^c	6	7887131	intronic	A/G	0.89	28,691	-6.05	1.41E-09	---	43.2
rs11684404 ^c	2	88924622	intronic	T/C	0.66	28,809	-5.95	2.73E-09	---	0.0
rs112178027 ^c	17	27564013	intergenic	T/C	0.17	28,809	-5.90	3.67E-09	---	0.0

Caudate nucleus (n=37,741)

rs3133370	11	92026446	intergenic	T/C	0.67	37,741	7.52	5.59E-14	+++	44.9
rs6060983 ^c	20	30420924	intronic	T/C	0.70	37,741	7.04	1.95E-12	+++	0.0
rs7040561 ^c	9	128528978	intronic	A/T	0.85	34,049	-6.26	3.84E-10	---	0.0
rs2817145 ^c	1	3133422	intronic	A/T	0.19	35,598	6.20	5.71E-10	+++	65.3
rs148470213 ^c	14	56193700	intergenic	T/C	0.54	29,429	6.18	6.48E-10	++?	0.0
rs1987471 ^c	16	28825866	intergenic	T/G	0.63	37,741	5.87	4.40E-09	+++	0.0
rs12445022 ^c	16	87575332	intergenic	A/G	0.33	37,741	5.87	4.45E-09	+++	0.0
rs55989340 ^c	14	100635222	intergenic	A/G	0.74	37,741	-5.86	4.62E-09	---	52.0
rs4888010 ^c	16	73895046	intergenic	A/G	0.47	37,741	5.86	4.67E-09	+++	74.9

rs35305377 ^c	7	99938955	intronic	A/G	0.55	33,429	-5.84	5.36E-09	---	47.8
Globus pallidus (n=34,413)										
rs2923447	8	42439848	intergenic	T/G	0.59	34,413	8.11	4.88E-16	+++	34.0
rs10129414 ^c	14	56193272	intergenic	A/G	0.44	34,413	-7.53	5.11E-14	---	0.0
rs196807 ^c	8	24682649	intergenic	A/G	0.18	34,295	6.44	1.17E-10	+++	21.1
rs10439607 ^c	20	30258541	intronic	A/G	0.30	34,413	-6.28	3.35E-10	---	0.0
rs4952211 ^c	2	32611512	intronic	T/C	0.43	34,252	-5.86	4.72E-09	---	61.9
rs12567402 ^c	1	21870213	intronic	T/C	0.33	34,214	5.81	6.17E-09	+++	0.0
Putamen (n=37,571)										
rs945270	14	56200473	intergenic	C/G	0.58	37,571	15.03	5.02E-51	+++	57.3
rs62098013	18	50863861	intronic	A/G	0.38	37,571	8.92	4.59E-19	+++	33.9
rs6087771	20	30306724	intronic	T/C	0.71	36,291	8.69	3.75E-18	+++	7.5
rs35200015 ^c	11	117383215	intronic	A/G	0.19	37,571	-8.19	2.51E-16	---	0.0
rs1432054	11	83260225	intronic	A/G	0.64	37,571	-7.94	2.10E-15	---	0.0
rs7902527 ^c	10	118715399	intronic	A/G	0.24	37,108	6.29	3.13E-10	+++	0.0
rs2244479 ^c	7	50738987	intronic	T/C	0.65	36,291	-5.92	3.17E-09	---	32.1
rs2410767 ^c	5	87705268	intronic	C/G	0.78	37,571	5.88	3.99E-09	+++	0.0
rs1187162 ^c	11	92011126	intergenic	T/C	0.42	37,571	5.84	5.14E-09	+++	0.0

Thalamus (n=34,464)											
rs12600720 ^c	17	78448640	intronic	C/G	0.69	33,023	6.25	4.06E-10	+++	0.0	
rs142461330 ^c	7	55012097	intergenic	T/C	0.92	34,185	-5.90	3.69E-09	---	0.0	

546 ^a Linear regression models are adjusted for sex, age, age², total intracranial volume (CHARGE) or total brain volume (UKBB),
 547 and population stratification.

