Supplementary Information: APOE4 and sedentary lifestyle synergistically impair neurovascular function in the visual cortex of awake mice

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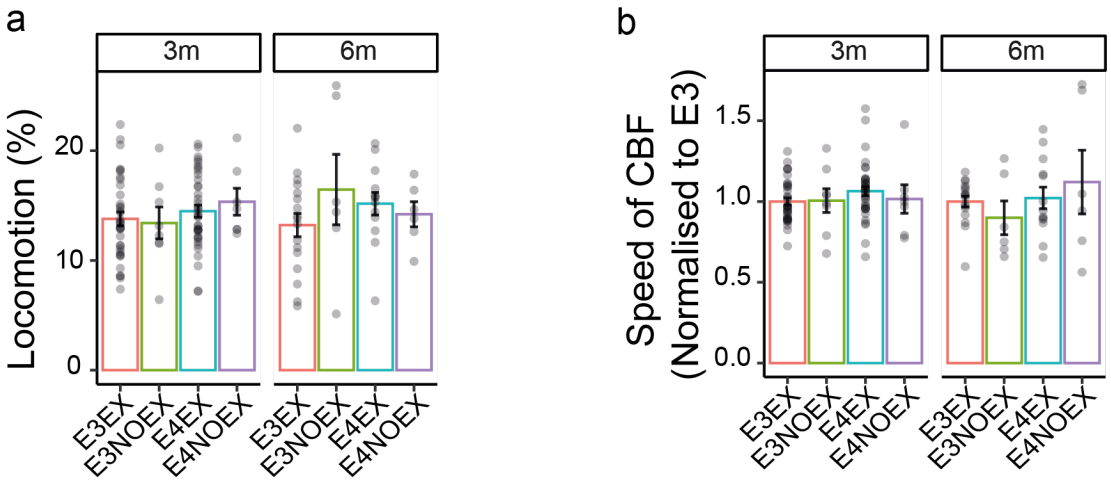
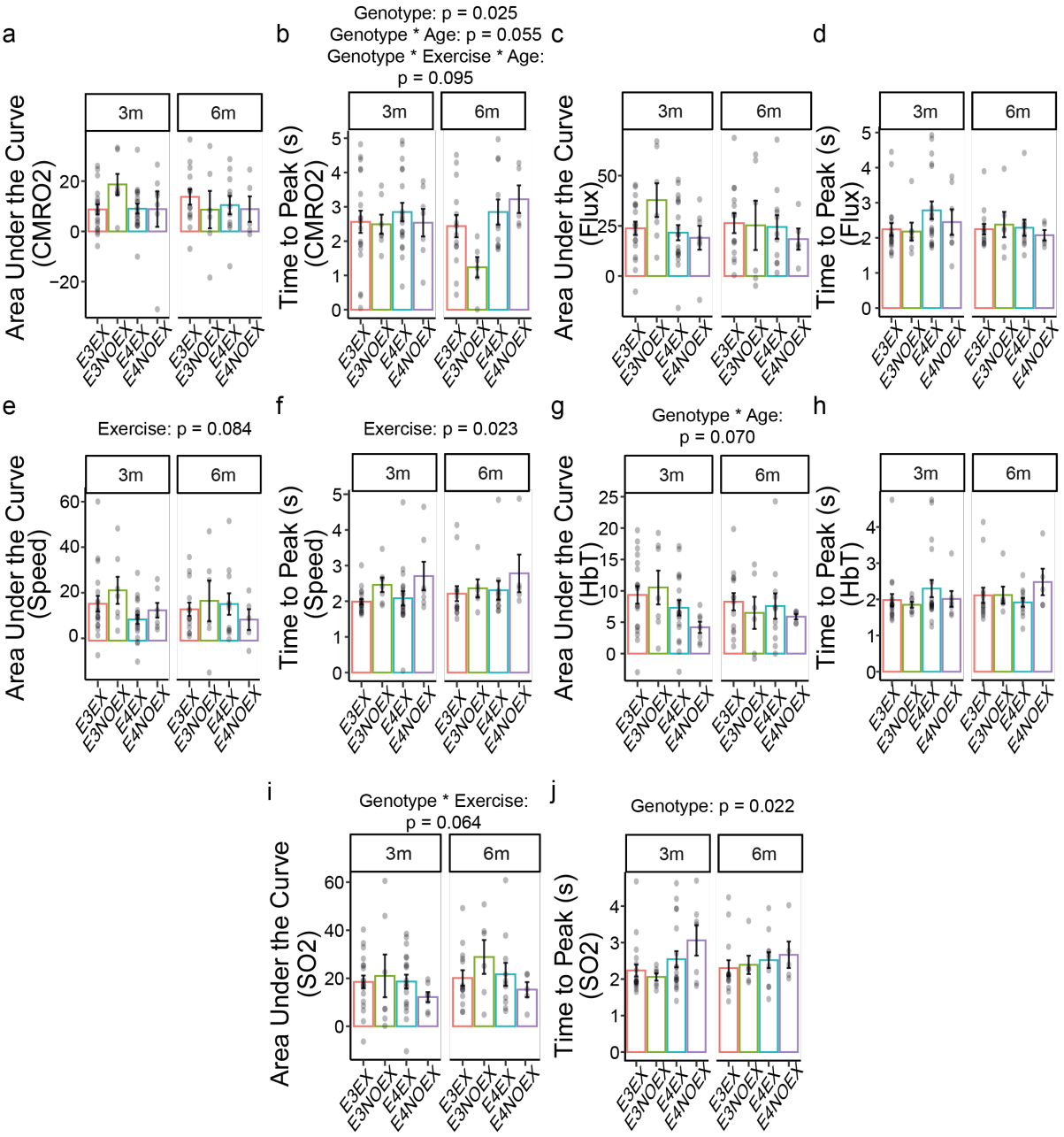


