Hypertension is associated with reduced hippocampal connectivity and impaired memory

Supplementary Material

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EBioMedicine (2020) 61: 103082

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Figure S1. Cross-validation with the HCP dataset for functional connectivity associated with high vs normal blood pressure. The threshold for high blood pressure was 130/85. **A) The differences of functional connectivity between the group with high blood pressure and the control group, with 726 participants.** The lower triangle matrix shows t values for the functional connectivity differences for the whole brain. Negative t values (blue) indicate reduced functional connectivity. The upper triangle matrix shows the significant links after FDR correction ($p<0.01$, threshold=4.6×10^{-4}). The regions are the AAL2 regions in the order shown in Table S1. **B) The AAL2 areas with significantly different functional connectivity between the high and control blood pressure groups.** The measure shown is the number of significant links FDR corrected, $p<0.01$, corresponding to an uncorrected $p=4.6\times10^{-4}$, using a threshold of 3 links per region.

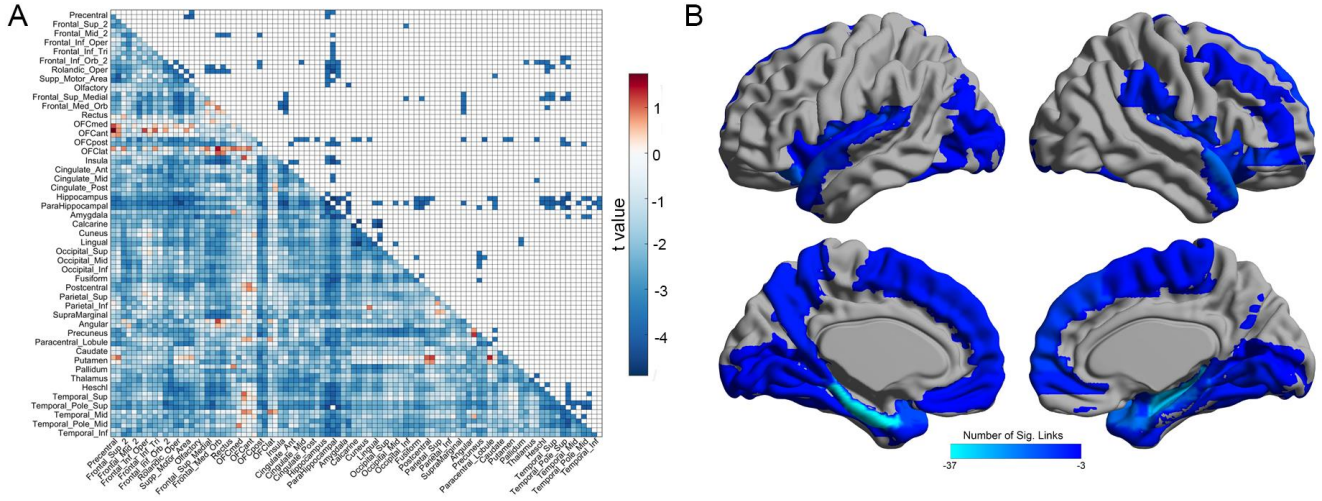
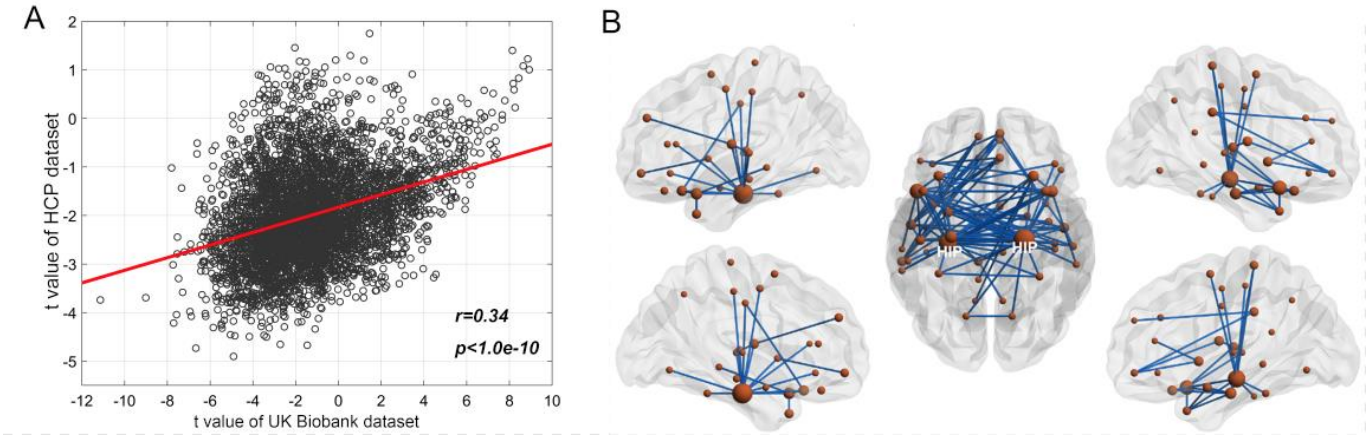


Figure S2. A. Correlation between the t values for the comparison between the high blood pressure and control groups of the 4,371 whole brain functional connectivity links for the HCP and UK Biobank data sets. The analysis with the UK Biobank dataset used the same high blood pressure measure as the HCP group. **B. The common links associated with high blood pressure in both the HCP and UK Biobank data sets.** The size of the nodes indicates the number of common links, with the largest node the hippocampus.



Tests of whether the associations between hypertension, and functional connectivity and measures of memory, were different for different ages or gender

This was analysed by setting up 2-way ANOVAs, with one factor hypertension, and the second factor age or gender. A significant interaction would indicate that some of the associations were age- or gender-dependent. The dependent measures investigated in different 2-way ANOVAs were hippocampal functional connectivity, prospective memory, and numeric memory. Almost no significant interactions were found, indicating that the effects described in the paper were not in general different for participants of different ages or gender. Some details of the analyses, and results where small interactions were found, are described next. The groups used were set to have approximately equal numbers of participants where possible. The covariates of no interest described in the paper were regressed out. The analysis was performed with the data from the UK Biobank release 1.

The hypertension measures investigated were (1) a history of hypertension or not; and (2) a low diastolic blood pressure group (<70 mm Hg), a mid group (70-110 mm Hg), and a high group (>110 mm Hg); and (3) a low systolic blood pressure group (<120mm Hg), a mid group (120-160 mm Hg), and a high group (>160 mm Hg). The age groups investigated were low group age<53 years; mid group age 53-61; high group age>61.

Many two-way ANOVAs to test all possible interaction effects were performed. Almost no interaction effects were statistically significant. The most significant interaction effect found was as follows. For the interaction between the history of hypertension and gender with the dependent variable hippocampal functional connectivity, the main effect of hypertension history was significant ($F=30.6$, $df=1,15082$, $p<1.0\times10^{-10}$), the main effect of gender was significant ($F=33.31$, $df=1, 15082$, $p<1.0\times10^{-10}$), and the interaction term between hypertension history and gender was significant ($F=11.12$, $df=1,15082$, $p=0.001$). The interaction was related to an especially high hippocampal functional connectivity in the male group without a history of hypertension, as shown in Fig. S3.

