Association of Peripheral Blood Pressure with Grey Matter Volume in 19- to 40-Year-Old Adults

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Research in Context

Evidence before this study

We searched PubMed for reports on associations between blood pressure (BP) and grey matter volumes (GMV) in young adults by use of the MeSH terms [hypertension OR blood pressure] AND [atrophy OR grey matter OR gray matter OR brain volume] and no language or date restrictions. We found a systematic review and meta-analysis from 2013 which identified 28 studies that investigated associations of higher BP with GMV across ages. In the majority of studies, higher BP or hypertension was associated with lower total or regional GMV. Qualitatively, these reductions were predominant in frontal and (medial) temporal lobes. The meta-analysis revealed consistent reductions in hippocampal volumes with high BP/hypertension across studies. However, none of the reports investigated BP-GMV associations in young adults, i.e. younger than 40 years of age.

Added value of this study

In this image-based meta-analysis of four previously unpublished cross-sectional studies that included 423 healthy young adults in total, resting BP ≥120/80 mmHg was associated with lower grey matter volume in several brain regions, including frontal, parietal and subcortical structures (including hippocampus). Our study suggests that subtle pressure-related brain alterations can be observed before 40 years of age and in ranges where BP is still considered “normal” by current guidelines for the management of hypertension.

Implications of all the available evidence

Our study is the first to show that BP-associated grey matter alterations emerge continuously across the range of BP and earlier in adulthood than previously assumed. Elevated BP is globally highly prevalent and an important risk factor for cerebrovascular disease and overall health loss. Our results suggest that treating hypertension or maintaining a lower BP in early adulthood might be essential for preventing the pathophysiological cascade of asymptomatic cerebrovascular disease to symptomatic end-organ damage, such as stroke and dementia.

In light of our results, large-scale prospective brain imaging studies should include young adults to investigate whether brain changes related to sub-hypertensive BP in early adulthood could serve as early biomarkers for subsequent development of cerebrovascular disease later in life. Such data would provide evidence for future recommendation guidelines for the management of elevated BP in young adults and for the prevention of cerebrovascular disease at older ages. Our results also speak in favor of considering individual BP levels as continuous measures – in addition to a categorical cut-off – which could facilitate the initiation of early preventive actions.

Summary

Background: Arterial hypertension (HTN) dramatically increases the risk for stroke and neurodegenerative disease, but signatures of macro- and microangiopathic brain damage are already visible in magnetic resonance imaging (MRI) of asymptomatic HTN patients. Blood pressure (BP) levels that initiate detrimental effects on brain tissue are still undefined. Their identification may be important for successful BP-management and prevention of subsequent cerebrovascular disease. Our objective was to test whether elevated BP relates to lower grey matter volume (GMV) in young adults who had not been diagnosed as hypertensive (≥140/90 mmHg) previously.

Methods: We related BP and GMV from structural 3 Tesla T1-weighted MRI of 423 healthy adults between 19-40 years (age=27.7±5.3 years, 177 women, systolic BP (SBP)=123.2±12.2 mmHg, diastolic BP (DBP)=73.4±8.5 mmHg). Data originated from four previously unpublished cross-sectional studies conducted in Leipzig, Germany. We performed voxel-based morphometry on each study separately and combined results in image-based meta-analyses (IBMA) to assess cumulative effects across studies. Resting BP was assigned to one of four categories: (1) SBP<120 mmHg and DBP<80 mmHg, (2) SBP 120-129 mmHg or DBP 80-84 mmHg, (3) SBP 130-139 mmHg or DBP 85-89 mmHg, (4) SBP≥140 mmHg or DBP≥90 mmHg.

Findings: IBMA yielded: (a) regional GMV decreased linearly as peripheral BP increased; (b) significantly decreased GMV with higher peripheral BP when comparing individuals in sub-hypertensive categories 3 and 2, respectively, to those in category 1; (c) lower BP-related GMV was found in regions including hippocampus, amygdala, thalamus, frontal and parietal structures (e.g. precuneus).

Interpretation: In young adults without previously diagnosed HTN, BP≥120/80 mmHg was associated with lower GMV in regions that have previously been related to GM decline in older individuals with manifest HTN. This suggests that subtle pressure-related brain

61 alterations might occur earlier in adulthood than previously assumed and already at sub-
62 hypertensive BP levels.

Introduction

Hypertension (HTN) is highly prevalent and the leading single risk factor for global burden of disease and overall health loss[1]. In 2015, the global prevalence of HTN, i.e. raised blood pressure (BP) at or above levels of systolic 140 or diastolic 90 mmHg was around 22%, affecting 1.13 billion adults worldwide[2]. It is expected that the global number of persons with HTN increases with population growth and aging[3].

HTN primarily damages peripheral and cerebral blood vessels, where chronically elevated BP initiates pathophysiological mechanisms (e.g. vascular stiffening, endothelial failure, and dysfunction of the blood-brain barrier) that result in structural and functional alterations of the vasculature and insidious brain damage[4].

The risk for symptomatic cerebrovascular disease (CVD, e.g. stroke and vascular dementia) dramatically increases with manifestation of HTN[4]. Midlife HTN is a major risk factor for cognitive decline in late-life and has been associated with risk for dementia, including late-onset Alzheimer's disease (AD)[4–6].

Importantly, HTN is also related to *asymptomatic* cerebrovascular disease, including sub-clinical functional[7,8] and structural[6–15] brain changes. HTN-related markers of asymptomatic structural brain damage include white matter (WM) hyperintensities, cortical microbleeds, microinfarcts, and brain atrophy[15], that can be evaluated in-vivo with neuroimaging methods like structural magnetic resonance imaging (MRI). Elevated BP has often been related to sub-clinical brain volume reductions in the medial temporal and frontal lobes[6,7,10–12,16]. Hippocampal volumes, in particular, have been consistently associated with HTN-related reductions[6,10,11,16]. Frontal and medial temporal regions have been proposed to be especially sensitive to effects of pulsation, hypoperfusion and ischemia, which often result from increasing pressure[4,16].

Furthermore, computational anatomy analyses have been used to detect subtle cerebral changes, such as microstructural WM alterations[14] or reductions in regional grey matter[6,12], in middle-aged and older adults with elevated BP. However, in addition to HTN, aging and

comorbid symptoms (e.g. obesity) also act on brain structure and can hardly be disentangled from effects of BP. In young, healthy adults, the influence of these confounds should be minimal, but studies that relate brain volumes to elevated BP in adults younger than 40 years are lacking. Preliminary evidence from 32 young, normotensive adults, showed that BP-reactivity correlated with lower amygdala volume[17].

Recent statements suggest that symptomatic clinical disease, as a consequence of elevated BP, could be prevented by avoiding primary BP elevations and sub-clinical target organ damage (including brain damage) in early adulthood and middle-age[3,4,18]. However, the impact of elevated BP on adult brains before the age of 40 is unclear. Moreover, while the overall burden of raised BP has been addressed by (rather arbitrarily) adjusting the diagnostic thresholds of HTN downwards, it is still unknown which BP levels initiate deleterious effects on cerebral tissue.

The aim of this study was to investigate if subtle structural brain changes occur in early adulthood (<40 years) at sub-hypertensive BP levels. We hypothesized that higher BP would relate to lower regional grey matter volume (GMV) and that this would predominantly affect frontal and medial temporal lobes, including amygdala and hippocampus.

Methods

We applied voxel-based morphometry[19,20] (VBM) to four previously unpublished independent datasets including young adults aged between 19-40 years without previous diagnosis of HTN or any other severe, chronic or acute disease. Results from each dataset were combined in image-based meta-analyses (IBMA) for well-powered, cumulative evaluation of findings across study differences (i.e. recruitment procedure, inclusion criteria and data acquisition, supplementary Table 1, supplementary Figure 1). Details on all methods can be found in supplementary methods.

Participants

We included cross-sectional data of 423 young participants from four samples. The samples were drawn from larger studies that were conducted in Leipzig, Germany, between 2010-2015: 1. Leipzig Study for Mind-Body-Emotion Interactions, 2. Neural Consequences of Stress Study, 3. Neuroanatomy and Connectivity Protocol[21], 4. Leipzig Research Centre for Civilization Diseases[22]. Inclusion criteria were age between 19-40 years, availability of high-resolution structural T1-weighted MRI and ≥1 BP measurements. Participants were excluded in case of previously diagnosed HTN, intake of antihypertensive drugs or severe diseases (supplementary Table 1, supplementary Figure 1). The studies were in agreement with the Declaration of Helsinki and approved by the ethics committee of the medical faculty at the University of Leipzig, Germany.

Data Processing and Statistical Analysis

Blood pressure classification

For statistical analyses, all available BP measurements per participant were averaged to one mean SBP and DBP, respectively (supplementary methods). Based on these averages, we categorized BP according to the European guidelines for the management of arterial hypertension[23]: *category 1* (SBP<120 mmHg and DBP<80 mmHg), *category 2* (SBP 120-129 mmHg or DBP 80-84 mmHg), *category 3* (SBP 130-139 mmHg or DBP 85-89 mmHg) and *category 4* (SBP≥140 mmHg or DBP≥90 mmHg).