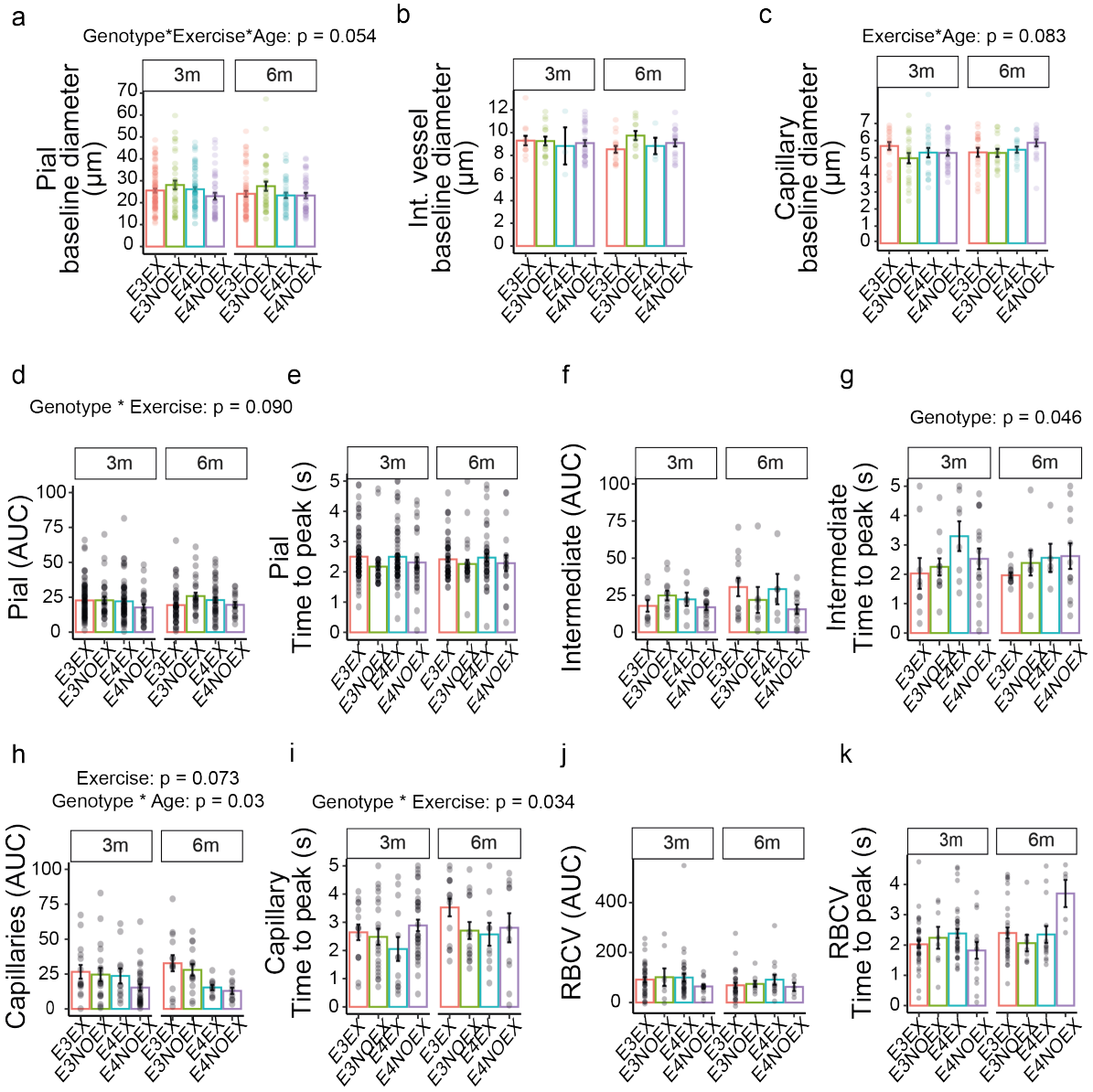
Supp. Figure 1. There was no difference in locomotion or speed of CBF between groups during resting periods.