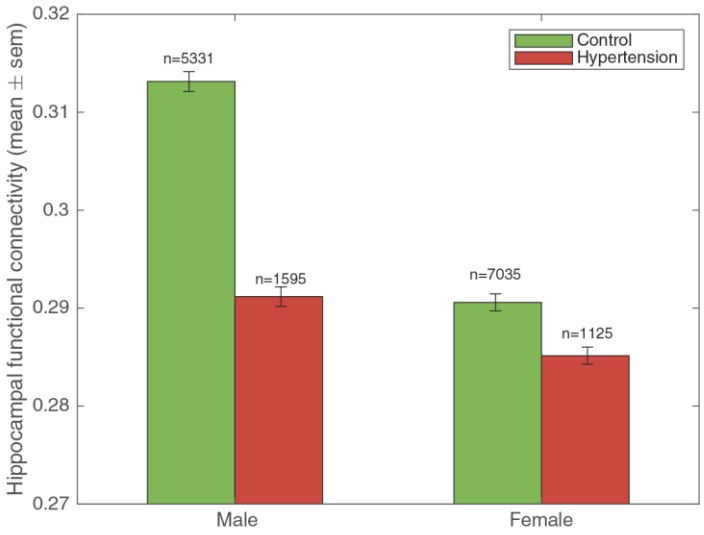


Fig. S3. Gender differences in the relation between hippocampal functional connectivity between the group with hypertension and the controls reflected in the significant interaction between a history of hypertension and gender described in the text.

The only other interaction effects were small. For the interaction between the history of hypertension and gender with the dependent variable prospective memory, the interaction term was significant ($F=6.34$, $df=1,138508$, $p=0.01$). This reflected a larger effect of hypertension history in males. For the interaction between the history of hypertension and gender with the dependent variable numeric memory, the interaction term was significant ($F=6.5$, $df=1,42325$, $p=0.01$). This reflected a larger effect of hypertension history in males.

In conclusion, significant age effects were not found for the relation between any measure of hypertension, and age, on hippocampal functional connectivity or measure of prospective and numeric memory. For gender, there was some tendency for the effects of a history of hypertension on functional connectivity, prospective memory, and numeric memory, to be greater in males, but that is in the context that many different tests were performed.

Table S1. The anatomical regions defined in each hemisphere and their label in the automated anatomical labelling atlas AAL2 [1]. Column 4 provides a set of possible abbreviations for the anatomical descriptions.

NO.	ANATOMICAL DESCRIPTION	LABEL aal2.nii.gz	POSSIBLE ABBREVIATION
1,2	Precentral gyrus	Precentral	PreCG
3, 4	Superior frontal gyrus, dorsolateral	Frontal_Sup	SFG
5, 6	Middle frontal gyrus	Frontal_Mid	MFG
7, 8	Inferior frontal gyrus, opercular part	Frontal_Inf_Oper	IFGoperc
9, 10	Inferior frontal gyrus, triangular part	Frontal_Inf_Tri	IFGtriang
11, 12	IFG pars orbitalis,	Frontal_Inf_Orb	IFGorb
13, 14	Rolandic operculum	Rolandic_Oper	ROL
15, 16	Supplementary motor area	Supp_Motor_Area	SMA
17, 18	Olfactory cortex	Olfactory	OLF
19, 20	Superior frontal gyrus, medial	Frontal_Sup_Med	SFGmedial
21, 22	Superior frontal gyrus, medial orbital	Frontal_Med_Orb	PFCventmed
23, 24	Gyrus rectus	Rectus	REC
25, 26	Medial orbital gyrus	OFCmed	OFCmed
27, 28	Anterior orbital gyrus	OFCant	OFCant
29, 30	Posterior orbital gyrus	OFCpost	OFCpost
31, 32	Lateral orbital gyrus	OFClat	OFClat
33, 34	Insula	Insula	INS
35, 36	Anterior cingulate & paracingulate gyri	Cingulate_Ant	ACC
37, 38	Middle cingulate & paracingulate gyri	Cingulate_Mid	MCC
39, 40	Posterior cingulate gyrus	Cingulate_Post	PCC
41, 42	Hippocampus	Hippocampus	HIP
43, 44	Parahippocampal gyrus	ParaHippocampal	PHG
45, 46	Amygdala	Amygdala	AMYG
47, 48	Calcarine fissure and surrounding cortex	Calcarine	CAL
49, 50	Cuneus	Cuneus	CUN
51, 52	Lingual gyrus	Lingual	LING
53, 54	Superior occipital gyrus	Occipital_Sup	SOG
55, 56	Middle occipital gyrus	Occipital_Mid	MOG
57, 58	Inferior occipital gyrus	Occipital_Inf	IOG
59, 60	Fusiform gyrus	Fusiform	FFG
61, 62	Postcentral gyrus	Postcentral	PoCG
63, 64	Superior parietal gyrus	Parietal_Sup	SPG
65, 66	Inferior parietal gyrus, excluding supramarginal and angular gyri	Parietal_Inf	IPG
67, 68	SupraMarginal gyrus	SupraMarginal	SMG
69, 70	Angular gyrus	Angular	ANG
71, 72	Precuneus	Precuneus	PCUN
73, 74	Paracentral lobule	Paracentral_Lobule	PCL
75, 76	Caudate nucleus	Caudate	CAU
77, 78	Lenticular nucleus, Putamen	Putamen	PUT
79, 80	Lenticular nucleus, Pallidum	Pallidum	PAL
81, 82	Thalamus	Thalamus	THA
83, 84	Heschl's gyrus	Heschl	HES
85, 86	Superior temporal gyrus	Temporal_Sup	STG
87, 88	Temporal pole: superior temporal gyrus	Temporal_Pole_Sup	TPOsup
89, 90	Middle temporal gyrus	Temporal_Mid	MTG
91, 92	Temporal pole: middle temporal gyrus	Temporal_Pole_Mid	TPOmid
93, 94	Inferior temporal gyrus	Temporal_Inf	ITG

Table S2. The demographic characteristics of participants in the HCP dataset.