Voxel-based morphometry (VBM): association of regional GMV and BP within each sample

For each of the four samples, 3 Tesla high-resolution T1-weighted 3-D whole-brain images (imaging parameters in supplementary Table 2) were processed using VBM and the diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) method[19,20] within SPM12. Voxel-wise general linear models (GLM) were performed to relate BP and GMV within each sample: we tested for a continuous relationship between GMV and SBP or DBP, in separate models, with a multiple linear regression *t*-contrast. The overall effect of BP category on GMV was tested with an Analysis of Variance (ANOVA) *F*-contrast. To assess differences in GMV between BP categories, the following pairwise *t*-comparisons were tested: (a) category 4 vs. category 1, (b) category 3 vs. category 1, (c) category 2 vs. category 1. All analyses included total intracranial volume (TIV), gender and age as covariates. The influence of body mass index (BMI) did not significantly contribute to the models and was thus not included as covariate in the analyses.

Image-based meta-analysis (IBMA): association of regional GMV and BP across samples

To evaluate cumulative results from all samples while considering their heterogeneities, we combined the VBM outcome of each sample in IBMA. Meta-analyses were performed on the unthresholded *t*-maps with SDM software using default parameters[24]. Statistical significance of mean effect size maps was evaluated according to validated thresholds of high meta-analytic sensitivity and specificity[24]: voxel threshold=$p<0.005$, peak height threshold=SDM-$Z>1.0$ and cluster extent threshold=$k\geq10$ voxels.

IBMA of regions of interest (ROI): association of regional GMV and BP across samples in hippocampus and amygdala

We performed IBMA within atlas-defined masks to test if regional bilateral hippocampal and amygdalar volumes related to SBP, DBP and BP categories, respectively. The statistical thresholds were defined as $p<0.05$, SDM-$Z>1.0$ and $k\geq1$ voxels.

Data Sharing

Results (i.e. unthresholded whole-brain statistical maps) from VBM analyses of each sample and from all IBMAs can be found online in the public repository NeuroVault for detailed inspection (http://neurovault.org/collections/FDWHFSYZ/). Raw data of samples 1-3 can be found at https://www.openfmri.org/dataset/ds000221/.

Results

Sample characteristics

The characteristics of the total sample by BP category are reported in Table 1. The total sample included 423 participants between 19-40 years of whom 177 were women (42%). Mean (SD) age was 27.7 (5.3) years. Gender, age, SBP, DBP, and body mass index differed significantly between BP categories (all $p<0.001$).

VBM: association of regional GMV and BP within each sample

Figure 1 shows differences in regional GMV between BP categories for each of the four samples at a voxel threshold of $p_{uncorrected}<0.001$ (ANOVA *F*-contrast). Results show significant clusters of various extents that were distributed heterogeneously between the samples. In sample 1, one cluster in the left posterior insula survived correction for multiple comparisons (cluster $p_{FamilyWiseError}<0.05$).

IBMA: association of regional GMV and BP across samples

Meta-analytic linear relations between GMV and BP

As expected, increases in systolic and diastolic BP were associated with lower GMV. Specifically, higher SBP related to lower GMV in right paracentral/cingulate areas, bilateral inferior frontal gyrus (IFG), bilateral sensorimotor cortex, bilateral superior temporal gyrus, bilateral cuneus cortex, and right thalamus (Figure 2A, Table 2). Increases in diastolic BP were related to lower GMV in bilateral anterior insula, frontal regions, right midcingulate cortex, bilateral inferior parietal areas, and right superior temporal gyrus (Figure 2B, Table 2).

Meta-analytic differences in regional GMV between BP categories

Meta-analytic results for category 4 (highest BP) compared to category 1 (lowest BP) yielded lower regional GMV in frontal, cerebellar, parietal, occipital, and cingulate regions (Figure 2C). Table 2 describes the specific regions with lower GMV, including bilateral IFG, right midcingulate cortex, and right precuneus.

We also compared GMV of individuals at sub-hypertensive levels (category 3 and 2, respectively) to GMV of individuals in category 1. Figure 2D shows meta-analysis results for the comparison between category 3 and category 1. Compared to category 1, category 3 was associated with lower GMV in bilateral IFG, sensorimotor cortices, bilateral middle temporal gyrus, right insula, right occipital regions, left parietal, bilateral thalamus, left anterior cingulate cortex, and left precuneus (Table 2).

Figure 2E illustrates brain regions that yielded meta-analytic GMV decreases for category 2 compared to category 1. These include left frontal regions, right inferior occipital gyrus, bilateral temporal regions, precuneus and inferior parietal regions (supramarginal and angular gyri), as well as midcingulate cortex (Table 2).

Meta-analytic differences in regional hippocampal and amygdalar volumes between BP categories

In this IBMA ROI comparison, SBP was negatively correlated with bilateral posterior medial hippocampal volume (Figure 3). DBP negatively correlated with left hippocampal volume and right anterior hippocampal volume. Furthermore, all higher BP categories were associated with lower regional hippocampal volume when compared to the lowest BP category 1 (Figure 3). Compared to category 1 and across samples, BP category 4 was predominantly associated with lower left medial posterior hippocampus volume and category 3 with lower bilateral posterior and left medial hippocampus volume. Smaller volume associated with category 2 was predominantly located in left lateral anterior hippocampus. Category 4 vs. category 1 and the correlation with SBP and DBP also yielded significantly lower regional volume in bilateral amygdala, respectively. Effect sizes highly varied across samples (Figure 3).

Discussion

In this image-based meta-analysis of four previously unpublished independent samples, we found that elevated, sub-hypertensive BP was correlated with lower GMV in several brain regions, including parietal, frontal, and subcortical structures in young adults (<40 years). These regions are consistent with the regional GM reductions observed in middle-aged and older individuals with HTN[6,7,10–12,16]. Our results show that BP-associated GM alterations emerge earlier in adulthood than previously assumed and continuously across the range of BP.

Specifically, we found that BP was associated with lower hippocampal volume. The hippocampal formation and surrounding structures are known to be affected by HTN[6,9–11,16] but also by neurodegenerative diseases, such as AD[25]. Raised midlife BP is a major risk factor for vascular dementia and has been hypothesized to interact with AD pathology[4,5]. Raised midlife BP has been associated with lower post-mortem brain weight, increased numbers of hippocampal neurofibrillary tangles, and increased numbers of hippocampal and cortical neuritic plaques[9]. In a meta-analytic evaluation of HTN-effects on total GMV and on hippocampal volume, volume reductions across studies were only consistently found for the hippocampus[16]. In line with these findings, our results showed that hippocampal volume was affected by higher BP also in a considerably younger sample. The effects in hippocampus, however, only exceeded statistical thresholds in ROI analyses, similar to previous reports of hippocampal volume reductions in older samples with manifest HTN that were all ROI-based[6,10,11,16].

We furthermore observed reductions in amygdalar volume and thalamic volume with increasing BP, notably already below levels which are currently regarded as hypertensive. Amygdalar and thalamic nuclei are substantially involved in BP regulation as they receive baroreceptor afferent signals via the brainstem and mesencephalic nuclei, relaying these signals to primary cortical regions of viscerosensory integration, such as anterior cingulate cortex and insula[26]. It has been shown that lower amygdalar volume correlates with increased BP-reactivity during cognitive demand among young normotensive adults[17].

Previous studies have reported lower thalamic volume in HTN[6], heart failure[27], asymptomatic carotid stenosis[28], and aging[29]. Higher systolic BP has also been related to higher mean diffusivity of white matter thalamic radiations[14]. Occurrence of neurofibrillary tangles in thalamus has been described in the earliest stages of AD neuropathology[25], which could be mediated by elevated BP as described above. Our results are in line with accumulating evidence of amygdalar and thalamic involvement in cardiovascular (dys-) regulation, but may also reflect early pathology in these regions.

Beyond subcortical structures, we found volume reductions in cortical regions: cingulate volume and insular volume were markedly reduced with increasing DBP. As noted above, these regions constitute primary cortical sites of afferent viscerosensory integration and modulate homeostasis via efferents to brainstem nuclei[26]. Lesions in cingulate cortex and insula result in altered cardiovascular regulation, increased sympathetic tone[30,31] and myocardial injury[32]. Both regions are also critical for the appraisal and regulation of emotion and stress[26]. Thus, structural alterations in these regions may contribute to insidious BP elevations via sympathetic pathways.