(a) The percentage of time spent in locomotion during the length of spontaneous net haemodynamic recordings is not different between experimental groups. (b) Speed of CBF at baseline was not affected by genotype, exercise or age. Dots represent average per mouse. Bars indicate mean and error bars indicate mean +/- SEM.



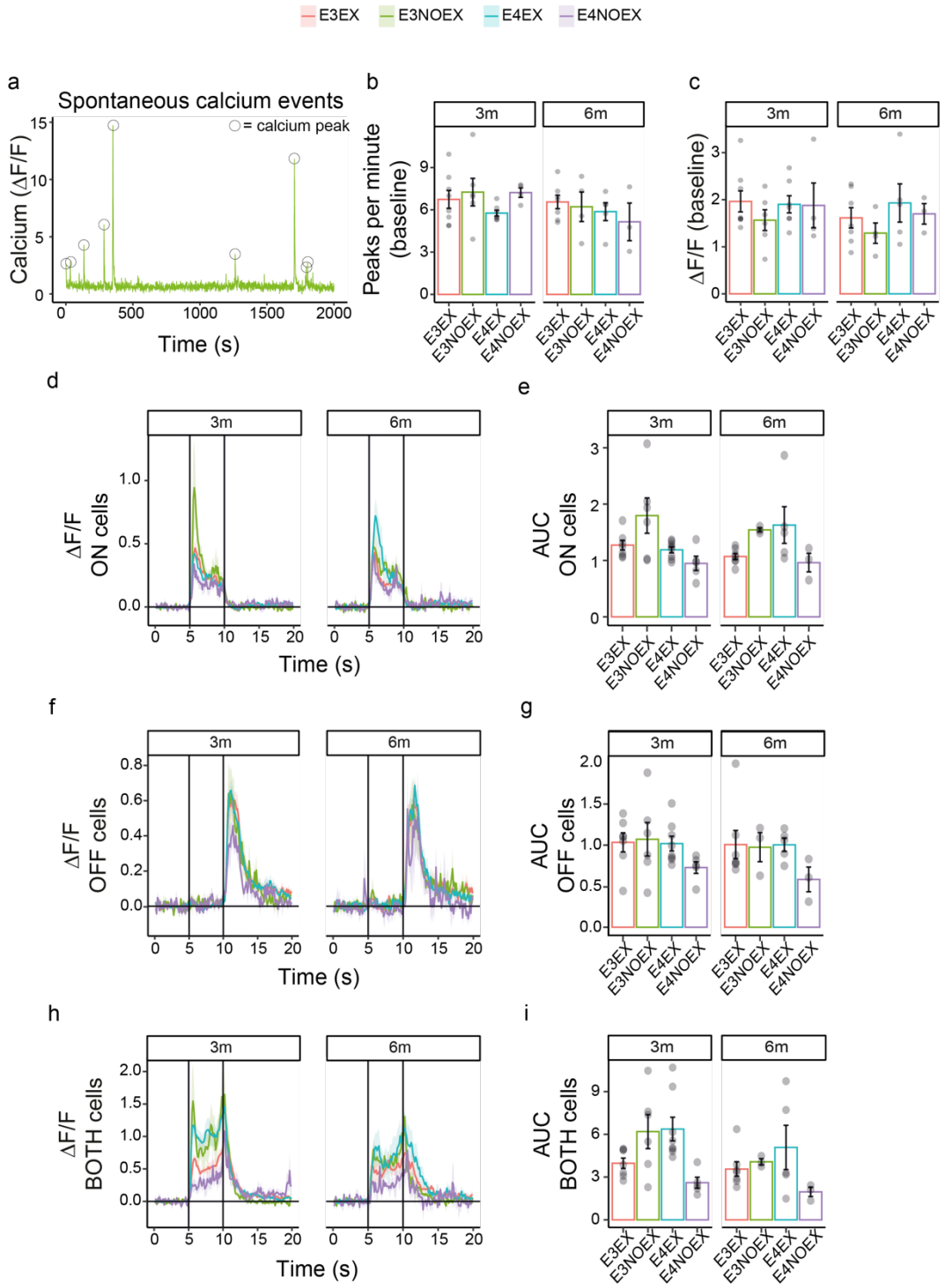
Supp. Figure 2. Area Under the Curve (AUC) and time to peak of net haemodynamic measures during visual stimulus. (a,c,e,g,i) AUC and (b,d,f,h,j) time to peak response for different haemodynamic measures during visual stimulation. There was no genotype, exercise or age effect on the AUC of CMRO2 (a) and flux (c), but there was a trend effect of exercise in increasing the Speed of CBF (e), a trend level interaction between genotype and age on HbT (g) and a trend level interaction between genotype and exercise on sO2 AUC (i). APOE4 mice has lower CMRO2 (b) and sO2 responses (j). Exercise fasted the response time of Speed of CBF (f). Flux (d) and HbT (h)