	Control group (N=582)	**Hypertension group (N=144)**
Characteristics	**No. (%)**	**No. (%)**
Age, mean (SD), y	28.86 (3.68)	28.74 (3.53)
Female	356 (61.17%)	50 (34.72%)
Education, mean (SD), y	15.04 (1.73)	14.67 (1.84)
Drinking Frequency		
4-7 days/week	20 (3.44%)	14 (9.72%)
3 days/week	92 (15.81%)	27 (18.75%)
2 days/week	266 (45.70%)	50 (34.72%)
1 days/week	204 (35.05%)	53 (36.81%)
1-3 days/month	0 (0.00%)	0 (0.00%)
1-11 days/year	0 (0.00%)	0 (0.00%)
never in past 12 months	0 (0.00%)	0 (0.00%)
Smoking Status		
Never	321 (55.15%)	66 (45.83%)
Previous	174 (29.90%)	38 (26.39%)
Current	87 (14.95%)	40 (27.78%)

Table S3. The most significant 50 Functional Connectivity Links associated with Hypertension from the UK Biobank analysis using 15,086 participants. A t test was performed for different functional connectivities between the group categorized as having a history of hypertension (n=2,720) and the participants without a history of hypertension (n=12,366). The significance value for the links is $p<0.005$ corrected by the FDR method. Each link is between two areas defined in the atlas by AAL2. A link negatively correlated with hypertension indicates that the functional connectivity of that link is decreased in hypertension compared to healthy controls. The brain area names used are those for the corresponding AAL2 area as shown in Table S1.

Functional Connectivity		t value	Cohen's d	p value	Functional Connectivity		t value	Cohen's d	p value
Temporal_Pole_Sup_L	Temporal_Pole_Mid_L	-6.94	-0.113	4.20E-12	Angular_L	Temporal_Pole_Sup_L	-5.12	-0.083	3.06E-07
Hippocampus_L	Hippocampus_R	-6.82	-0.111	9.72E-12	Temporal_Mid_R	Temporal_Inf_R	-5.11	-0.083	3.24E-07
Fusiform_L	Fusiform_R	-6.56	-0.107	5.39E-11	Occipital_Mid_L	Fusiform_R	-5.11	-0.083	3.25E-07
Hippocampus_R	Temporal_Pole_Sup_L	-6.49	-0.106	8.62E-11	Temporal_Pole_Sup_L	Temporal_Inf_L	-5.10	-0.083	3.38E-07
Occipital_Inf_L	Occipital_Inf_R	-6.27	-0.102	3.65E-10	OFCpost_L	Hippocampus_R	-5.10	-0.083	3.39E-07
Lingual_L	Lingual_R	-6.21	-0.101	5.57E-10	Caudate_R	Thalamus_L	-5.10	-0.083	3.41E-07
Hippocampus_R	Temporal_Inf_R	-6.19	-0.101	6.12E-10	Lingual_R	Fusiform_L	-5.07	-0.083	4.00E-07
Hippocampus_R	Temporal_Pole_Sup_R	-6.17	-0.100	7.04E-10	Hippocampus_R	Temporal_Sup_L	-5.04	-0.082	4.71E-07
Hippocampus_R	Occipital_Inf_L	-6.11	-0.099	1.03E-09	Caudate_L	Putamen_R	-5.03	-0.082	4.99E-07
Hippocampus_R	Temporal_Mid_L	-5.99	-0.098	2.16E-09	Thalamus_L	Heschl_L	-5.03	-0.082	5.03E-07
Hippocampus_R	Heschl_R	-5.96	-0.097	2.56E-09	Hippocampus_R	Parietal_Sup_R	-5.02	-0.082	5.24E-07
Hippocampus_R	Temporal_Inf_L	-5.92	-0.096	3.31E-09	Hippocampus_R	ParaHippocampal_L	-5.02	-0.082	5.32E-07
Temporal_Pole_Sup_L	Temporal_Mid_L	-5.92	-0.096	3.39E-09	OFCpost_R	Hippocampus_R	-5.01	-0.082	5.45E-07
Hippocampus_R	Occipital_Inf_R	-5.89	-0.096	3.89E-09	Hippocampus_R	Lingual_L	-5.01	-0.082	5.51E-07
Temporal_Pole_Sup_L	Temporal_Pole_Mid_R	-5.86	-0.095	4.73E-09	Frontal_Mid_2_L	Thalamus_L	-5.00	-0.081	5.73E-07
Hippocampus_R	Paracentral_Lobule_L	-5.83	-0.095	5.57E-09	Lingual_R	Fusiform_R	-4.99	-0.081	5.96E-07
Insula_R	SupraMarginal_R	-5.82	-0.095	6.06E-09	Frontal_Med_Orb_L	Hippocampus_R	-4.99	-0.081	5.96E-07
Thalamus_L	Thalamus_R	-5.82	-0.095	6.17E-09	Hippocampus_L	Temporal_Pole_Sup_R	-4.99	-0.081	6.00E-07