Frontal and parietal volumes were affected in all our statistical comparisons. The precuneus cortex, especially, was associated with lower GMV in BP categories 4, 3, and 2 compared to category 1. Inferior parietal and precuneus cortex, in addition to medial temporal structures, have been described as AD-signature regions, where cortical thinning can be observed years before clinical symptoms arise[33]. HTN is a risk factor for vascular dementia and AD and increasing BP has been shown to predict volume reductions in AD-signature regions longitudinally[6]. In the same study, BP also predicted volume loss in other brain regions, such as frontal lobe and subcortical gray matter[6]. Similarly, albeit cross-sectionally, our results indicate BP-related GMV decreases in *specific* regions, such as hippocampal, frontal and AD-related regions which have been suggested to be especially vulnerable to vascular and neurodegenerative changes[6,7,9–12,16,33]. Evaluating our results overall, we found GMV reductions in all major brain lobes which additionally hints to a *diffuse* effect of vascular

damage on brain tissue. Some previous studies did not find relations between HTN and brain volume reductions, but associated HTN with other forms of structural or functional brain damage, such as white matter injury[34] or reduced cerebral perfusion[35].

A key aspect of diverging results is the heterogeneity of methods used to assess brain volumes. Earlier investigations of BP effects on brain tissues have applied manual or automated volumetric methods to quantify total brain volumes in pre-selected ROIs[10,11,13]. The focus of this study was to employ computational anatomy methods to assess *regional GM differences across the whole brain*. We found significant differences between BP groups using VBM but not in the analysis of total brain volumes (see supplementary methods and results). This supports the view that VBM is a sensitive measure to quantify regional morphological differences[36] which might be undetected from the analysis of total brain volumes alone. In addition, we employed IBMA which results in effects that are consistent across studies and that may otherwise be neglected at sub-threshold. Investigating effects of BP on regional vs. total brain volumes at all stages of health and disease thus warrants further research with standardized methods to identify neuropathological mechanisms.

The causes of brain volume loss in HTN involve complex interactions of different pathophysiological mechanisms that still need to be fully elucidated and cannot be addressed with our data. It is assumed that vascular stiffness, endothelial failure and a dysfunctional blood-brain barrier are precursors of cerebral small and large vessel disease that reduce cerebral blood flow, disturb autoregulatory adjustment and decrease vasomotor reactivity, which may impair perivascular central nervous waste clearance systems[4]. Consequently, demyelination, apoptosis and intoxication of neurons and glial cells, as well as grey and white matter necrosis accumulate and can be observed with neuroimaging on a macroscopic scale. GMV reductions assessed by VBM, as reported in our study, can thus arise from neuronal loss, but also from alterations of glial cells or composition of microstructural or metabolic tissue properties[37]. Our findings point to an early effect of such mechanisms on GM integrity which is present in the absence of overt disease, such as HTN,

and in young age. Indicators of early atherosclerosis in major peripheral arteries can already be detected in youth[38]. Recently, arterial stiffness has also been associated with WM and GM alterations among adults between 24 and 76 years of age[39]. Thus, already early and subtle vascular changes, deficient cerebral perfusion and impaired perivascular clearance systems may initiate and sustain neuropathology from early to late adulthood.

The cross-sectional design of our four study samples limits the interpretation frame for the results presented. Causality between BP and brain damage cannot be assessed with these data, but is crucial for implications of early signs of cerebrovascular disease. Furthermore, the study samples differed regarding recruitment, gender distribution, sample size, prevalence of high BP, and data acquisition methods (BP and MRI) which might not represent the general population or standard acquisition protocols (e.g. only one BP measurement in sample 3). However, by combining the samples in IBMA, we addressed this limitation and accounted for within and between sample heterogeneity and evaluated effects cumulatively. Moreover, this approach enabled us to investigate the expected small effects of BP-related GM alterations in a well-powered total sample of over 400 young adults. HTN is also the most important risk factor for WM damage[4,13] and sub-clinical WM injury in relation to elevated BP levels has recently been reported in 19- to 63-year-old adults[14]. As our study included only GM measures, we cannot assess mediating effects of WM injury on GMV differences. However, we did not observe any significant differences in Fazekas scores for WM lesions between BP categories.

For the first time, we show that BP-related brain alterations may occur in early adulthood and at BP levels below current thresholds for manifest HTN. Contrary to assumptions that BP-related brain damage arises over years of manifest disease our data suggest that subtle pressure-related GM alterations can be observed in young adults without previously diagnosed HTN. In light of our results, large-scale cohort studies should investigate whether sub-hypertensive BP and related brain changes in early adulthood increase the risk for subsequent development of CVD later in life. Gaining insights whether and how the brain is

globally affected by vascular changes or if these are specific to susceptible regions could help identifying neuroimaging biomarkers for the earliest stages of CVD. Such data would provide evidence for future guidelines to formulate informed recommendations for BP-management in young adults, which are critical for the prevention of CVD. Lifestyle interventions and neurobehavioral therapy have recently been suggested to benefit CVD prevention[18]. Our results highlight the importance of taking BP levels as a continuous measure into consideration which could help initiate such early preventive measures.

Author Contributions

Study concept and design: Schaare, Villringer.

Statistical analysis: Schaare.

Acquisition or interpretation of data: All authors.

Drafting of the manuscript: Schaare, Villringer.

Critical revision of the manuscript: All authors.

Declaration of Interests

We have no competing interests.

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References

1. Forouzanfar MH, Afshin A, Alexander LT, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1659-1724. doi:10.1016/S0140-6736(16)31679-8.

2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet*. 2016;389(10064):634-647. doi:10.1016/S0140-6736(16)31919-5.

3. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *Lancet*. 2016;388(10060):2665-2712. doi:10.1016/S0140-6736(16)31134-5.

4. Iadecola C, Yaffe K, Biller J, et al. Impact of hypertension on cognitive function : a scientific statement from the American Heart Association. *Hypertension*. 2016;68:e67–e94. doi:10.1161/HYP.0000000000000053.

5. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurol*. 2014;13(8):788-794. doi:10.1016/S1474-4422(14)70136-X.

6. Power MC, Schneider ALC, Wruck L, et al. Life-course blood pressure in relation to brain volumes. *Alzheimer's Dement*. 2016;12(8):890-899. doi:10.1016/j.jalz.2016.03.012.

7. Hajjar I, Zhao P, Alsop D, et al. Association of blood pressure elevation and nocturnal dipping with brain atrophy, perfusion and functional measures in stroke and nonstroke individuals. *Am J Hypertens*. 2010;23(1):17-23. doi:10.1038/ajh.2009.187.

8. Launer LJ, Lewis CE, Schreiner PJ, et al. Vascular factors and multiple measures of early brain health: CARDIA brain MRI study. Ikram MA, ed. *PLoS One*. 2015;10(3):e0122138. doi:10.1371/journal.pone.0122138.

9. Petrovitch H, White LR, Izmirilian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. *Neurobiol Aging*. 2000;21(1):57-62. doi:10.1016/S0197-4580(00)00106-8.

10. den Heijer T, Launer LJ, Prins ND, et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology*. 2005;64(2):263-267. doi:10.1212/01.WNL.0000149641.55751.2E.

11. Raz N, Lindenberger U, Rodrigue KM, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex*. 2005;15(11):1676-1689. doi:10.1093/cercor/bhi044.

12. Leritz EC, Salat DH, Williams VJ, et al. Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. *Neuroimage*. 2011;54(4):2659-2671. doi:10.1016/j.neuroimage.2010.10.050.

13. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77(5):461-468. doi:10.1212/WNL.0b013e318227b227.

14. Maillard P, Seshadri S, Beiser A, et al. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. *Lancet Neurol*. 2012;11(12):1039-1047. doi:10.1016/S1474-4422(12)70241-7.

15. Muller M, Sigurdsson S, Kjartansson O, et al. Joint effect of mid- and late-life blood pressure on the brain: the AGES-Reykjavik study. *Neurology*. 2014;82(24):2187-2195. doi:10.1212/WNL.0000000000000517.

16. Beauchet O, Celle S, Roche F, et al. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. *J Hypertens*. 2013;31(8):1502-1516. doi:10.1097/HJH.0b013e32836184b5.

17. Gianaros PJ, Sheu LK, Matthews K a, Jennings JR, Manuck SB, Hariri AR. Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *J Neurosci*. 2008;28(4):990-999. doi:10.1523/JNEUROSCI.3606-07.2008.

18. Grossman DC, Bibbins-Domingo K, Curry SJ, et al. Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Cardiovascular Risk Factors. *JAMA*. 2017;318(2):167. doi:10.1001/jama.2017.7171.

19. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage*. 2000;11(6 Pt 1):805-821. doi:10.1006/nimg.2000.0582.

20. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage*. 2007;38(1):95-113. doi:10.1016/j.neuroimage.2007.07.007.

21. Mendes N, Oligschlaeger S, Lauckner ME, et al. A functional connectome phenotyping dataset including cognitive state and personality measures. *bioRxiv*. 2017. http://www.biorxiv.org/content/early/2017/07/18/164764. Accessed July 19, 2017.

22. Loeffler M, Engel C, Ahnert P, et al. The LIFE-Adult-Study: objectives and design of a population-based cohort study with 10,000 deeply phenotyped adults in Germany. *BMC Public Health*. 2015;15:691. doi:10.1186/s12889-015-1983-z.

23. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;34(28):2159-2219. doi:10.1093/eurheartj/eht151.

24. Radua J, Mataix-Cols D, Phillips ML, et al. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *Eur Psychiatry*. 2012;27(8):605-611. doi:10.1016/j.eurpsy.2011.04.001.

25. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82:239-259. doi:10.1007/BF00308809.

26. Critchley HD, Harrison N a. Visceral influences on brain and behavior. *Neuron*. 2013;77(4):624-638. doi:10.1016/j.neuron.2013.02.008.

27. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. *J Appl Physiol*. 2003;95(2):677-684. doi:10.1152/japplphysiol.00101.2003.

28. Avelar WM, D'Abreu A, Coan AC, et al. Asymptomatic carotid stenosis is associated with gray and white matter damage. *Int J Stroke*. 2015;10(8):1197-1203. doi:10.1111/ijs.12574.

29. Lorio S, Lutti A, Kherif F, et al. Disentangling in vivo the effects of iron content and atrophy on the ageing human brain. *Neuroimage*. 2014;103:280-289. doi:10.1016/j.neuroimage.2014.09.044.

30. Critchley HD, Mathias CJ, Josephs O, et al. Human cingulate cortex and autonomic control: Converging neuroimaging and clinical evidence. *Brain*. 2003;126(10):2139-2152. doi:10.1093/brain/awg216.

31. Oppenheimer SM, Kedem G, Martin WM. Left-insular cortex lesions perturb cardiac autonomic tone in humans. *Clin Auton Res*. 1996;6(3):131-140. doi:10.1007/BF02281899.

32. Krause T, Werner K, Fiebach JB, et al. Stroke in right dorsal anterior insular cortex Is related to myocardial injury. *Ann Neurol*. 2017;81(4):502-511. doi:10.1002/ana.24906.

33. Dickerson BC, Stoub TR, Shah RC, et al. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology*. 2011;76(16):1395-1402. doi:10.1212/WNL.0b013e3182166e96.

34. Allan CL, Zsoldos E, Filippini N, et al. Lifetime hypertension as a predictor of brain structure in older adults: cohort study with a 28-year follow-up. *Br J Psychiatry*. 2015;206(4).

35. Muller M, van der Graaf Y, Visseren FL, Vlek AL, Mali WPt, Geerlings MI. Blood pressure, cerebral blood flow, and brain volumes. The SMART-MR study. *J Hypertens*. 2010;28(7):1498-1505. doi:10.1097/HJH.0b013e32833951ef.

36. Kennedy KM, Erickson KI, Rodrigue KM, et al. Age-related differences in regional brain volumes: A comparison of optimized voxel-based morphometry to manual volumetry. *Neurobiol Aging*. 2009;30(10):1657-1676. doi:10.1016/j.neurobiolaging.2007.12.020.

37. Tardif CL, Steele CJ, Lampe L, et al. Investigation of the confounding effects of vasculature and metabolism on computational anatomy studies. *Neuroimage*. 2017;149:233-243. doi:10.1016/j.neuroimage.2017.01.025.

38. Strong JP, Malcom GT, Mcmahan CA, et al. Prevalence and Extent of Atherosclerosis in Adolescents and Young Adults. *JAMA*. 1999;281(8):727-735. doi:10.1001/jama.281.8.727.

39. Maillard P, Mitchell GF, Himali JJ, et al. Effects of arterial stiffness on brain integrity in young adults from the framingham heart study. *Stroke*. 2016;47(4):1030-1036. doi:10.1161/STROKEAHA.116.012949.

Tables and Figures

Table 1 – Sample characteristics.

Characteristics of the total sample by blood pressure categories in means (standard deviations) for continuous variables or number of cases, n, (percentages) for categorical variables. Column *p* specifies significant results of comparisons between blood pressure categories: empty cells = $p>0.05$. Column *Pairwise comparisons* specifies significant post-hoc comparisons for: 2=category 1 vs. 2, 3=category 1 vs. 3, 4=category 1 vs. 4. ***= $p<0.001$, **=$p<0.01$, *=$p<0.05$. Definition of blood pressure categories: *category 1* (SBP<120 mmHg and DBP<80 mmHg), *category 2* (SBP 120-129 mmHg or DBP 80-84 mmHg), *category 3* (SBP 130-139 mmHg or DBP 85-89 mmHg) and *category 4* (SBP≥140 mmHg or DBP≥90 mmHg).

	Total		Category 1		Category 2		Category 3		Category 4			
	Mean (*standard deviation*) or n (%)										*p*	Pairwise comparisons
n	423	*100*	175	*41*	121	*29*	80	*19*	47	*11*		
Women	177	*42*	117	*67*	40	*33*	11	*14*	9	*19*	***	2***, 3***, 4***
Age (years)	27.66	*5.27*	27.61	*5.53*	27.30	*4.95*	28.01	*5.24*	28.21	*5.23*		
Min-Max	19-40		19-40		20-40		20-40		20-39			
Systolic Blood Pressure (SBP, mmHg)	123.2	*12.19*	111.91	*5.44*	123.99	*3.62*	134.57	*3.48*	143.56	*7.76*	***	2***, 3***, 4***
Diastolic Blood Pressure (DBP, mmHg)	73.38	*8.49*	67.67	*5.81*	73.64	*5.77*	78.79	*6.46*	84.75	*8.26*	***	2***, 3***, 4***
Body Mass Index (kg/m²)	23.48	*3.25*	22.60	*2.74*	23.45	*3.23*	24.22	*3.42*	25.59	*3.62*	***	2*, 3**, 4***
missing values	13	*3*	5	*3*	4	*3*	1	*1*	3	*6*		
Min-Max	17.96-36.93											
Smoking status												
non-smoker	273	*65*	113	*65*	78	*64*	53	*66*	29	*62*		
occasional smoker	57	*13*	23	*13*	17	*14*	13	*16*	4	*9*		
smoker	73	*17*	29	*17*	21	*17*	13	*16*	10	*21*		
missing values	20	*5*	10	*6*	5	*4*	1	*1*	4	*9*		
Fazekas score												
0	303	*72*	123	*70*	85	*70*	59	*74*	36	*77*		
1	72	*17*	39	*22*	16	*13*	10	*13*	7	*15*		
2	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*		
3	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*		

missing values	48	*11*	13	*7*	20	*17*	11	*14*	4	*9*
Total intracranial volume (ml)	1450.05	*137.39*	1400.49	*127.47*	1457.43	*142.07*	1508.05	*116.23*	1516.90	*126.29*
Grey matter volume (ml)	777.41	*88.69*	748.55	*79.50*	784.29	*90.41*	809.72	*87.36*	812.16	*86.47*
White matter volume (ml)	449.79	*55.74*	435.84	*53.56*	452.75	*55.93*	464.19	*53.34*	469.58	*55.52*
Cerebrospinal fluid volume (ml)	222.86	*56.60*	216.09	*54.57*	220.40	*59.53*	234.14	*54.14*	235.16	*57.34*
Hippocampal volume, left (ml)	3.90	*0.45*	3.77	*0.41*	3.93	*0.46*	4.06	*0.43*	4.09	*0.43*
Hippocampal volume, right (ml)	3.97	*0.43*	3.83	*0.40*	4.00	*0.44*	4.12	*0.40*	4.14	*0.39*
Amygdalar volume, left (ml)	1.68	*0.19*	1.62	*0.18*	1.68	*0.19*	1.75	*0.18*	1.75	*0.18*
Amygdalar volume, right (ml)	1.50	*0.16*	1.45	*0.15*	1.51	*0.17*	1.56	*0.16*	1.57	*0.15*

Table 2 – Image-based meta-analysis results of regional grey matter volume differences associated with blood pressure.