response time was similar between groups. Dots represent average per mouse. Bars and error bars: mean +/- SEM.



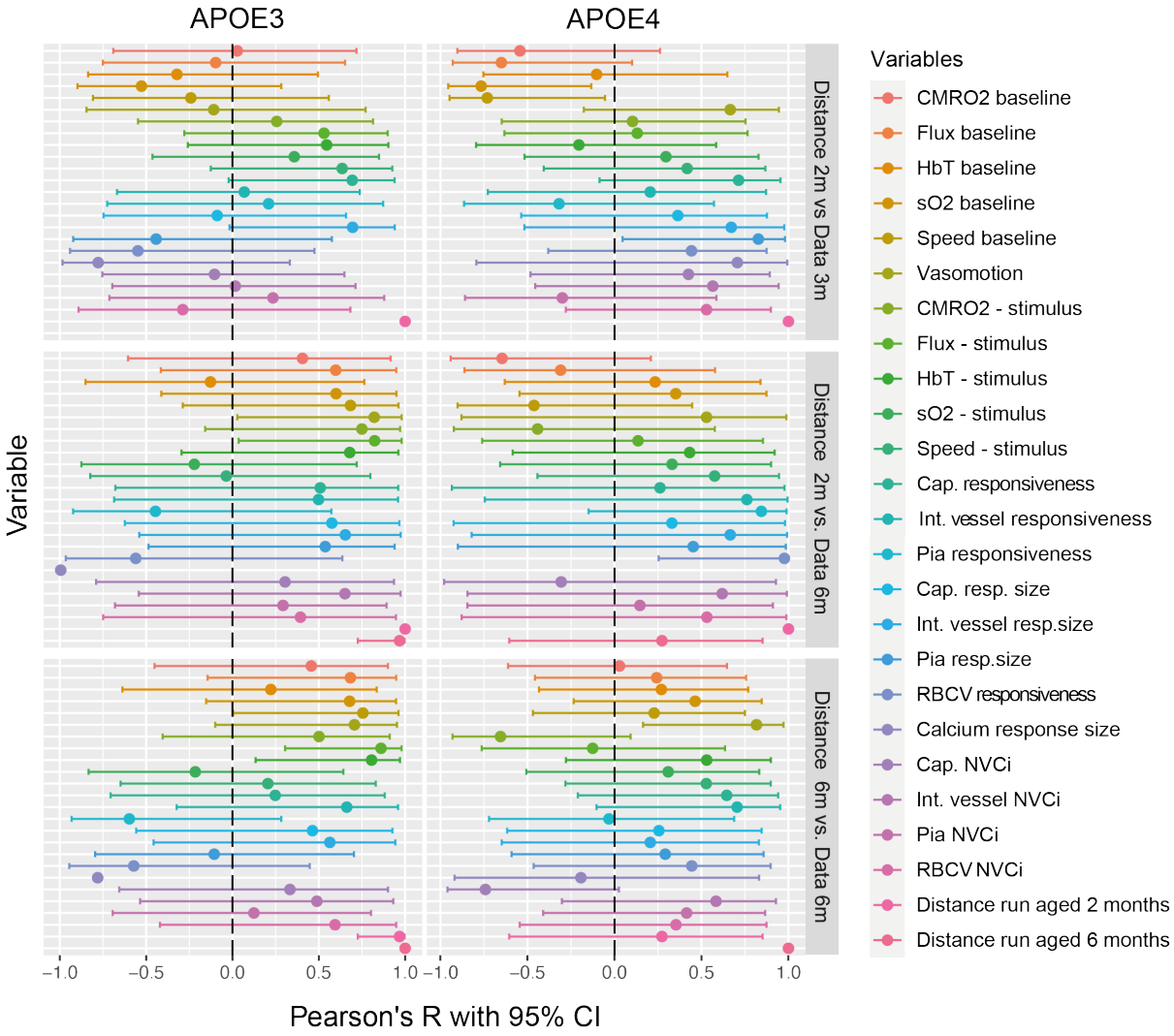
Supp. Figure 3. Additional properties of different vascular segments. Vessel diameter at baseline in (a) pial arteries, (b) intermediate vessels and (c) capillaries. Vessels sampled were the same size across genotype, exercise or age groups. (d,f,h,j) Area Under the Curve (AUC) of vessel dilation responses during visual stimulation. This was unchanged by genotype, exercise or age for pial vessels (d), intermediate vessels (f) and RBCV (j), whereas there was an interaction between genotype and age on the AUC of capillaries, with capillaries of old