Hippocampus_L	Temporal_Pole_Sup_L	-5.77	-0.094	8.30E-09	Frontal_Sup_Medial_L	Hippocampus_R	-4.99	-0.081	6.17E-07
Frontal_Sup_2_L	Hippocampus_R	-5.74	-0.093	9.67E-09	Hippocampus_R	Occipital_Sup_R	-4.99	-0.081	6.25E-07
Frontal_Med_Orb_R	Hippocampus_R	-5.69	-0.093	1.31E-08	Heschl_L	Heschl_R	-4.97	-0.081	6.72E-07
Precentral_R	Hippocampus_R	-5.59	-0.091	2.29E-08	Hippocampus_R	Occipital_Sup_L	-4.97	-0.081	6.86E-07
Caudate_L	Caudate_R	-5.58	-0.091	2.39E-08	ParaHippocampal_R	Amygdala_R	-4.96	-0.081	7.19E-07
Hippocampus_R	Paracentral_Lobule_R	-5.56	-0.091	2.77E-08	Hippocampus_L	Occipital_Inf_L	-4.95	-0.081	7.54E-07
Hippocampus_R	Fusiform_L	-5.51	-0.090	3.64E-08	Hippocampus_R	Parietal_Inf_L	-4.94	-0.081	7.71E-07
Cingulate_Mid_R	Thalamus_L	-5.47	-0.089	4.57E-08	Cingulate_Mid_R	Hippocampus_R	-4.94	-0.080	7.94E-07
Occipital_Inf_R	Temporal_Mid_R	-5.46	-0.089	4.81E-08	Frontal_Inf_Oper_R	Thalamus_R	-4.93	-0.080	8.16E-07
Precentral_L	Hippocampus_R	-5.45	-0.089	5.06E-08	Hippocampus_L	Paracentral_Lobule_R	-4.93	-0.080	8.30E-07
Hippocampus_R	Amygdala_R	-5.42	-0.088	5.90E-08	Hippocampus_R	Temporal_Pole_Mid_R	-4.93	-0.080	8.31E-07
Hippocampus_R	Parietal_Sup_L	-5.42	-0.088	5.95E-08	Frontal_Inf_Orb_2_L	Temporal_Pole_Sup_L	-4.92	-0.080	8.65E-07
Hippocampus_R	Temporal_Sup_R	-5.40	-0.088	6.58E-08	Frontal_Mid_2_R	Thalamus_R	-4.92	-0.080	8.86E-07
SupraMarginal_R	Thalamus_R	-5.40	-0.088	6.62E-08	Hippocampus_R	Lingual_R	-4.91	-0.080	9.41E-07
Cingulate_Mid_R	Thalamus_R	-5.37	-0.088	7.80E-08	Frontal_Sup_2_R	Parietal_Sup_R	-4.90	-0.080	9.61E-07
Cingulate_Mid_L	Hippocampus_R	-5.37	-0.087	7.91E-08	Frontal_Mid_2_R	Thalamus_L	-4.90	-0.080	9.91E-07
Hippocampus_R	Postcentral_L	-5.36	-0.087	8.47E-08	Insula_L	SupraMarginal_R	-4.89	-0.080	1.00E-06
Occipital_Inf_L	Temporal_Mid_R	-5.35	-0.087	9.01E-08	Heschl_L	Temporal_Sup_L	-4.88	-0.079	1.08E-06
Hippocampus_L	Occipital_Inf_R	-5.33	-0.087	1.02E-07	Thalamus_R	Heschl_L	-4.87	-0.079	1.10E-06
Hippocampus_R	Precuneus_L	-5.32	-0.087	1.08E-07	Hippocampus_R	Occipital_Mid_L	-4.87	-0.079	1.15E-06
Occipital_Inf_L	Temporal_Inf_R	-5.31	-0.087	1.10E-07	Rolandic_Oper_L	Heschl_L	-4.87	-0.079	1.15E-06
Hippocampus_R	Postcentral_R	-5.30	-0.086	1.18E-07	OFCant_R	Caudate_L	-4.86	-0.079	1.17E-06
Cingulate_Mid_L	Thalamus_L	-5.29	-0.086	1.24E-07	Temporal_Pole_Sup_R	Temporal_Mid_L	-4.86	-0.079	1.18E-06
Frontal_Inf_Oper_R	Thalamus_L	-5.27	-0.086	1.41E-07	Hippocampus_R	Precuneus_R	-4.86	-0.079	1.19E-06
Insula_L	Insula_R	-5.23	-0.085	1.73E-07	Cingulate_Ant_L	Hippocampus_R	-4.86	-0.079	1.20E-06
Rectus_R	Hippocampus_R	-5.21	-0.085	1.97E-07	Precuneus_R	Thalamus_L	-4.85	-0.079	1.23E-06
Rolandic_Oper_L	Rolandic_Oper_R	-5.20	-0.085	1.97E-07	Caudate_L	Thalamus_L	-4.85	-0.079	1.23E-06
Lingual_L	Fusiform_R	-5.19	-0.085	2.11E-07	Rolandic_Oper_L	Hippocampus_R	-4.85	-0.079	1.26E-06
Paracentral_Lobule_L	Paracentral_Lobule_R	-5.16	-0.084	2.54E-07	Hippocampus_L	Paracentral_Lobule_L	-4.85	-0.079	1.26E-06
Frontal_Sup_Medial_R	Hippocampus_R	-5.15	-0.084	2.63E-07	OFCpost_L	Temporal_Pole_Sup_L	-4.84	-0.079	1.29E-06
Hippocampus_R	Fusiform_R	-5.14	-0.084	2.72E-07	Caudate_R	Putamen_R	-4.84	-0.079	1.31E-06
SupraMarginal_R	Thalamus_L	-5.13	-0.083	2.98E-07	Temporal_Pole_Sup_R	Temporal_Pole_Mid_R	-4.83	-0.079	1.38E-06