Image-based meta-analysis results of significant clusters yielding lower grey matter volume for the respective contrast of interest. Columns indicate cluster-specific MNI coordinates of peak voxels, meta-analytic SDM-*Z*-value, meta-analytic *p*-value, number of voxels in cluster and anatomical label of the peak voxel. Anatomical labels were assigned using SPM's Anatomy toolbox. Voxel threshold was set to $p<0.005$, peak height threshold was set to SDM-$Z>1.0$ and cluster extent threshold was set to $k\geq10$ voxels as recommended by [24]. Final voxel size was 2 x 2 x 2 mm^3. MNI: Montreal Neurological Institute. SDM: Seed-based *d* Mapping. SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

MNI coordinates (x, y, z)	SDM-*Z*	*P*-value	# Voxels	Peak Description
Negative Correlation with Systolic Blood Pressure				
8,-30,56	-3.859	0.000	288	Right paracentral lobule
-40,30,0	-3.590	0.000	49	Left inferior frontal gyrus (p. triangularis)
36,6,34	-3.394	0.000	16	Right inferior frontal gyrus (p. opercularis)
10,2,40	-3.325	0.001	45	Right midcingulate cortex
-58,-20,24	-3.290	0.001	146	Left postcentral gyrus
-52,-10,6	-3.268	0.001	78	Left superior temporal gyrus
48,32,10	-3.204	0.001	27	Right inferior frontal gyrus (p. triangularis)
48,0,48	-3.196	0.001	127	Right precentral gyrus
64,-42,12	-3.192	0.001	42	Right superior temporal gyrus
6,8,-18	-3.110	0.001	40	Right subgenual cingulate cortex
50,8,28	-3.045	0.002	26	Right inferior frontal gyrus (p. opercularis)
-8,-76,18	-3.019	0.002	27	Left cuneus cortex
8,-28,2	-2.977	0.002	45	Right thalamus
10,-68,26	-2.937	0.002	18	Right cuneus cortex
58,4,-8	-2.934	0.002	32	Right temporal pole
-28,10,60	-2.896	0.003	19	Left middle frontal gyrus
-52,-12,42	-2.860	0.003	10	Left postcentral gyrus
Negative Correlation with Diastolic Blood Pressure				
-36,26,6	-3.876	0.000	266	Left insula
-26,24,54	-3.820	0.000	62	Left middle frontal gyrus
4,-34,50	-3.545	0.000	246	Right midcingulate cortex
-60,-24,14	-3.462	0.000	90	Left supramarginal gyrus
-46,-26,48	-3.239	0.001	59	Left inferior parietal lobule
44,-44,50	-3.188	0.001	18	Right inferior parietal lobule
36,8,32	-3.180	0.001	25	Right inferior frontal gyrus (p. opercularis)
34,10,8	-3.139	0.001	100	Right insula
28,14,60	-3.069	0.001	12	Right superior frontal gyrus
62,-44,16	-2.991	0.002	35	Right superior temporal gyrus
-38,14,-20	-2.983	0.002	30	Left temporal pole
60,2,-12	-2.862	0.003	13	Right superior temporal gyrus
-38,40,32	-2.845	0.003	14	Left middle frontal gyrus
30,28,0	-2.796	0.003	14	Right insula
-36,8,10	-2.788	0.003	24	Left insula
-58,-46,30	-2.750	0.004	11	Left supramarginal gyrus
-34,32,32	-2.734	0.004	11	Left middle frontal gyrus
category 4 (SBP≥140 mmHg or DBP≥90 mmHg) < category 1 (SBP<120 mmHg and DBP<80 mmHg)				

-52,28,12	-3.473	0.000	107	Left inferior frontal gyrus (p. triangularis)
-48,-4,4	-3.322	0.000	93	Left rolandic operculum
18,-52,-48	-3.097	0.001	40	Right cerebellum, hemispheric lobule VIIIb
40,30,26	-3.093	0.001	10	Right inferior frontal gyrus (p. triangularis)
48,32,10	-3.064	0.001	48	Right inferior frontal gyrus (p. triangularis)
-38,48,-16	-3.014	0.001	40	Left inferior frontal gyrus (p. orbitalis)
-54,-12,42	-2.940	0.002	30	Left postcentral gyrus
-8,-76,18	-2.936	0.002	14	Left cuneus
-16,-36,-18	-2.872	0.002	24	Left cerebellum, hemispheric lobule V
12,-42,48	-2.854	0.002	11	Right midcingulate cortex
-12,-50,-56	-2.849	0.002	30	Left cerebellum, hemispheric lobule IX
10,-52,18	-2.836	0.002	21	Right precuneus
64,-44,14	-2.824	0.002	26	Right superior temporal gyrus
10,-66,28	-2.821	0.002	56	Right precuneus
6,-28,50	-2.792	0.003	16	Right midcingulate cortex
18,-54,22	-2.765	0.003	15	Right precuneus
category 3 (SBP 130-139 mmHg or DBP 85-89 mmHg) < category 1				
36,6,34	-3.474	0.000	179	Right inferior frontal gyrus (p. opercularis)
6,-28,54	-3.119	0.000	179	Right posterior-medial frontal gyrus
48,-50,20	-2.917	0.000	74	Right middle temporal gyrus
-60,-20,36	-2.857	0.000	205	Left postcentral gyrus
-40,30,2	-2.598	0.000	24	Left inferior frontal gyrus (p. triangularis)
36,8,-18	-2.523	0.001	123	N/A (Right insula)
42,-74,12	-2.454	0.001	25	Right middle occipital gyrus
-62,-42,28	-2.433	0.001	41	Left supramarginal gyrus
20,-32,6	-2.384	0.001	133	Right thalamus
-10,36,-6	-2.384	0.001	102	Left anterior cingulate cortex
28,-94,-4	-2.373	0.001	14	Right inferior occipital gyrus
-12,-32,0	-2.264	0.002	133	Left thalamus
-56,-64,16	-2.222	0.002	28	Left middle temporal gyrus
-40,8,30	-2.197	0.002	82	Left precentral gyrus
-12,-54,14	-2.187	0.002	20	Left precuneus
category 2 (SBP 120-129 mmHg or DBP 80-84 mmHg) < category 1				
-54,-10,14	-3.407	0.000	230	Left rolandic operculum
30,-96,-8	-3.290	0.000	102	Right inferior occipital gyrus
-34,-16,-30	-3.164	0.000	133	Left fusiform gyrus
-8,-54,22	-3.084	0.000	433	Left precuneus
54,-24,32	-2.968	0.000	31	Right supramarginal gyrus
-46,28,0	-2.942	0.000	41	Left inferior frontal gyrus (p. triangularis)
-64,-20,30	-2.939	0.000	227	Left postcentral gyrus
-62,-42,34	-2.876	0.000	68	Left supramarginal gyrus
-36,-64,42	-2.827	0.001	30	Left angular gyrus
18,-72,54	-2.804	0.001	40	Right superior parietal lobule
46,-74,12	-2.734	0.001	26	Right middle temporal gyrus
8,-18,46	-2.647	0.001	32	Right midcingulate cortex
56,-32,12	-2.470	0.002	52	Right superior temporal gyrus

28,-72,-38	-2.413	0.002	23	Right cerebellum, crus I
-62,-22,-30	-2.403	0.003	11	N/A (Left inferior temporal gyrus)

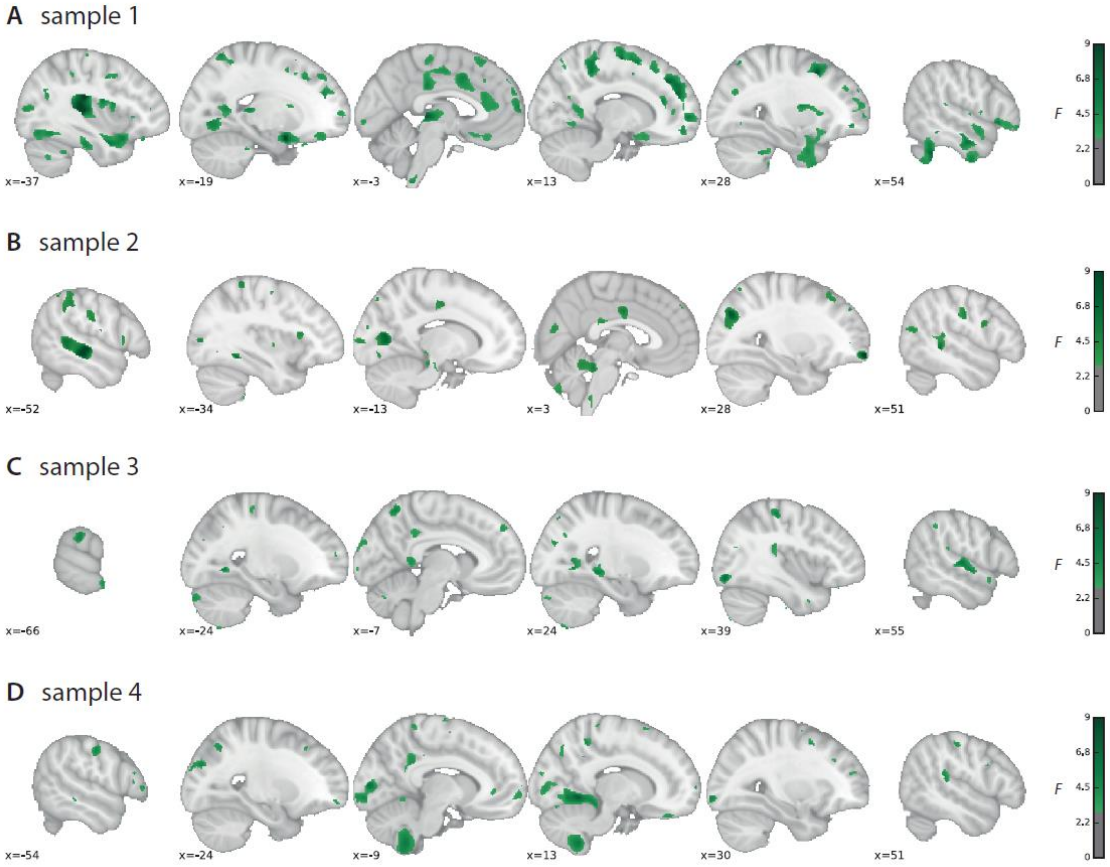


Figure 1 – Associations between grey matter volume and blood pressure within each sample. Sagittal views of VBM *F*-contrast results showing the overall effect of BP category on GM volume per sample. Each sample is represented in one row (**A-D**). Slice order runs from left hemisphere (left-hand side of the plot) to right hemisphere (right-hand side of the plot). Color bars represent *F*-values (uncorrected). Sample sizes: sample 1 n = 81; sample 2 n = 52; sample 3 n = 70; sample 4 n = 220. 3D-volumetric results of these analyses can be inspected in detail on http://neurovault.org/collections/FDWHFSYZ/. VBM: Voxel-based morphometry. BP: Blood Pressure. GM: Grey Matter.