548 ^b P-values are two-tailed. Significance was set at $P < 8.3 \times 10^{-9}$ after additional Bonferroni correction for six independent traits
 549 ($5 \times 10^{-8}/6$).

550 ^c Novel SNPs

551 Chr = chromosome; Freq. = frequency of the coded allele; A1 = coded allele; A2 = non-coded allele

552 **ONLINE METHODS**

553

554 ***Study population***

555 The present effort included 53 study samples from the Cohorts of Heart and Aging
556 Research in Genomic Epidemiology (CHARGE) consortium⁷⁴, the Enhancing Neuro Imaging
557 Genetics through Meta-Analysis (ENIGMA) consortium⁷⁵, and the United Kingdom Biobank
558 (UKBB)⁷⁶. Briefly, the CHARGE consortium is a collaboration of predominantly population-
559 based cohort studies investigating the genomics of age-related complex diseases, including
560 those of the brain (depts.washington.edu/chargeco/wiki/). The ENIGMA consortium brings
561 together various studies, approximately 75% of which are population-based, with the
562 remainder using case-control designs for various neuropsychiatric or neurodegenerative
563 diseases (enigma.ini.usc.edu/). The UKBB is a large-scale prospective epidemiological
564 study of over 500,000 individuals aged 40-69 years from the United Kingdom, established
565 to investigate the genetic and non-genetic determinants of middle and old age diseases
566 (www.ukbiobank.ac.uk/).

567 Our sample consisted of up to n=37,741 individuals of European ancestry. We
568 additionally included three generalization samples of African-Americans (up to n=769),
569 and two generalization samples of Asians (n=341). All participants have provided written
570 informed consent and participating studies obtained approval from their institutional
571 review board or equivalent organization. The institutional review boards of Boston
572 University and the University of Southern California, as well as the local ethics board of
573 Erasmus University Medical Center approved this study.

574 Exclusion criteria comprised prevalent dementia or stroke at the time of the MRI scan,
575 and when available, presence of large brain infarcts or other neurological pathologies seen
576 at the MRI that could substantially influence the measurement of brain volumes (e.g. brain
577 tumor, trauma). Individual studies applied the exclusion criteria prior to analyses.

578

579 ***Definition of phenotypes***

580 Our study investigated the volumes of seven subcortical structures: nucleus accumbens,
581 amygdala, brainstem, caudate nucleus, globus pallidus, putamen, and thalamus. These
582 phenotypes were defined as the mean volume (in cm³) of the left and right hemispheres,
583 with the exception if the brainstem that was simply defined as total volume (in cm³). Each
584 study contributed magnetic resonance imaging (MRI) data obtained using diverse
585 scanners, field strengths, and acquisition protocols. The estimation of volumes for the
586 seven subcortical brain structures and total intracranial volume was generated by freely
587 available and in-house segmentation methods previously described and validated.
588 Summary statistics for subcortical brain volumes in CHARGE study samples are presented
589 in Supplementary Table 3, and the study-specific MRI protocols and software are described
590 in Supplementary Table 5. We have recently published results describing the genetic
591 variation associated with hippocampal volumes²⁰, and therefore, we have not included that
592 brain structure in this report.

593

594 ***Genotyping***

595 Genotyping was performed using a variety of commercial arrays across the
596 participating studies. Study samples and genetic variants underwent similar quality control

597 procedures based on genetic homogeneity, call rate, minor allele frequency (MAF), and
598 Hardy-Weinberg Equilibrium. Good quality variants were used as input for imputation to
599 the 1000 Genomes Project (phase 1, version 3) reference panel¹⁶, or the Haplotype
600 Reference Consortium (HRC, version 1.1)¹⁷ in the UKBB, using validated software packages.
601 A detailed description of the genotyping and quality control carried by each study is
602 described in Supplementary Table 6.