Table S4. The most significant 50 Functional Connectivity Links associated with prospective memory from the UK Biobank analysis using 19,507 participants. A partial correlation was performed for different functional connectivity with the graded prospective memory test score. The significance value for the links is $p<0.01$ corrected by the FDR method. Each link is between two areas defined in the atlas by AAL2. The r values measuring the strength of the partial correlations are positive if the functional connectivity of that link is positively correlated with the prospective memory score. The brain area names used are those for the corresponding AAL2 area as shown in Table S1.

Functional Connectivity		r value	Cohen's d	p value	Functional Connectivity		r value	Cohen's d	p value
Parietal_Sup_R	Angular_R	0.05	0.090	1.37E-09	ParaHippocampal_L	Parietal_Inf_L	0.03	0.066	9.36E-06
Frontal_Mid_2_L	Rectus_L	0.04	0.089	2.15E-09	Paracentral_Lobule_L	Temporal_Sup_R	0.03	0.066	9.94E-06
Frontal_Inf_Tri_L	Hippocampus_L	0.04	0.088	3.29E-09	Frontal_Sup_Medial_R	Cingulate_Ant_R	0.03	0.066	1.02E-05
Parietal_Sup_R	Temporal_Inf_R	0.04	0.087	5.27E-09	Frontal_Mid_2_L	Frontal_Med_Orb_R	0.03	0.066	1.08E-05
Frontal_Inf_Tri_L	Rectus_L	0.04	0.084	1.65E-08	Precentral_R	OFCant_R	0.03	0.065	1.18E-05
Frontal_Inf_Orb_2_L	Hippocampus_L	0.04	0.081	6.16E-08	Cuneus_L	Cuneus_R	0.03	0.065	1.19E-05
ParaHippocampal_L	Occipital_Inf_L	0.04	0.080	7.73E-08	Paracentral_Lobule_R	Temporal_Mid_R	0.03	0.065	1.20E-05
Frontal_Inf_Orb_2_L	Rectus_L	0.04	0.080	9.30E-08	Frontal_Inf_Oper_L	Hippocampus_L	0.03	0.065	1.21E-05
Precentral_L	Temporal_Inf_L	0.04	0.079	1.01E-07	Occipital_Sup_R	Occipital_Mid_L	0.03	0.065	1.26E-05
Parietal_Sup_R	Precuneus_R	0.04	0.079	1.28E-07	Hippocampus_R	Parietal_Inf_L	0.03	0.065	1.29E-05
Paracentral_Lobule_L	Temporal_Mid_L	0.04	0.078	1.91E-07	Paracentral_Lobule_L	Temporal_Sup_L	0.03	0.065	1.32E-05
Parietal_Sup_R	Precuneus_L	0.04	0.077	2.25E-07	Supp_Motor_Area_L	Rectus_L	0.03	0.065	1.40E-05
Cingulate_Post_L	SupraMarginal_R	0.04	0.075	4.07E-07	Parietal_Sup_R	Temporal_Mid_R	0.03	0.065	1.41E-05
Frontal_Sup_2_L	OFClat_L	0.04	0.075	4.21E-07	Rectus_L	SupraMarginal_L	0.03	0.065	1.42E-05
Cingulate_Post_L	SupraMarginal_L	0.04	0.075	5.41E-07	Postcentral_R	Temporal_Mid_R	0.03	0.065	1.44E-05
Frontal_Inf_Orb_2_L	Frontal_Med_Orb_L	0.04	0.074	5.90E-07	Parietal_Inf_R	Angular_R	0.03	0.065	1.47E-05
Precentral_L	Temporal_Mid_L	0.04	0.074	6.33E-07	ParaHippocampal_L	SupraMarginal_L	0.03	0.064	1.48E-05
Insula_L	Cingulate_Post_L	0.04	0.074	7.69E-07	Parietal_Inf_L	Precuneus_L	0.03	0.064	1.57E-05
Precentral_L	Temporal_Mid_R	0.04	0.073	8.83E-07	Frontal_Inf_Oper_R	OFCant_R	0.03	0.064	1.64E-05
Frontal_Sup_2_R	Frontal_Mid_2_R	0.04	0.071	1.72E-06	Paracentral_Lobule_L	Temporal_Inf_L	0.03	0.064	1.76E-05
Cingulate_Post_R	SupraMarginal_R	0.04	0.071	1.81E-06	OFCpost_R	Cingulate_Ant_R	0.03	0.064	1.82E-05
Rectus_L	Parietal_Inf_L	0.04	0.071	1.96E-06	OFCpost_R	Cingulate_Mid_L	0.03	0.064	1.85E-05
Parietal_Sup_L	Temporal_Inf_R	0.04	0.070	2.38E-06	Precentral_R	Temporal_Mid_L	0.03	0.064	1.87E-05
Cingulate_Post_R	SupraMarginal_L	0.04	0.070	2.42E-06	Precentral_R	Frontal_Inf_Tri_R	0.03	0.064	1.90E-05
Parietal_Sup_L	Precuneus_L	0.04	0.070	2.43E-06	Frontal_Sup_2_R	OFCpost_R	0.03	0.064	1.94E-05
Insula_R	Cingulate_Post_L	0.03	0.070	2.75E-06	Precentral_R	Temporal_Inf_R	0.03	0.063	2.12E-05
Frontal_Inf_Tri_L	ParaHippocampal_L	0.03	0.070	3.02E-06	Frontal_Inf_Orb_2_L	Paracentral_Lobule_L	0.03	0.063	2.21E-05
Frontal_Inf_Tri_L	Amygdala_L	0.03	0.069	3.51E-06	Cingulate_Post_L	Parietal_Sup_R	0.03	0.063	2.21E-05
Frontal_Sup_2_L	Rectus_L	0.03	0.069	3.55E-06	Frontal_Mid_2_R	Angular_R	0.03	0.063	2.22E-05
Frontal_Inf_Tri_L	Frontal_Med_Orb_L	0.03	0.069	3.61E-06	Hippocampus_L	Temporal_Mid_L	0.03	0.063	2.24E-05
Frontal_Inf_Tri_L	Paracentral_Lobule_L	0.03	0.069	3.62E-06	Precentral_L	Angular_R	0.03	0.063	2.29E-05
Cingulate_Ant_L	Cingulate_Post_L	0.03	0.069	3.66E-06	Frontal_Inf_Oper_L	Hippocampus_R	0.03	0.063	2.35E-05
Frontal_Sup_Medial_R	Cingulate_Ant_L	0.03	0.069	3.82E-06	Precentral_R	Frontal_Inf_Tri_L	0.03	0.063	2.35E-05
Frontal_Mid_2_L	Temporal_Mid_R	0.03	0.069	3.93E-06	Supp_Motor_Area_L	Hippocampus_L	0.03	0.063	2.37E-05
Frontal_Inf_Orb_2_L	Hippocampus_R	0.03	0.069	3.96E-06	Occipital_Mid_L	Parietal_Sup_R	0.03	0.063	2.38E-05
Frontal_Inf_Tri_L	Hippocampus_R	0.03	0.069	4.18E-06	Precentral_L	OFCant_L	0.03	0.063	2.51E-05
Rectus_L	Insula_L	0.03	0.067	5.90E-06	Precentral_R	Temporal_Inf_L	0.03	0.063	2.53E-05
Supp_Motor_Area_L	Hippocampus_R	0.03	0.067	6.08E-06	Rectus_L	OFCpost_L	0.03	0.063	2.56E-05
Precentral_L	Temporal_Inf_R	0.03	0.067	6.18E-06	Frontal_Mid_2_L	Rectus_R	0.03	0.063	2.61E-05
Frontal_Mid_2_L	Frontal_Med_Orb_L	0.03	0.067	6.20E-06	Frontal_Inf_Tri_R	Rectus_L	0.03	0.063	2.62E-05
Precentral_R	Temporal_Mid_R	0.03	0.067	6.27E-06	Cingulate_Mid_L	Cingulate_Post_L	0.03	0.063	2.70E-05
Supp_Motor_Area_L	OFCpost_R	0.03	0.067	6.80E-06	Precentral_R	Temporal_Sup_R	0.03	0.062	2.79E-05
Hippocampus_L	Parietal_Inf_L	0.03	0.067	7.03E-06	Cingulate_Post_L	Temporal_Sup_L	0.03	0.062	2.79E-05
Frontal_Mid_2_L	Hippocampus_L	0.03	0.067	7.15E-06	Parietal_Sup_R	Temporal_Mid_L	0.03	0.062	2.91E-05
Frontal_Inf_Oper_L	ParaHippocampal_L	0.03	0.067	7.37E-06	Frontal_Sup_2_L	Temporal_Mid_L	0.03	0.062	3.22E-05
Paracentral_Lobule_R	Temporal_Mid_L	0.03	0.067	7.55E-06	Supp_Motor_Area_R	OFCpost_R	0.03	0.062	3.30E-05
Cingulate_Mid_R	Cingulate_Post_L	0.03	0.067	7.82E-06	Hippocampus_R	SupraMarginal_L	0.03	0.062	3.54E-05
Postcentral_L	Temporal_Mid_L	0.03	0.066	8.10E-06	Frontal_Inf_Tri_R	OFCant_R	0.03	0.062	3.54E-05
Postcentral_R	Temporal_Mid_L	0.03	0.066	8.69E-06	Occipital_Sup_R	Angular_R	0.03	0.061	3.64E-05
Parietal_Inf_L	Temporal_Inf_R	0.03	0.066	9.26E-06	Postcentral_L	Temporal_Mid_R	0.03	0.061	3.67E-05

Table S5. The results of the mediation analysis performed for the 88 individual links that were correlated with hypertension history and prospective memory. The analysis is analogous to that shown in Fig. 1E, but here is for individual links, instead of for the mean value of the functional connectivity of these 88 links. The paths correspond to those shown in Fig. 1E. All 88 links were found to underlie the relation between hypertension history and prospective memory in this analysis. A negative beta for path A indicates participants with a hypertension history have a reduced strength of the functional connectivity.