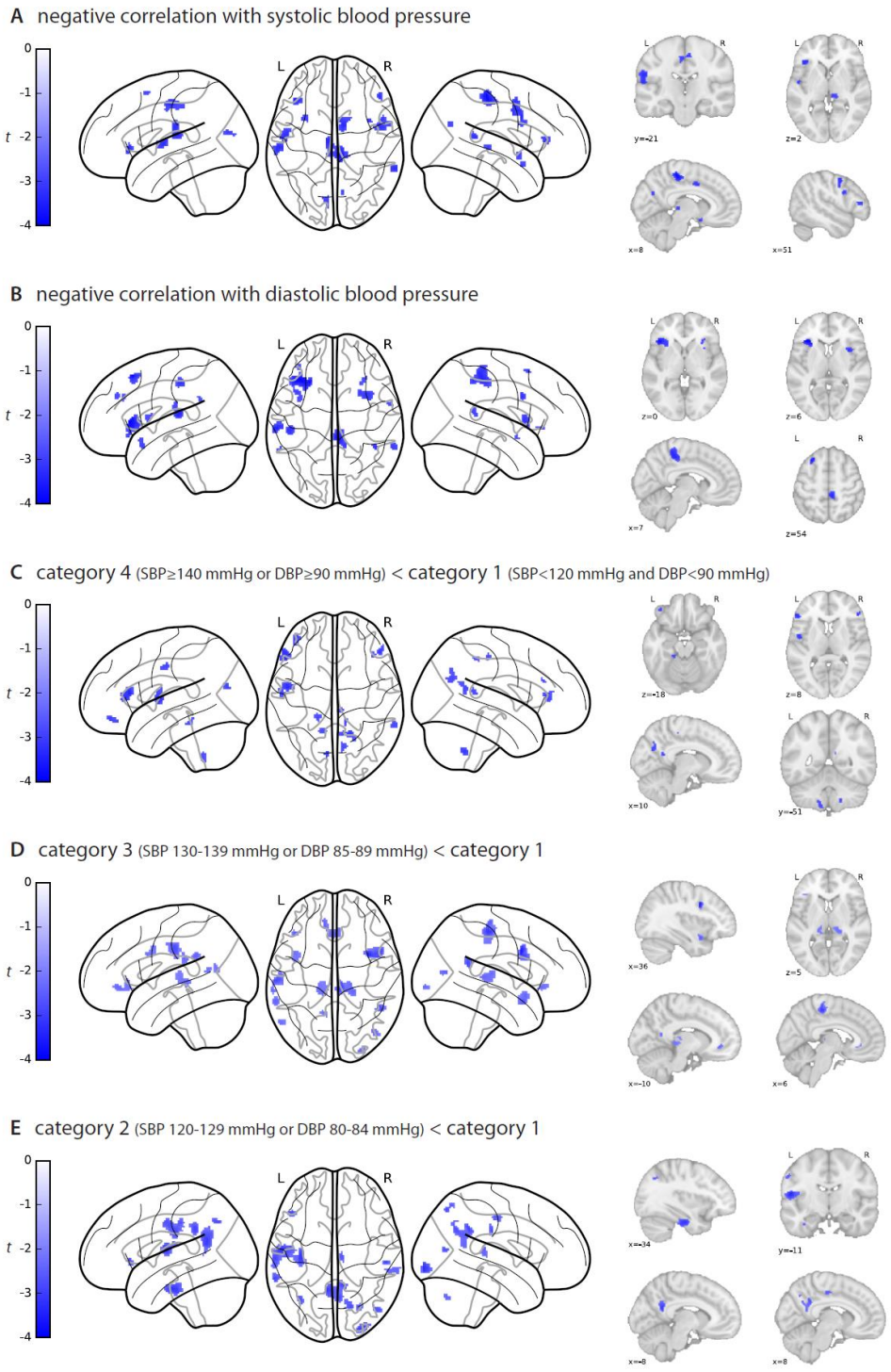


Figure 2 – Meta-analytic differences in grey matter volume between blood pressure categories. Glass brain views of image-based meta-analysis results for the blood pressure category contrasts of interest with relevant slice views below (**A-E**). **A** and **B** depict negative correlations between SBP/DBP and gray matter volume, respectively. Blue clusters indicate meta-analytic grey matter volume differences for the given contrast at a voxel threshold of $p<0.005$ with peak height threshold of SDM-$Z<-1.0$ and cluster extent threshold of $k\geq10$ (validated for high meta-analytic sensitivity and specificity[24]). Color bars represent SDM-*Z*-values. 3D-volumetric results of these analyses can be inspected in detail on http://neurovault.org/collections/FDWHFSYZ/.. SDM: Seed-based *d* Mapping. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. L: Left hemisphere. R: Right hemisphere.

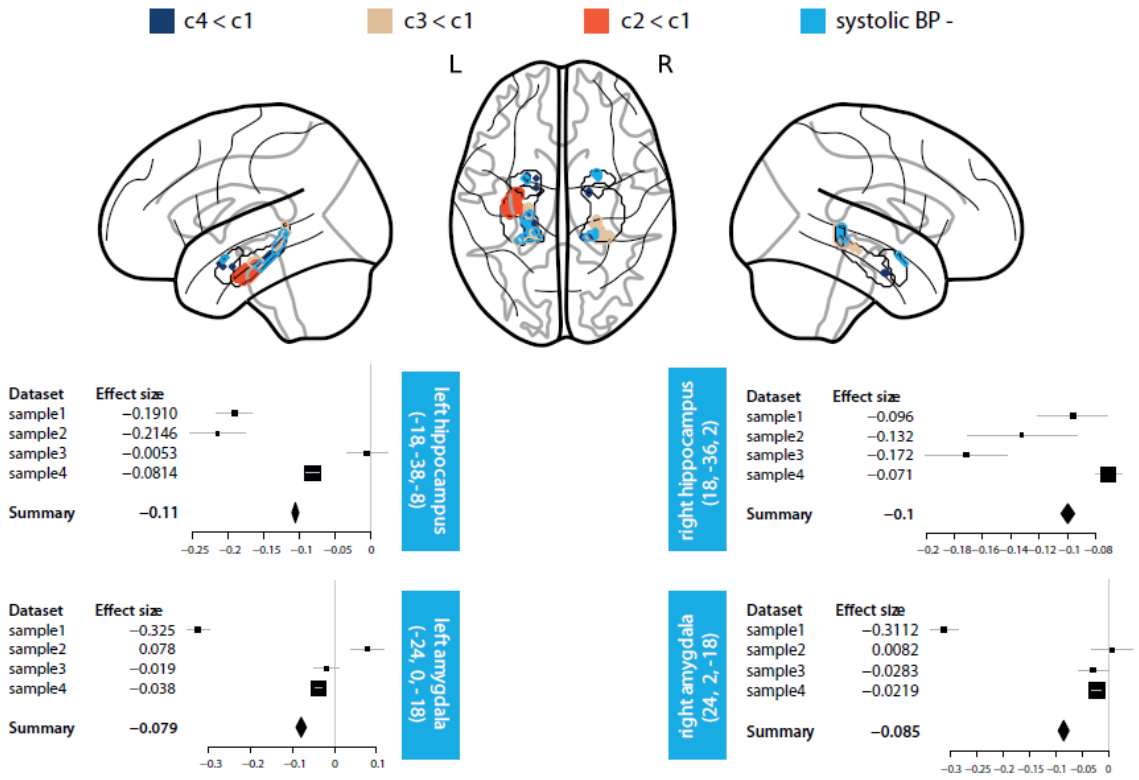


Figure 3 – Meta-analytic differences in volumes of hippocampus and amygdala (Region-of-Interest analysis). Upper part of plot: Glass brain views of image-based meta-analysis ROI results for the blood pressure category contrasts of interest in bilateral hippocampus and amygdala masks. Voxel threshold was set to $p<0.05$ with a peak height threshold of SDM-$Z<-1.0$ and a cluster extent threshold of $k\geq1$. Lower part of plot: Exemplary forest plots of sample-specific peak voxels' effect sizes for the negative correlation with SBP in the respective ROI. The box sizes are determined by each sample's weight. Light blue boxes include ROI name and MNI coordinates of the peak voxel. Definition of blood pressure categories: *category 1* (SBP<120 mmHg and DBP<80 mmHg), *category 2* (SBP 120-129 mmHg or DBP 80-84 mmHg), *category 3* (SBP 130-139 mmHg or DBP 85-89 mmHg) and *category 4* (SBP≥140 mmHg or DBP≥90 mmHg). ROI: Region of Interest. SDM: Seed-based *d* Mapping. MNI: Montreal Neurological Institute. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. L: Left hemisphere. R: Right hemisphere.