APOE4 mice showing lower AUC (h). The time it took for the vessel to reach its maximum peak dilation (e,g,i,k) was similar between groups in pial vessels (e) and RBCV (k), whereas APOE4 mice shower slower time to peak of intermediate vessels (g) and APOE3 exercise mice showed slower time to peak in capillaries (i). APOE4 sedentary mice had slower increase in RBCV following stim (k). Dots representing individual vessels. Bars and errors bars: mean +/-SEM.

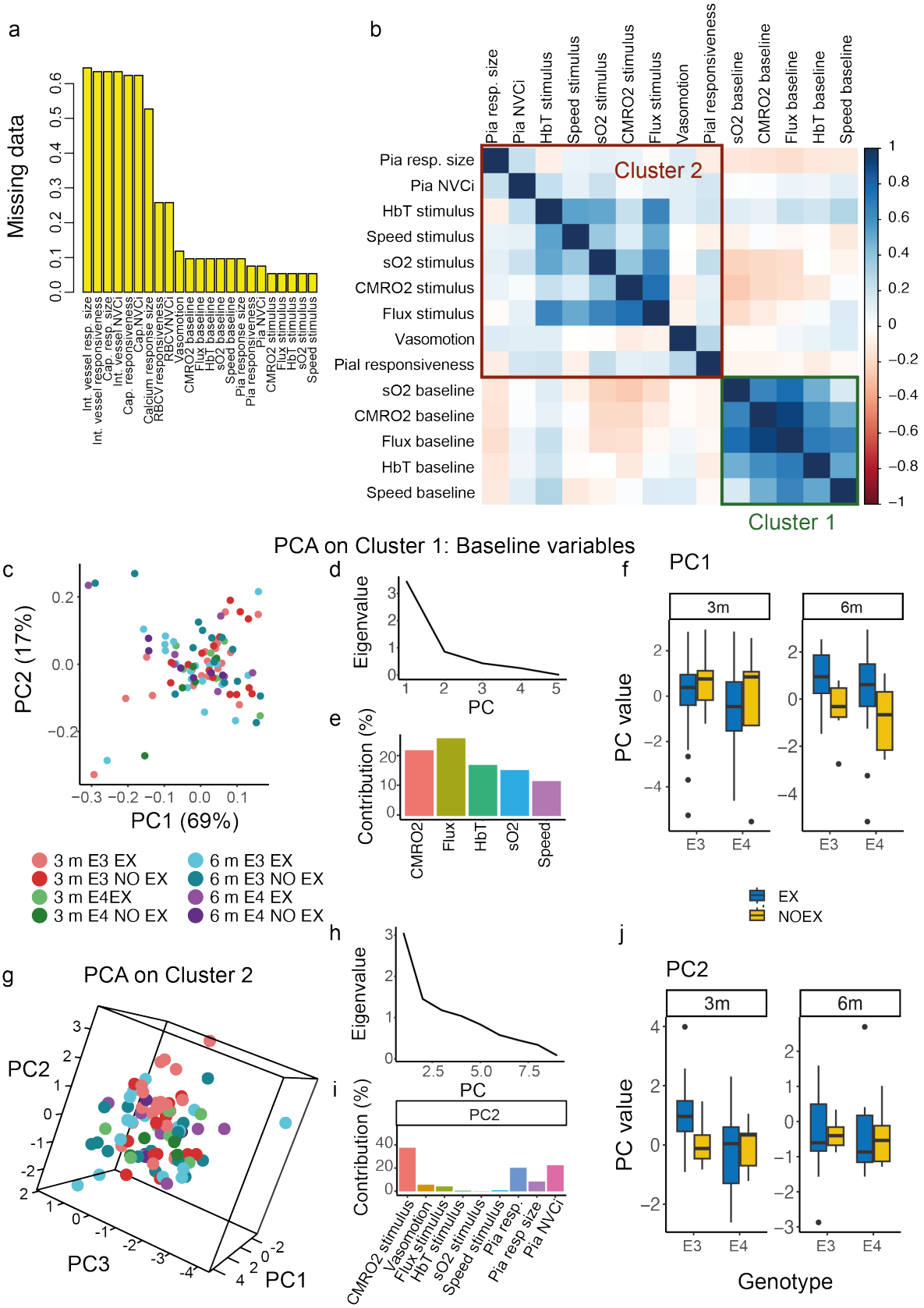


Supp. Figure 4. Baseline neuronal activity is similar between experimental groups but APOE4 sedentary mice have lower activation of neurons that respond during stimulus onset and offset. (a) Example trace of spontaneous calcium events during baseline recordings. Peaks (indicated by circles) were identified as changes in signal larger than at least 2 s.d. from average baseline signal. (b) The number of detected peaks per minute during baseline did not differ between genotypes, exercise conditions or age nor did the size of the spontaneous