Functional Connectivity		Path A		Path B		Path C'		Path C		Path AB	
Region A	**Region B**	**beta**	**p value**	**beta**	**p value**	**beta**	**p value**	**beta**	**p value**	**beta**	**p value**
Cingulate_Post_R	SupraMarginal_R	-0.017	1.60E-04	0.080	2.33E-04	-0.025	3.20E-02	-0.026	2.31E-02	-0.001	3.17E-04
Frontal_Inf_Orb_2_L	Hippocampus_R	-0.017	2.25E-04	0.095	2.40E-04	-0.025	3.37E-02	-0.026	2.28E-02	-0.002	3.33E-04
Hippocampus_R	SupraMarginal_L	-0.017	1.99E-04	0.073	2.28E-04	-0.025	3.69E-02	-0.026	2.84E-02	-0.001	3.45E-04
Frontal_Inf_Tri_L	Hippocampus_R	-0.017	1.95E-04	0.095	2.10E-04	-0.025	3.46E-02	-0.026	2.40E-02	-0.002	3.49E-04
Supp_Motor_Area_L	Hippocampus_R	-0.018	1.99E-04	0.088	1.96E-04	-0.025	3.22E-02	-0.026	2.40E-02	-0.002	3.52E-04
Insula_R	Cingulate_Post_R	-0.017	1.74E-04	0.085	2.13E-04	-0.025	3.25E-02	-0.026	2.34E-02	-0.001	3.80E-04
Cingulate_Post_R	SupraMarginal_L	-0.016	2.32E-04	0.079	2.45E-04	-0.025	3.55E-02	-0.026	2.77E-02	-0.001	3.85E-04
Hippocampus_R	Parietal_Inf_L	-0.018	2.06E-04	0.087	2.16E-04	-0.025	3.79E-02	-0.026	2.89E-02	-0.002	3.86E-04
Occipital_Mid_L	Occipital_Mid_R	-0.006	3.58E-04	0.298	8.95E-05	-0.025	3.24E-02	-0.026	2.18E-02	-0.002	6.58E-04
Frontal_Inf_Orb_2_R	OFCpost_R	-0.013	4.22E-04	0.091	1.83E-04	-0.025	3.12E-02	-0.026	2.41E-02	-0.001	7.91E-04
Postcentral_R	Temporal_Inf_R	-0.016	2.20E-04	0.078	1.71E-04	-0.025	3.15E-02	-0.026	2.46E-02	-0.001	9.00E-04
Frontal_Inf_Tri_R	Hippocampus_R	-0.018	1.97E-04	0.073	5.85E-04	-0.025	3.65E-02	-0.026	2.32E-02	-0.001	1.05E-03
Frontal_Inf_Oper_L	Hippocampus_R	-0.016	1.89E-04	0.081	6.40E-04	-0.025	3.82E-02	-0.026	2.94E-02	-0.001	1.07E-03
Hippocampus_R	Temporal_Pole_Sup_L	-0.022	1.93E-04	0.086	8.05E-04	-0.024	3.85E-02	-0.026	2.62E-02	-0.002	1.17E-03
Frontal_Inf_Orb_2_L	Hippocampus_L	-0.013	6.23E-04	0.104	2.02E-04	-0.025	3.64E-02	-0.026	2.79E-02	-0.001	1.23E-03
SupraMarginal_R	Caudate_R	-0.016	4.63E-04	0.075	1.94E-04	-0.025	3.79E-02	-0.026	2.88E-02	-0.001	1.28E-03
Postcentral_L	Temporal_Mid_R	-0.017	2.23E-04	0.074	5.50E-04	-0.025	3.46E-02	-0.026	2.63E-02	-0.001	1.28E-03
Precentral_L	Hippocampus_R	-0.021	1.97E-04	0.071	8.06E-04	-0.025	3.44E-02	-0.026	2.39E-02	-0.001	1.29E-03
Supp_Motor_Area_R	Hippocampus_R	-0.019	2.06E-04	0.075	8.41E-04	-0.025	3.60E-02	-0.026	2.44E-02	-0.001	1.32E-03
Cingulate_Mid_L	Cingulate_Post_R	-0.014	1.93E-04	0.083	7.88E-04	-0.025	3.63E-02	-0.026	2.77E-02	-0.001	1.35E-03
Frontal_Inf_Tri_R	Caudate_L	-0.016	2.02E-04	0.076	6.08E-04	-0.025	3.53E-02	-0.026	2.81E-02	-0.001	1.42E-03
OFClat_L	Hippocampus_L	-0.011	2.91E-04	0.091	6.29E-04	-0.025	2.86E-02	-0.026	2.39E-02	-0.001	1.60E-03
Precentral_R	Temporal_Inf_R	-0.016	3.98E-04	0.085	3.40E-04	-0.025	4.26E-02	-0.026	3.04E-02	-0.001	1.61E-03
Frontal_Mid_2_L	Hippocampus_R	-0.018	2.33E-04	0.077	1.03E-03	-0.025	2.97E-02	-0.026	2.21E-02	-0.001	1.63E-03
Cingulate_Mid_L	Temporal_Mid_R	-0.014	5.17E-04	0.092	1.65E-04	-0.025	3.29E-02	-0.026	2.82E-02	-0.001	1.72E-03
Frontal_Inf_Tri_R	Caudate_R	-0.015	2.20E-04	0.079	5.23E-04	-0.025	3.16E-02	-0.026	2.38E-02	-0.001	1.74E-03
Cingulate_Mid_R	Cingulate_Post_R	-0.012	7.06E-04	0.096	1.69E-04	-0.025	2.95E-02	-0.026	2.24E-02	-0.001	1.82E-03
Supp_Motor_Area_L	Hippocampus_L	-0.014	3.52E-04	0.071	6.35E-04	-0.025	2.95E-02	-0.026	2.24E-02	-0.001	1.86E-03
Precentral_L	Occipital_Inf_L	-0.014	1.75E-04	0.077	1.04E-03	-0.025	3.54E-02	-0.026	2.85E-02	-0.001	2.08E-03
Frontal_Sup_2_R	Parietal_Sup_R	-0.018	2.27E-04	0.073	8.39E-04	-0.025	3.54E-02	-0.026	2.72E-02	-0.001	2.15E-03
OFCpost_R	Cingulate_Mid_L	-0.015	1.17E-03	0.074	2.60E-04	-0.025	2.99E-02	-0.026	2.34E-02	-0.001	2.16E-03
Occipital_Inf_L	Fusiform_L	-0.011	2.59E-04	0.126	7.69E-04	-0.025	3.92E-02	-0.026	2.82E-02	-0.001	2.21E-03
Supp_Motor_Area_R	Caudate_R	-0.015	1.21E-03	0.079	1.62E-04	-0.025	3.36E-02	-0.026	2.47E-02	-0.001	2.38E-03
Postcentral_L	Temporal_Inf_L	-0.015	8.50E-04	0.073	4.17E-04	-0.025	3.42E-02	-0.026	2.85E-02	-0.001	2.38E-03
OFCant_L	Hippocampus_R	-0.012	1.14E-03	0.089	2.17E-04	-0.025	3.22E-02	-0.026	2.81E-02	-0.001	2.47E-03
Temporal_Pole_Sup_R	Temporal_Mid_L	-0.020	2.23E-04	0.068	1.39E-03	-0.025	3.51E-02	-0.026	2.73E-02	-0.001	2.53E-03
Precentral_R	Temporal_Inf_L	-0.015	1.10E-03	0.083	1.51E-04	-0.025	2.85E-02	-0.026	2.20E-02	-0.001	2.59E-03
Insula_L	Cingulate_Post_R	-0.013	1.35E-03	0.087	1.92E-04	-0.025	2.44E-02	-0.026	1.93E-02	-0.001	2.89E-03
Cingulate_Ant_L	Cingulate_Post_R	-0.014	2.27E-04	0.094	1.27E-03	-0.025	3.69E-02	-0.026	2.66E-02	-0.001	2.93E-03
Hippocampus_R	Parietal_Sup_L	-0.021	1.97E-04	0.066	2.33E-03	-0.025	3.26E-02	-0.026	2.53E-02	-0.001	3.26E-03
OFCpost_R	Cingulate_Mid_R	-0.015	9.46E-04	0.064	1.23E-03	-0.025	3.51E-02	-0.026	2.97E-02	-0.001	3.80E-03
Fusiform_L	Fusiform_R	-0.013	2.13E-04	0.119	1.40E-03	-0.025	3.20E-02	-0.026	2.25E-02	-0.002	3.88E-03
Cingulate_Post_R	Parietal_Sup_R	-0.014	1.75E-03	0.077	6.06E-04	-0.025	3.00E-02	-0.026	2.36E-02	-0.001	3.97E-03
Precentral_L	Fusiform_L	-0.015	2.35E-04	0.072	1.83E-03	-0.025	2.64E-02	-0.026	1.92E-02	-0.001	4.43E-03
Parietal_Sup_R	Precuneus_L	-0.012	2.59E-03	0.107	1.28E-04	-0.025	2.86E-02	-0.026	2.17E-02	-0.001	4.45E-03
Occipital_Mid_L	Fusiform_L	-0.007	2.26E-03	0.159	1.27E-04	-0.025	3.68E-02	-0.026	2.82E-02	-0.001	4.56E-03
Parietal_Sup_R	Precuneus_R	-0.010	2.48E-03	0.141	1.60E-04	-0.025	3.52E-02	-0.026	2.50E-02	-0.001	4.71E-03
Insula_L	Hippocampus_R	-0.015	1.75E-04	0.070	2.82E-03	-0.025	3.38E-02	-0.026	2.56E-02	-0.001	5.41E-03
Cingulate_Ant_R	Cingulate_Post_R	-0.012	2.29E-04	0.086	2.46E-03	-0.025	2.96E-02	-0.026	2.19E-02	-0.001	5.60E-03