Supplementary Material

Methods

Blood pressure measurements

Systolic (SBP) and diastolic blood pressure (DBP) were measured using an automatic oscillometric blood pressure monitor (OMRON M500 (samples 1-3), 705IT (sample 4), OMRON Medizintechnik, Mannheim, Germany) after a seated resting period of 5 min. In sample 1, measurements were taken from participants' left arms on three separate occasions within two weeks. In sample 2, measurements were taken from participants' left arms on two separate occasions on the same day. In sample 3, blood pressure was measured once before participants underwent MRI. In sample 4, the procedure consisted of three consecutive blood pressure measurements, taken from the right arm in intervals of 3 minutes. In each sample, all available measurements per participant were averaged to one systolic and one diastolic blood pressure value. These averages were used for classification of BP.

Neuroimaging

MRI was performed at the same 3 Tesla MAGNETOM Verio Scanner (Siemens, Erlangen, Germany) for all studies with a 32-channel head coil. Whole-brain 3-dimensional T1-weighted volumes with a resolution of 1 mm isotropic were acquired for the assessment of brain structure. T1-weighted images in sample 4 were acquired with a standard MPRAGE protocol, while T1-weighted images in samples 1-3 resulted from an MP2RAGE protocol (sequence parameters in supplementary Table 2). Grey and white matter contrast are comparable for the two sequence protocols[1,2], but additional preprocessing steps were performed for MP2RAGE T1-weighted images (see below). Fluid-attenuated inversion recovery (FLAIR) images were acquired in all samples for radiological examination for incidental findings and for Fazekas scale ratings for white matter lesions (Table 1).

Additional preprocessing steps for MP2RAGE images

Before segmentation, T1-weighted images acquired with an MP2RAGE sequence were additionally masked to remove noise signal outside of the brain (following the procedure described in[2]): a binarized brain mask was created from the second inversion-contrast volume by setting voxels with intensities of less than 10% of the maximum signal to zero. Any holes in the mask were filled. For the final image, the mask was multiplied with the T1-weighted volume which eliminated background noise but preserved signals from the brain and other tissues. All of these steps were performed with tools in FSL 5.0[3] (www.fmrib.ox.ac.uk/fsl).

T1-weighted images from MP2RAGE are free of magnetic field inhomogeneity (they are also named *uniform*). Thus, a correction for this bias was omitted and only applied to MPRAGE images. Bias correction for MPRAGE images followed the default settings within SPM12's *segment* batch. All other processing steps were identical for the pulse sequences.

Voxel-based morphometry (VBM) and statistical analysis of regional GMV and BP within each sample

T1-weighted images were processed by using voxel-based morphometry (VBM) and the diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) method[4,5] within SPM12 (12.6685, Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm12/) running under Matlab 9.0.0 (R2016a, MathWorks, Natick, MA, USA). In short, processing of grey matter volume (GMV) probabilities included segmentation into tissue types, sample-specific DARTEL template creation, modulation of grey matter voxels to preserve tissue properties, normalization to MNI space, and 8 mm full-width-at-half-maximum Gaussian smoothing.

Voxel-wise statistical tests were performed in SPM12 to relate BP and GMV within each sample. We first performed a whole-brain analysis, testing for a continuous relationship between GMV and SBP and DBP, respectively, with a linear regression t-contrast. Next we tested for differences in GMV between BP categories. The general linear model for this whole-brain analysis included a factor for BP as variable of interest (levels: (1) category 4, (2) category 3, (3) category 2, (4) category 1). Within each sample, the overall effect of BP category on GMV was tested with an Analysis of Variance (ANOVA) *F*-contrast and the following *t*-contrasts tested pairwise comparisons of interest: (1) category 4 vs. category 1, (2) category 3 vs. category 1, (3) category 2 vs. category 1. All models included total intracranial volume (TIV), gender and age as covariates of no interest. Each *t*-contrast was tested in negative and positive direction (i.e. category A<category B and category A>category B). Data on all effects can be found online in the public repository NeuroVault[6] (http://neurovault.org/collections/FDWHFSYZ/).

Image-based meta-analysis (IBMA): association of regional GMV and BP across samples

To evaluate cumulative results from all samples, we combined the results of each sample in an image-based meta-analysis. The meta-analysis was performed with Anisotropic Effect-Size Signed Differential Mapping (AES-SDM) implemented in the SDM software package using default parameters[7] (http://www.sdmproject.com/, http://www.sdmproject.com/software/tutorial.pdf). For each sample and *t*-contrast, unthresholded whole-brain *t*-statistic maps were converted to Hedges' *g* effect size maps and variance maps. To assess weighted mean differences in grey matter across all samples, a meta-analytic model was set up for each voxel. Within this random-effects model, samples are weighted by their sample size, within-study variance and between-study heterogeneity. The result is a mean map of *z*-values which are quotients of the mean effect-sizes and their standard errors. Since these *z*-values are not normally distributed, null distributions were estimated empirically by Monte Carlo randomizations. Voxels in the mean map were randomly permuted within a software-implemented grey matter mask to create null distributions for the assessment of critical *z*-values. We applied 50 permutations, while statistical stability has been shown from 20 permutations on[7]. Statistical significance was evaluated according to validated thresholds of high meta-analytic sensitivity and specificity[7]: voxel threshold=$p<0.005$, peak height threshold=SDM-$Z>1.0$ and cluster extent threshold=$k\geq10$ voxels. Anatomy toolbox[8] (version 2.2 for SPM8) was used to automatically label significant clusters in all analyses. Nilearn[9] (version 0.2.6, https://nilearn.github.io/index.html) was used to visualize statistical brain maps.

IBMA of regions of interest (ROI): association of regional GMV and BP across samples in hippocampus and amygdala

With the meta-analysis approach we also tested if specific regions of interest (ROI) that included bilateral hippocampus and bilateral amygdala differed in their volumes related to SBP, DBP and between BP categories. Separate IBMAs were calculated within binary atlas-defined masks for bilateral hippocampus and bilateral amygdala that were retrieved from the latest available version of the Anatomy toolbox[8] (2.2 for SPM8). Peak voxels' effect sizes were extracted with SDM software's *Extract* option and plotted as forest plots (Figure 3) with R (3.2.3, R Core Team, 2015, Vienna, Austria; https://www.R-project.org/) and the package *rmeta* (2.16).

Volumetry: association of total brain volumes and BP within the pooled sample

In addition to VBM and IBMA, we explored if total brain volumes (average volume over all voxels within a region) differed between BP categories. Specifically, we tested if estimated total intracranial volume, total grey matter volume, total white matter volume (WMV), total cerebrospinal fluid volume (CSFV), total left and right hippocampal and amygdalar volume differed between BP categories. For these comparisons within the total sample, we defined correlation models (for SBP and DBP as independent variable, respectively) and ANOVA models for BP category as independent variable. The models included the respective volume as dependent variable, as well as TIV (where applicable), gender, age, and sample (where applicable) as covariates. We considered *p*-values<0.05 as significant. The analyses were performed with R (3.2.3, R Core Team, 2015, Vienna, Austria; https://www.R-project.org/).

Supplementary Results

Volumetry in pooled sample: association of total brain volumes and BP

None of the volumetric brain measures (TIV, total GMV, total, WMV, total CSFV, total hippocampal and total amygdalar volume) were significantly associated with SBP or DBP in the correlation models, nor with BP categories in the ANOVA models (all $p>0.05$, Table 1).

Supplementary Tables

Supplementary Table (eTable) 1 – List of exclusion criteria for each study from which the samples were drawn.