603

604 ***Heritability***

605 Heritability of subcortical brain volumes was estimated in the Framingham Heart Study
606 (FHS)⁷⁷ and the Austrian Stroke Prevention Study Family Study (ASPS Fam)⁷⁸, two
607 population-based cohorts with family structure. We used SOLAR⁷⁹ to determine the ratio of
608 the genetic variance to the phenotypic variance, including variance component models that
609 were adjusted for age, sex, total intracranial volume, as well as age squared and principal
610 components if required, in the same way it is described for the genome-wide association
611 (GWA) analysis. We also estimated the variance of subcortical structures explained by SNPs
612 in a sample of n=3,486 unrelated participants from the Rotterdam Study using GCTA⁸⁰, and
613 additionally in the full European sample using LDSC regression methods⁸¹. Supplementary
614 Table 4 provides family- and SNP-based heritabilities for subcortical structures.

615

616 ***Genome-wide associations and meta-analysis***

617 In CHARGE and ENIGMA, each study undertook a GWA analysis on the volumes of seven
618 MRI subcortical brain structures (or those that were available to each study) according to a
619 common predefined analysis plan. Studies including unrelated participants performed

620 linear regression analyses, whereas those including related participants conducted linear
621 mixed models to account for familial relationships. Models assumed additive genetic effects
622 and were adjusted for age, sex, total intracranial volume and, if applicable, they were
623 additionally adjusted for age², principal components to account for population
624 stratification, psychiatric diagnosis (ENIGMA cohorts), and study site. Individual studies
625 shared summary statistics to a centralized, secured computing space. Analysis in the UKBB
626 sample followed a similar approach in n=8,312 unrelated participants although the genetic
627 data used for these analyses uses only those variants imputed using the HRC¹⁷ reference
628 panel. As the data released by the UKBB did not include total intracranial volume, linear
629 regression models in this sample are adjusted for age, age², sex, *total brain volume*, and
630 principal components. We used LDSC methods⁸¹ to investigate the genetic correlations for
631 all subcortical structures between the CHARGE-ENIGMA and the UKBB. There was no
632 evidence suggesting differences in the genetic architecture of both samples.

633 Prior to meta-analysis, we performed quality control at the study-level summary
634 statistics using a series of quality checks implemented in EasyQC⁸². Filters were set to
635 remove SNPs with poor imputation ($R^2 < 0.5$), rare (MAF < 0.1%), or with an effective allele
636 count ($2 \times \text{MAF} \times \text{study sample size} \times \text{imputation quality}$) < 20. Finally, we only considered
637 variants present in at least 70% of the total European sample for each structure.

638 Fixed-effects meta-analyses weighting for sample size were performed using METAL¹⁸,
639 given that not all samples used the same methods for acquisition and post-processing of
640 brain images. We used the LD score regression intercept to correct for population
641 stratification and cryptic relatedness⁸¹. Quantile and Manhattan plots are presented for
642 each subcortical structure in Supplementary Figure 1. To correct for multiple comparisons

643 across our seven traits, we calculated the Pearson's correlation among subcortical
644 structures adjusting for age, sex and intracranial volume in n=4,459 participants from the
645 Rotterdam Study. After 1,000 permutations, the resulting number of independent traits
646 was of six, leading to the definition of a significant threshold as $P < (5 \times 10^{-8}/6) = 8.3 \times 10^{-9}$.
647 To select our top independent SNPs in the European meta-analysis, we ran a multi-SNP-
648 based conditional & joint association analysis (GCTA-COJO)⁸⁰ using n=6,921 participants
649 from the Rotterdam Study as the reference sample. In secondary analyses, we looked for
650 the association of our index SNPs (the most significant variant in each locus) with the other
651 six subcortical structures.

652 We conducted separate meta-analyses by ancestry, and further performed a combined
653 meta-analysis including all samples. Forest plots were created to explore the contribution
654 of participating studies to each of the significant SNPs (Supplementary Figure 4). To assess
655 signal overlap with African-American and Asian samples, we first clumped variants with P
656 $< 1 \times 10^{-4}$ in the European sample, and then ran binomial sign tests for the correlation of
657 the direction of association across ethnic groups.