Postcentral_L	Temporal_Inf_R	-0.017	4.26E-04	0.062	2.23E-03	-0.025	3.28E-02	-0.026	2.67E-02	-0.001	5.62E-03
Precentral_L	Hippocampus_L	-0.019	2.31E-04	0.065	1.93E-03	-0.025	3.75E-02	-0.026	2.94E-02	-0.001	5.99E-03
Hippocampus_R	Temporal_Mid_L	-0.022	1.84E-04	0.067	3.91E-03	-0.025	3.35E-02	-0.026	2.48E-02	-0.001	6.16E-03
Cingulate_Post_R	Temporal_Sup_L	-0.018	1.66E-04	0.065	3.66E-03	-0.025	3.17E-02	-0.026	2.33E-02	-0.001	6.37E-03
Cuneus_L	Cuneus_R	-0.004	4.06E-03	0.320	1.34E-04	-0.025	3.63E-02	-0.026	2.65E-02	-0.001	6.71E-03
Hippocampus_L	Temporal_Pole_Sup_L	-0.021	2.03E-04	0.073	4.45E-03	-0.025	3.78E-02	-0.026	2.84E-02	-0.002	6.84E-03
SupraMarginal_L	Caudate_R	-0.015	7.49E-04	0.067	2.25E-03	-0.025	2.81E-02	-0.026	2.24E-02	-0.001	7.02E-03
Frontal_Inf_Orb_2_L	OFCpost_L	-0.012	1.09E-03	0.075	2.64E-03	-0.025	3.21E-02	-0.026	2.63E-02	-0.001	7.22E-03
Hippocampus_L	Temporal_Mid_L	-0.014	7.91E-04	0.072	3.21E-03	-0.025	3.23E-02	-0.026	2.83E-02	-0.001	7.43E-03
Rectus_L	OFCpost_L	-0.010	2.79E-03	0.093	1.05E-03	-0.025	2.88E-02	-0.026	2.14E-02	-0.001	7.45E-03
Frontal_Inf_Orb_2_L	Temporal_Pole_Sup_R	-0.014	3.96E-03	0.073	6.26E-04	-0.025	2.81E-02	-0.026	2.21E-02	-0.001	8.08E-03
Supp_Motor_Area_R	Cingulate_Post_R	-0.014	8.60E-04	0.064	4.43E-03	-0.025	3.54E-02	-0.026	2.96E-02	-0.001	8.21E-03
Frontal_Inf_Tri_R	OFCpost_R	-0.013	5.06E-03	0.082	1.80E-04	-0.025	3.51E-02	-0.026	2.59E-02	-0.001	8.45E-03
Precuneus_L	Temporal_Inf_R	-0.012	6.39E-04	0.072	3.80E-03	-0.025	3.23E-02	-0.026	2.46E-02	-0.001	8.72E-03
Paracentral_Lobule_L	Heschl_L	-0.014	8.45E-04	0.059	4.13E-03	-0.025	2.88E-02	-0.026	2.46E-02	-0.001	9.95E-03
Cuneus_L	Occipital_Sup_L	-0.005	5.15E-03	0.192	2.78E-04	-0.025	3.42E-02	-0.026	2.73E-02	-0.001	1.01E-02
Caudate_L	Temporal_Sup_R	-0.017	2.07E-04	0.058	4.69E-03	-0.025	3.19E-02	-0.026	2.61E-02	-0.001	1.11E-02
Occipital_Sup_R	Fusiform_L	-0.008	6.65E-03	0.120	1.96E-04	-0.025	3.09E-02	-0.026	2.41E-02	-0.001	1.12E-02
Frontal_Med_Orb_L	Temporal_Pole_Sup_L	-0.016	2.12E-04	0.064	5.45E-03	-0.025	2.79E-02	-0.026	2.32E-02	-0.001	1.15E-02
Hippocampus_L	Temporal_Inf_L	-0.015	3.90E-04	0.064	5.05E-03	-0.025	3.66E-02	-0.026	2.93E-02	-0.001	1.18E-02
OFCpost_R	Temporal_Mid_R	-0.017	2.29E-04	0.056	8.72E-03	-0.025	2.52E-02	-0.026	2.03E-02	-0.001	1.35E-02
Paracentral_Lobule_L	Temporal_Inf_R	-0.019	2.22E-04	0.053	9.63E-03	-0.025	3.61E-02	-0.026	2.81E-02	-0.001	1.53E-02
Precuneus_L	Precuneus_R	-0.004	6.11E-03	0.237	1.68E-03	-0.025	2.49E-02	-0.026	2.17E-02	-0.001	1.55E-02
OFCpost_R	Temporal_Pole_Sup_L	-0.013	3.91E-04	0.062	7.90E-03	-0.026	3.07E-02	-0.026	2.64E-02	-0.001	1.62E-02
Supp_Motor_Area_R	Heschl_L	-0.014	6.31E-04	0.060	8.02E-03	-0.026	2.82E-02	-0.026	2.32E-02	-0.001	1.63E-02
Caudate_L	Temporal_Mid_R	-0.017	2.14E-04	0.052	7.27E-03	-0.025	3.27E-02	-0.026	2.79E-02	-0.001	1.63E-02
Calcarine_R	Fusiform_L	-0.010	2.54E-03	0.081	5.67E-03	-0.026	3.25E-02	-0.026	2.51E-02	-0.001	1.64E-02
Supp_Motor_Area_R	Hippocampus_L	-0.015	5.93E-04	0.053	1.13E-02	-0.026	3.29E-02	-0.026	2.67E-02	-0.001	1.85E-02
Hippocampus_R	Occipital_Inf_L	-0.023	1.98E-04	0.053	1.40E-02	-0.025	3.35E-02	-0.026	2.61E-02	-0.001	1.87E-02
Hippocampus_L	Occipital_Inf_L	-0.019	1.81E-04	0.053	1.29E-02	-0.025	2.72E-02	-0.026	2.23E-02	-0.001	1.88E-02
Hippocampus_L	Temporal_Sup_L	-0.014	9.79E-04	0.054	1.11E-02	-0.026	3.29E-02	-0.026	2.78E-02	-0.001	2.04E-02
Heschl_L	Temporal_Sup_R	-0.014	1.07E-03	0.062	9.62E-03	-0.025	2.99E-02	-0.026	2.59E-02	-0.001	2.26E-02
Thalamus_L	Temporal_Mid_R	-0.020	2.16E-04	0.051	2.35E-02	-0.025	2.73E-02	-0.026	2.30E-02	-0.001	3.08E-02
OFCpost_R	Precuneus_R	-0.014	3.13E-03	0.049	1.37E-02	-0.026	2.67E-02	-0.026	2.27E-02	-0.001	3.20E-02
Frontal_Inf_Tri_L	OFCpost_L	-0.010	1.03E-02	0.061	7.80E-03	-0.026	2.78E-02	-0.026	2.38E-02	-0.001	4.17E-02
Temporal_Mid_R	Temporal_Inf_R	-0.017	2.42E-04	0.066	2.90E-02	-0.025	3.54E-02	-0.026	2.68E-02	-0.001	4.56E-02
Frontal_Sup_2_R	SupraMarginal_R	-0.015	1.92E-03	0.044	2.36E-02	-0.026	3.29E-02	-0.026	2.92E-02	-0.001	5.03E-02
Rectus_L	Temporal_Pole_Sup_L	-0.015	2.30E-04	0.053	3.14E-02	-0.026	3.44E-02	-0.026	2.80E-02	-0.001	5.11E-02
Frontal_Mid_2_L	Temporal_Inf_R	-0.012	3.81E-03	0.047	4.08E-02	-0.026	2.59E-02	-0.026	2.19E-02	-0.001	8.43E-02