Study	Exclusion criteria

Leipzig Study for Mind-Body-Emotion Interactions (sample 1)	• Age <20 or 36-58 or >77
	• Self-reported diagnosis of hypertension without intake of antihypertensive medication
	• Any other cardiovascular disease (e.g. heart attack, congenital heart defect)
	• History of psychiatric diseases that required inpatient treatment for longer than 2 weeks within the last 10 years (e.g. psychosis, attempted suicide, post-traumatic stress disorder)
	• History of neurological disorders (incl. multiple sclerosis, stroke, epilepsy, brain tumor, meningoencephalitis, severe concussion)
	• History of malignant diseases
	• Intake of one of the following medications:
	  • Any centrally active drugs (including Hypericum perforatum)
	  • Beta- and alpha-blocker
	  • Cortisol
	  • Any chemotherapeutic or psychopharmacological medication
	• Positive drug anamnesis (extensive alcohol, MDMA, amphetamines, cocaine, opiates, benzodiazepine, cannabis)
	• Body Mass Index < 18 or > 30
	• Previous participation in any scientific study
	• Past or present student of Psychology
	• MRI exclusion criteria including:
	  • Any metallic implants, braces, non-removable piercings
	  • Tattoos
	  • Pregnancy
	  • Claustrophobia
	  • Tinnitus
	  • Surgical operation in the last 3 months

Neural Consequences of Stress Study (sample 2)	• Female gender
	• Age < 20 or >35
	• Smoking
	• Past or present student of Psychology
	• Excessive alcohol or drug consumption
	• Regular medication intake
	• History of cardiovascular or neurological diseases
	• Body Mass Index > 27
	• Positive drug anamnesis (extensive alcohol, MDMA, amphetamines, cocaine, opiates, benzodiazepine, cannabis)
	• Positive diagnosis in psychiatric screening of axis I disorders
	• Abnormalities in analysis of blood screening
	• MRI exclusion criteria including:
	  • Any metallic implants, braces, non-removable piercings
	  • Tattoos
	  • Pregnancy
	  • Claustrophobia
	  • Tinnitus
	  • Surgical operation in the last 3 months

Neuroanatomy and Connectivity Protocol[10] (sample 3)	• Age < 20 or >75
	• History of psychiatric diseases that required inpatient treatment for longer than 2 weeks within the last 10 years (e.g. psychosis, attempted suicide, post-traumatic stress disorder)
	• History of neurological disorders (incl. multiple sclerosis, stroke, epilepsy, brain tumor, meningoencephalitis, severe concussion)
	• History of malignant diseases
	• Intake of one of the following medications:
	  • Any centrally active drugs (including Hypericum perforatum)
	  • Beta-and alpha-blocker
	  • Cortisol
	  • Any chemotherapeutic or psychopharmacological medication
	• Positive drug anamnesis (extensive alcohol, MDMA, amphetamines, cocaine, opiates, benzodiazepine, cannabis)
	• Body Mass Index <18 or >30
	• Extensive testing experience at the Max-Planck-Institute or other academic institution
	• Past or present student of Psychology
	• MRI exclusion criteria:
	  • Any metallic implants, braces, non-removable piercings
	  • Tattoos
	  • Pregnancy
	  • Claustrophobia

	• Tinnitus • Surgical operation in the last 3 months

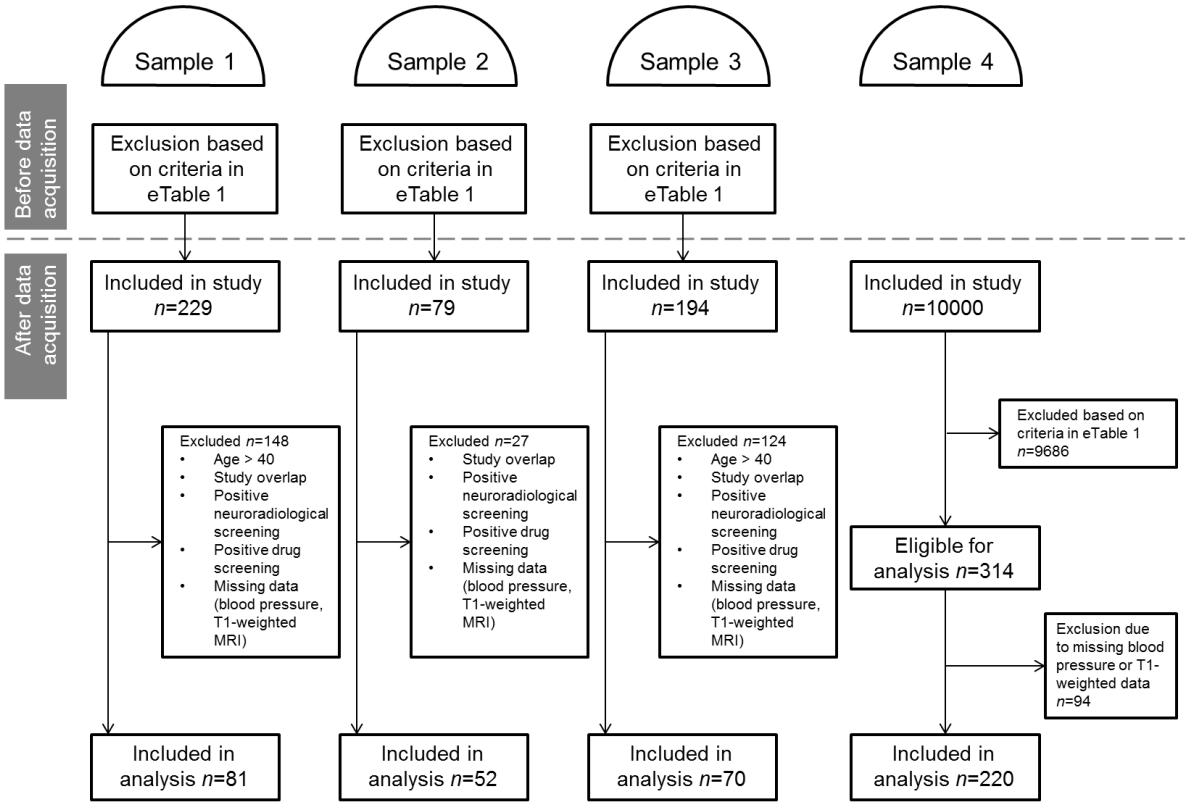
Leipzig Research Centre for Civilization Diseases[11] (sample 4)	• History of neurological disorders (incl. multiple sclerosis, stroke, epilepsy, parkinson's disease, brain tumor)
	• History of malignant diseases
	• History of depression
	• History of cardiovascular disease (e.g. myoinfarction, coronary heart disease, heart surgery, bypass, catheter, stent)
	• Hypertension
	• Intake of anti-hypertensive drugs
	• Intake of centrally-active drugs
	• Diabetes (Type I or II)
	• MRI exclusion criteria:
	  • Any metallic implants, braces, non-removable piercings
	  • Tattoos
	  • Pregnancy
	  • Claustrophobia
	  • Tinnitus
	  • Surgical operation in the last 3 months

Supplementary Table 2 - T1-weighted imaging protocols.

	MPRAGE (sample 4)	MP2RAGE (samples 1-3)
TI (ms)	900	1) 700, 2) 2500
TR (ms)	2300	5000
TE (ms)	2.98	2.92
FA (°)	9	1) 4, 2) 5
FOV (mm^3)	256 x 240 x 176	256 x 240 x 176
voxel size (mm^3)	1 x 1 x 1	1 x 1 x 1

TI: inversion time; TR: repetition time; TE: echo time; FA: flip angle; FOV: field of view

Supplementary Figures



Supplementary Figure 1 – Flow chart with inclusion procedure for the four samples. Sample 1: Leipzig Study for Mind-Body-Emotion Interactions. Sample 2: Neural Consequences of Stress Study. 3: Neuroanatomy and Connectivity Protocol[10]. 4: Leipzig Research Centre for Civilization Diseases[11].

References

1 Marques JP, Kober T, Krueger G, van der Zwaag W, Van de Moortele P-F, Gruetter R. MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. *Neuroimage* 2010; **49**: 1271–81.

2 Streitbürger D-P, Pampel A, Krueger G, *et al.* Impact of image acquisition on voxel-based-morphometry investigations of age-related structural brain changes. *Neuroimage* 2014; **87**: 170–82.

3 Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. *Neuroimage* 2012; **62**: 782–90.

4 Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage* 2000; **11**: 805–21.

5 Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007; **38**: 95–113.

6 Gorgolewski KJ, Varoquaux G, Rivera G, *et al.* NeuroVault.org: a web-based repository for collecting and sharing unthresholded statistical maps of the human brain. *Front Neuroinform* 2015; **9**: 8.

7 Radua J, Mataix-Cols D, Phillips ML, *et al.* A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *Eur Psychiatry* 2012; **27**: 605–11.

8 Eickhoff SB, Paus T, Caspers S, *et al.* Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *Neuroimage* 2007; **36**: 511–21.

9 Abraham A, Pedregosa F, Eickenberg M, *et al.* Machine learning for neuroimaging with scikit-learn. *Front Neuroinform* 2014; **8**: 14.

10 Mendes N, Oligschlaeger S, Lauckner ME, *et al.* A functional connectome phenotyping dataset including cognitive state and personality measures. *bioRxiv* 2017. http://www.biorxiv.org/content/early/2017/07/18/164764.

11 Loeffler M, Engel C, Ahnert P, *et al.* The LIFE-Adult-Study: objectives and design of a population-based cohort study with 10,000 deeply phenotyped adults in Germany. *BMC Public Health* 2015; **15**: 691.