neuronal activity events (c). Classifying neurons based on their responses during stimulus as ON (d,e) (when they activate as the stimulus comes on), OFF (f,g) (when they activate as the stimulus comes off) and BOTH (h,i) (when they activate as the stimulus comes on and as the stimulus comes off) we saw that APOE4 sedentary mice had BOTH neurons that activated more weakly compared to the other groups (i). Dots representing average ΔF/F per animal. Bars and error bars: mean +/- SEM.



Supp. Figure 5. Correlations between neurovascular function and exercise plotted by genotype. Data shows Pearson's R with 95% confidence intervals (CI) for the different variables measured per genotype at 3- and 6-month of age over the distance ran by the mice at 2- and 6-month of age.



Supp. Figure 6. Principal Component Analysis (PCA) over to identify underlying factors driving inter-variable correlations do not show any effect of exercise and genotype. (a) Percentage of missing data for each animal.

Animals that had >20% data missing were excluded from PCA analysis. (b) Correlation matrix of the neurovascular values studies showed the presence of two clusters of correlated variables, with one comprising the baseline haemodynamic measurements and the other including all other variables. (c) Plot of the first two principal components (PC) identified by conducting a PCA over the first cluster. PC1 accounts for 69% of the total variance and PC2 accounts to 17%. There was no clear distinction between the experimental groups. (d) Only PC1 had an eigenvalue over 1. (e) PC1 had similar contributions from all baseline variables. (f) PC1 value was not affected by genotype, exercise or age. (g) Distribution of PC1-3 obtained from conducting PCA on the second cluster. (h) PC1-4 had an eigenvalue higher than 1. Correction for multiple comparison using Bonferroni correction revealed that the only significant effect was found in PC2. (i) Vasomotion, pial responsivity and pial NVCi were the main contributing values for PC2. (j) PC2 was significantly affected by age, with APOE genotype trending towards significance.

Supplementary Statistical Information:

Supplementary Table 1: Statistical outputs from Figure 1

Figure Label	Experimental Groups	n mice	n data	Mean	SD	Test	Factor	F value	p-value
1H Exercise distance per day	2m-E3EX	3	14	2586.03	414.24	LMM with genotype, exercise and age as fixed factors and anID as random factor	genotype	0.06916	0.7961
	2m-E3NOEX	5	23	1360.68	541.59		exercise	17.0102	0.0009
	2m-E4EX	3	14	2884.53	470.13		age	467.6715	1.1456e-101
	2m-E4NOEX	5	25	1321.29	1042.56		genotype:exercise	0.2073	0.6554
	6m-E3EX	3	15	881.11	351.78		genotype:age	1.2689	0.2600
	6m-E3NOEX	4	17	254.45	119.96		exercise:age	43.7005	3.9985e-11
	6m-E4EX	4	18	383.17	345.90		genotype:exercise:age	11.7951	0.0006
	6m-E4NOEX	6	26	199.30	149.43				

Supplementary Table 2: Statistical outputs for Figure 2

Figure Label	Experimental Groups	n mice	n data	Mean	SD	Test	Factor	F value	p-value
2C capillary density	E3EX	4	9	1.53	0.63	LMM with genotype and exercise as fixed factors and anID as random factor	genotype	0.2425	0.6325
	E3NOEX	5	7	0.94	0.46		exercise	5.2076	0.0443
	E4EX	3	7	1.23	0.36		genotype:exercise	0.5054	0.4925
	E4NOEX	7	10	1.00	0.49				
2D Flux baseline	3m-E3EX	19	19	1.03	0.33	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype	0.0794	0.7795
	3m-E3NOEX	7	7	1.03	0.22		exercise	0.0208	0.8861
	3m-E4EX	19	19	0.95	0.27		age	0.5717	0.4545
	3m-E4NOEX	7	7	0.99	0.24		genotype:exercise	0.2757	0.6021
	6m-E3EX	11	11	0.98	0.31		genotype:age	0.2542	0.6172
	6m-E3NOEX	6	6	0.92	0.27		exercise:age	0.0133	0.9089
	6m-E4EX	9	9	0.95	0.30		genotype:exercise:age	0.1783	0.6754
	6m-E4NOEX	6	6	1.01	0.50				
2E HbT baseline	3m-E3EX	19	19	1.01	0.23	LMM with genotype,	genotype	0.3685	0.5466
	3m-E3NOEX	7	7	1.21	0.26		exercise	0.6301	0.4312