658

659 ***Functional annotations***

660 We used Locus Zoom¹⁹ based on the hg 19 UCSC Genome Browser assembly for the
661 visualization of the nearest genes within a ± 500 Kb genomic region. We also investigated
662 *cis* (1 Mb) expression quantitative trait loci (eQTL) and methylation QTL (meQTL) for our
663 index SNPs in post-mortem brains from the Religious Order Study and the Rush Memory
664 and Aging Project (ROSMAP). In ROSMAP, the dorsolateral prefrontal cortex (DLPFC) was
665 selected for initial multi-omics data generation, as it is relevant to multiple common

666 neuropathologies and cognitive phenotypes in the aging population⁸³. RNA was extracted
667 from the gray matter of DLPFC, and next-generation RNA sequencing (RNA-Seq) was done
668 on the Illumina HiSeq for samples with an RNA integrity score > 5 and a quantity threshold
669 > 5 ug, as previously described^{83,84}. We quantile-normalized the fragments per kilobase of
670 transcript per million fragments mapped (FPKM), correcting for batch effect with
671 Combat^{84,85}. These adjusted FPKM values were used for analysis. A subset of 407
672 participants had quality-controlled RNA-Seq data and were included in the eQTL analysis.

673 DNA methylation levels from the gray matter of DLPFC were measured using the
674 Illumina HumanMethylation450 BeadChip, and the measurements underwent QC
675 processing as previously described (i.e. detection $p < 0.01$ for all samples)⁸³, yielding 708
676 participants with 415,848 discrete CpG dinucleotide sites with methylation measurement.
677 Any missing methylation levels from any of quality-controlled CpG dinucleotide sites were
678 imputed using a k-nearest neighbor algorithm for $k = 100$ ⁸³. A subset of 488 participants in
679 our study had quality-controlled genome-wide methylation data and were included in the
680 *cis*-methylation QTL analysis. Finally, the associations between our index SNPs and CpG
681 sites were plotted along Roadmap Epigenomic chromatin states for ten brain tissues⁸⁶.

682 We further queried *cis* and *trans* eQTLs in non-brain and brain tissues from additional
683 eQTL repositories⁸⁷. We searched for proxies to our index SNPs with a $r^2 > 0.8$ using the
684 European population reference in rAggr (1000G, phase 1, Mar 2012), and then queried
685 index and proxy SNPs against eQTLs from diverse databases.⁸⁸ Blood cell related eQTL
686 studies included fresh lymphocytes and leukocytes, leukocyte samples in individuals with
687 Celiac disease, whole blood samples, lymphoblastoid cell lines (LCL) derived from
688 asthmatic children, HapMap LCL from 3 populations, a separate study on HapMap CEU LCL,

689 LCL population samples, neutrophils, CD19+ B cells, primary PHA-stimulated T cells, CD4+
690 T cells, peripheral blood monocytes, long non-coding RNAs in monocytes and CD14+
691 monocytes before and after stimulation with LPS or interferon-gamma, CD11+ dendritic
692 cells before and after *Mycobacterium tuberculosis* infection and a separate study of
693 dendritic cells before or after stimulation with lipopolysaccharide (LPS), influenza or
694 interferon-beta; micro-RNA QTLs, DNase-I QTLs, histone acetylation QTLs, and ribosomal
695 occupancy QTLs were also queried for LCL; splicing QTLs and micro-RNA QTLs were
696 queried in whole blood. Non-blood cell tissue eQTL searches included omental and
697 subcutaneous adipose, visceral fat stomach, endometrial carcinomas, ER+ and ER- breast
698 cancer tumor cells, liver, osteoblasts, intestine and normal and cancerous colon, skeletal
699 muscle, breast tissue (normal and cancer), lung, skin, primary fibroblasts, sputum,
700 pancreatic islet cells, prostate, rectal mucosa, arterial wall and heart tissue from left
701 ventricles and left and right atria. Micro-RNA QTLs were also queried for gluteal and
702 abdominal adipose and liver. Methylation QTLs were queried in pancreatic islet cells.
703 Further mRNA and micro-RNA QTLs were queried from ER+ invasive breast cancer
704 samples, colon-, kidney renal clear-, lung- and prostate-adenocarcinoma samples. Brain
705 eQTL studies included brain cortex, cerebellar cortex, cerebellum, frontal cortex, gliomas,
706 hippocampus, inferior olivary nucleus (from medulla), intralobular white matter, occipital
707 cortex, parietal lobe, pons, pre-frontal cortex, putamen (at the level of anterior
708 commissure), substantia nigra, temporal cortex, thalamus and visual cortex. eQTL data
709 was integrated from online sources including ScanDB⁸⁹, the GTEx Portal⁹⁰, and the
710 Pritchard Lab⁹¹. Cerebellum, parietal lobe and liver eQTL data was downloaded from
711 ScanDB and cis-eQTL were limited to those with $P < 1.0 \times 10^{-6}$ and trans-eQTLs with $P < 5.0$