Table S6. **Demographic Characteristics of the First UK Biobank Imaging Participants**

	Control Group (N=12,366)	**Hypertension History Group (N=2,720)**
Characteristics	**No. (%)**	**No. (%)**
Age, mean (SD), y	61.34 (7.49)	65.64 (6.51)
Female	7,035 (56.89%)	1,125 (41.36%)
Townsend deprivation index, mean (SD), points	-1.99 (2.65)	-1.91 (2.70)
Drinking Frequency		
Prefer not to answer	2 (0.02%)	1 (0.04%)
Daily or almost daily	2,602 (21.04%)	659 (24.23%)
Three or four times a week	3,449 (27.89%)	723 (26.58%)
Once or twice a week	3,278 (26.51%)	647 (23.79%)
One to three times a month	1,396 (11.29%)	291 (10.70%)
Special occasions only	1,070 (8.65%)	244 (8.97%)
Never	569 (4.60%)	155 (5.70%)
Smoking Status		
Prefer not to answer	22 (0.18%)	5 (0.18%)
Never	7,461 (60.33%)	1,449 (53.27%)
Previous	4,053 (32.78%)	1,109 (40.77%)
Current	830 (6.71%)	157 (5.77%)
Education Qualifications		
College or University degree	1,626 (13.15%)	314 (11.54%)
A levels/AS levels or equivalent	341 (2.76%)	72 (2.65%)
O levels/GCSEs or equivalent	2,266 (18.32%)	504 (18.53%)
CSEs or equivalent	878 (7.10%)	125 (4.60%)
NVQ or HND or HNC or equivalent	1,788 (14.46%)	436 (16.03%)
Other professional qualifications e.g.: nursing, teaching	5,467 (44.21%)	1,269 (46.65%)

Table S7. **Demographic Characteristics of the Second UK Biobank Imaging Participants**

	Control Group (N=11,241)	**Hypertension History Group (N=2,220)**
Characteristics	**No. (%)**	**No. (%)**
Age, mean (SD), y	56.32 (7.50)	60.32 (6.52)
Female	6,930 (56.85%)	934 (42.45%)
Townsend deprivation index, mean (SD), points	-1.74 (2.81)	-1.69 (2.78)
BMI	26.22 (4.04)	28.79 (4.73)
Drinking Status		
Prefer not to say	5 (0.04%)	0 (0.00%)
Never	271 (2.41%)	49 (2.23%)
Previous	260 (2.31%)	65 (2.95%)
Current	10,696 (95.23%)	2,086 (94.82%)
Smoking Status		
Never	6,896 (61.40%)	1,171 (53.23%)
Previous	3,610 (32.14%)	909 (41.32%)
Current	726 (6.46%)	120 (5.45%)
Education Qualifications		
College or University degree	5,411(48.62%)	850 (39.17%)
A levels/AS levels or equivalent	1,459 (13.11%)	265 (12.21%)
O levels/GCSEs or equivalent	2,034(18.27%)	442(20.37%)
CSEs or equivalent	444 (3.99%)	93 (4.29%)
NVQ or HND or HNC or equivalent	599 (5.38%)	155 (7.14%)
Other professional qualifications e.g.: nursing, teaching	523 (4.70%)	136 (6.27%)

Reference

1. Rolls ET, Joliot M, Tzourio-Mazoyer N. Implementation of a new parcellation of the orbitofrontal cortex in the automated anatomical labeling atlas. *Neuroimage* 2015; **122**: 1-5.