	3m-E4EX	19	19	1.11	0.31	exercise and age as fixed factors and anID and mouse cohort as random factors	age	3.6141	0.0649
	3m-E4NOEX	7	7	1.03	0.28		genotype:exercise	0.8350	0.3653
	6m-E3EX	11	11	0.99	0.22		genotype:age	0.0003	0.9865
	6m-E3NOEX	6	6	1.05	0.17		exercise:age	0.0082	0.9285
	6m-E4EX	9	9	0.99	0.18		genotype:exercise:age	2.2501	0.1419
	6m-E4NOEX	6	6	1.01	0.40				
2F CMRO2 baseline	3m-E3EX	19	19	1.02	0.32	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype	0.1650	0.6865
	3m-E3NOEX	7	7	0.95	0.24		exercise	0.2053	0.6527
	3m-E4EX	19	19	0.92	0.25		age	0.0634	0.8028
	3m-E4NOEX	7	7	0.94	0.15		genotype:exercise	0.5140	0.4771
	6m-E3EX	11	11	0.98	0.32		genotype:age	0.0833	0.7747
	6m-E3NOEX	6	6	1.00	0.22		exercise:age	1.5733	0.2183
	6m-E4EX	9	9	0.92	0.27		genotype:exercise:age	0.1811	0.6732
	6m-E4NOEX	6	6	1.08	0.45				
2G sO2 baseline	3m-E3EX	19	19	1.02	0.26	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype	0.2080	0.6506
	3m-E3NOEX	7	7	1.13	0.07		exercise	0.1768	0.6762
	3m-E4EX	19	19	0.95	0.16		age	10.3597	0.0033
	3m-E4NOEX	7	7	1.07	0.10		genotype:exercise	0.0164	0.8987
	6m-E3EX	11	11	0.98	0.27		genotype:age	0.7361	0.3983
	6m-E3NOEX	6	6	0.90	0.12		exercise:age	6.3405	0.0179
	6m-E4EX	9	9	1.02	0.26		genotype:exercise:age	0.0254	0.8745
	6m-E4NOEX	6	6	0.92	0.12				
2K Vasomotion	3m-E3EX	18	84	5.99	5.27	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype	3.2595	0.0794
	3m-E3NOEX	5	30	3.85	2.96		exercise	8.5983	0.0058
	3m-E4EX	18	70	3.62	3.18		age	0.7024	0.4026
	3m-E4NOEX	7	22	2.49	2.76		genotype:exercise	0.0196	0.8894
	6m-E3EX	14	51	5.47	4.15		genotype:age	1.3985	0.2378
	6m-E3NOEX	5	31	3.84	2.65		exercise:age	0.4240	0.5154

Supplementary Table 3: Statistical outputs from Figure 3

Figure Label	Experimental Groups	n mice	n data	Mean	SD	Test	Factor	F value	p-value