712 $\times 10^{-8}$. Results for GTEx Analysis V6 for 48 tissues were downloaded from the GTEx Portal
713 (www.gtexportal.org). For all gene-level eQTL, if at least 1 SNP passed the tissue-specific
714 empirical threshold in GTEx, the best SNP for that eQTL was always retained.

715

716 ***Associations of cognition and neuropathology phenotypes with gene expression in***
717 ***brain***

718 We further related cognitive function and neuropathological findings to the expression
719 of the 199 gene set influencing subcortical volumes in 508 brains from the ROSMAP
720 samples.

721 Briefly, brain autopsies were performed as previously described and each brain was
722 inspected for common pathologies relating to loss of cognition in aging populations^{92,93}. In
723 this report, we included: neurofibrillary tangles, neuritic plaques, β -amyloid load, tau
724 density, hippocampal sclerosis, Lewy bodies and neuronal loss in substantia nigra.
725 Neurofibrillary tangles and neuritic plaques were visualized by modified Bielschowsky
726 silver stain, then counted and scaled in five brain regions: mid-frontal, temporal, inferior
727 parietal, entorhinal cortex, and hippocampus CA1. Composite scores for each of these three
728 pathology types were derived by scaling the counts within each of the five regions, and
729 taking the square root of the average of the regional scaled values to account for their
730 positively skewed distribution⁹²⁻⁹⁴. β -amyloid load and tau tangle density were measured
731 by immunohistochemistry and square root transformed as previously described⁹⁵. Lewy
732 bodies were identified using immunohistochemistry and were further dichotomized as
733 present or absent based on the recommendations of the Report of the Consortium on DLB
734 International Workshop⁹⁶. Hippocampal sclerosis was recorded as either present or absent

735 as evaluated with H&E stain. Nigral neuronal loss was assessed in the substantia nigra in
736 the mid to rostral midbrain near or at the exit of the 3rd nerve using H&E stain and 6
737 micron sections using a semi-quantitative scale (0–3)⁹⁷.

738 Global cognition was computed as a composite score of 19 (ROS) and 17 (MAP)
739 cognitive tests performed at annual evaluations including five cognitive domains: episodic
740 memory, semantic memory, working memory, perceptual speed, and visuospatial
741 ability^{92,93}. From these scores, we created normalized summary measures to limit the
742 influence of outliers. We used global cognition proximate to death to derive cognitive
743 reserve. Separately, the residual slope of global cognitive change and the residual slopes of
744 cognitive change in the five cognitive domains were derived through general linear mixed
745 models, controlling for age at enrollment, sex, and education.

746

747 ***Phenotypic and genetic correlations***

748 We estimated the Pearson's partial phenotypic correlations among the volumes of
749 subcortical structures in 894 participants from the Framingham Heart Study. Similarly, to
750 the GWA, these analyses were corrected for the effects of sex, age, age², total intracranial
751 volume and PC1.

752 Genetic correlation analyses were performed using LDSC regression methods⁸¹. The
753 GWA meta-analysis results for the seven subcortical brain structures were correlated with
754 each other's, as well as with published GWA studies on the following traits: hippocampal
755 volume²⁰, intracranial volume²¹, white matter hyperintensities²², stroke subtypes²³, adult
756 height and body mass index²⁴, fat-free mass and whole-body water mass⁹⁸, Alzheimer's

757 disease²⁶, Parkinson's Disease²⁷, general cognitive function²⁵, bipolar disorder and
758 schizophrenia²⁸, and ADHD²⁹.

759

760 ***Look-up of functional orthologs in *Drosophila melanogaster****

761 For the cross-species assessment of gene-phenotype relationships in *Drosophila*, we
762 relied on a similar analytic approach as in prior work⁹⁹. Human genes were mapped to
763 corresponding *Drosophila* orthologs using DIOPT: *Drosophila* Integrated Ortholog
764 Prediction Tool (www.flyrnai.org/diopt)¹⁰⁰, which incorporates 14 distinct algorithms to
765 define orthology. Fly gene orthologs were defined based on a DIOPT score of 2 or greater,
766 indicating at least 2 algorithms were in agreement on the pairing. When more than one of
767 the fly ortholog was predicted, all such genes meeting this threshold were included in our
768 analyses. This resulted in a gene set consisting of 168 *Drosophila* homologs of human
769 candidate genes at subcortical volume susceptibility loci. The resulting 37 genes associated
770 with "neuroanatomy defective" phenotypes in *Drosophila* (22%) were annotated based on
771 the controlled vocabulary terms implemented in FlyBase (flybase.org/)¹⁰¹. Genes causing
772 "neuroanatomy defective" phenotypes in *Drosophila* include both loss- or gain-of-function
773 genetic manipulations of fly gene homologs. Loss-of-function studies included both
774 classical mutant alleles (e.g. point mutations, gene deletions, or transposon insertions) or
775 gene knockdown using RNA interference transgenic strains. Gain-of-function experiments
776 were based on tissue specific overexpression of the fly gene orthologs. The hypergeometric
777 overlap test was used to assess for enrichment of "neuroanatomy defective" phenotypes
778 among the conserved gene set.

779

780 Protein-protein interactions and network analysis

781 We used the human STRING database resource (string-db.org)³² for the exploration of
782 direct (physical) and indirect (functional) protein-protein interactions based on the gene
783 set derived from the GWA results and functional annotations (Supplementary Table 13).
784 The input parameters included a medium-confidence interaction scores (0.4) with first and
785 second shells of maximum 5 interactors. Finally, we generated a protein-protein
786 interaction network based on known and predicted interactions.

787

788 Partitioning heritability

789 Partitioned heritability was estimated with stratified LDSC methods³⁰. This method
790 partitions SNP heritability using GWAS summary results and accounting by LD. We used
791 the meta-analysis results from the European sample to partitioning SNPs by 28 functional
792 categories, including: coding, intron, promoter, 3'/5' UTRs, digital genomic footprint (DGF),
793 transcription factor binding sites, chromHMM and Segway annotations for six cell lines,
794 DNase I hypersensitivity sites (DHS), H3K4me1, H3K4me3 and H3K9ac marks, two sets of
795 H3K27ac marks, super-enhancers, conserved regions in mammals, and FANTOM5
796 enhancers. Significance was set at $P < (0.05/(28 \times 6)) = 3 \times 10^{-4}$.

797

798 Data availability

799 The genome-wide summary statistics that support the findings of this study will be made
800 available through the CHARGE dbGaP (accession number phs000930) and ENIGMA
801 (<http://enigma.ini.usc.edu/research/download-enigma-gwas-results>) websites.

802

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867 [Genome-wide analysis identifies variants associated with the volume of seven different sub-cortical](#)
868 [brain regions defined by magnetic resonance imaging. Implicated genes are involved in](#)
869 [neurodevelopmental and synaptic signaling pathways.](#)

870