3C CMRO2 stim	3m-E3EX	19	19	7.17	2.77	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype exercise age genotype:exercise genotype:age exercise:age genotype:exercise:age	2.3929 0.8967 0.0014 1.8948 0.2661 1.4987 0.1892	0.1281 0.3482 0.9701 0.1747 0.6086 0.2275 0.6658
	3m-E3NOEX	7	7	9.00	3.33				
	3m-E4EX	19	19	7.89	3.15				
	3m-E4NOEX	7	7	5.94	3.44				
	6m-E3EX	14	14	9.07	4.89				
	6m-E3NOEX	6	6	8.22	7.17				
	6m-E4EX	11	11	7.87	5.11				
	6m-E4NOEX	5	5	5.14	2.79				
3D Flux Stim	3m-E3EX	19	19	12.38	4.28	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype exercise age genotype:exercise genotype:age exercise:age genotype:exercise:age	3.1366 1.3940 0.3547 3.1764 0.4443 2.8085 0.2627	0.0831 0.3171 0.5548 0.0812 0.5089 0.1016 0.6111
	3m-E3NOEX	7	7	15.9	7.11				
	3m-E4EX	19	19	12.41	4.95				
	3m-E4NOEX	7	7	9.43	2.85				
	6m-E3EX	14	14	13.71	5.99				
	6m-E3NOEX	6	6	12.4	8.03				
	6m-E4EX	11	11	13.48	6.72				
	6m-E4NOEX	5	5	8.41	3.01				
3E Speed Stim	3m-E3EX	19	19	7.44	4.71	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype exercise age genotype:exercise genotype:age exercise:age genotype:exercise:age	6.4678 4.6006 0.2458 1.4670 0.0009 0.2220 2.4919	0.0144 0.0376 0.6224 0.2320 0.9755 0.6398 0.1212
	3m-E3NOEX	7	7	8.43	5.13				
	3m-E4EX	19	19	4.86	2.31				
	3m-E4NOEX	7	7	6.46	3.13				
	6m-E3EX	14	14	7.27	3.11				
	6m-E3NOEX	6	6	9.89	6.06				
	6m-E4EX	11	11	7.36	5.27				
	6m-E4NOEX	5	5	5.06	3.87				
3F HbT Stim	3m-E3EX	19	19	1.32	1.05	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype exercise age genotype:exercise genotype:age exercise:age genotype:exercise:age	3.8997 1.5213 0.7439 0.4927 1.2922 0.5355 0.1124	0.0543 0.2237 0.3937 0.4863 0.2626 0.4687 0.7392
	3m-E3NOEX	7	7	0.56	0.77				
	3m-E4EX	19	19	1.42	1.15				
	3m-E4NOEX	7	7	0.48	0.62				
	6m-E3EX	14	14	1.55	1.36				
	6m-E3NOEX	6	6	1.29	2.88				
	6m-E4EX	11	11	0.77	0.95				
	6m-E4NOEX	5	5	0.45	0.50				
3G sO2 Stim	3m-E3EX	19	19	9.25	3.32	LMM with genotype, exercise and age	genotype exercise age	3.9933 1.7815 1.1332	0.0491 0.1858 0.2903
	3m-E3NOEX	7	7	9.06	6.99				
	3m-E4EX	19	19	9.46	2.89				

	3m-E4NOEX	7	7	6.19	1.94	as fixed factors and anID and mouse cohort as random factors	genotype:exercise	6.5346	0.0125
	6m-E3EX	14	14	9.57	4.48		genotype:age	0.4544	0.5022
	6m-E3NOEX	6	6	12.21	4.66		exercise:age	0.1563	0.6937
	6m-E4EX	11	11	10.47	5.56		genotype:exercise:age	1.0299	0.3132
	6m-E4NOEX	5	5	5.96	3.54				

Supplementary Table 4: Statistical outputs for Figure 4

Figure Label	Experimental Groups	n mice	n data	Mean	SD	Test	Factor	F value	p-value
4C, G, K Vess Responsiveness	3m-E3EX-pial	19	95	64.78	30.03	LMM with genotype, exercise, vessel type and age as fixed factors and anID and mouse cohort as random factors	genotype	19.1180	0.0002
	3m-E3NOEX-pial	5	36	47.37	30.17		exercise	6.1709	0.0236
	3m-E4EX-pial	18	86	52.10	31.64		age	1.0545	0.3049
	3m-E4NOEX-pial	6	43	29.05	29.51		vess_type	4.0742	0.0174
	6m-E3EX-pial	14	66	49.88	26.73		genotype:exercise	1.6705	0.2072
	6m-E3NOEX-pial	5	34	45.09	30.57		genotype:age	5.5175	0.0191
	6m-E4EX-pial	13	51	52.22	33.64		exercise:age	0.3552	0.5514
	6m-E4NOEX-pial	4	30	18.54	21.02		genotype:vess_type	0.4234	0.6550
	3m-E3EX-int	4	10	53.38	31.14		exercise:vess_type	0.3870	0.6793
	3m-E3NOEX-int	6	12	53.26	26.86		age:vess_type	0.3926	0.6755
	3m-E4EX-int	3	9	48.02	29.75		genotype:exercise:age	0.0373	0.8468
	3m-E4NOEX-int	5	20	33.44	22.94		genotype:exercise:vess_type	1.0162	0.3627
	6m-E3EX-int	3	17	59.99	43.08		genotype:age:vess_type	4.7572	0.0089
	6m-E3NOEX-int	5	8	48.19	31.04		exercise:age:vess_type	1.3097	0.2706
	6m-E4EX-int	3	6	39.08	25.19		genotype:exercise:age:vess_type	1.8182	0.1631
	6m-E4NOEX-int	4	13	26.93	14.45				
	3m-E3EX-cap	3	17	39.07	22.34				
	3m-E3NOEX-cap	7	26	23.88	21.63				
	3m-E4EX-cap	3	14	46.86	34.23				
	3m-E4NOEX-cap	7	37	27.85	19.06				
	6m-E3EX-cap	4	15	50.61	30.60				
	6m-E3NOEX-cap	3	18	44.39	34.27				
	6m-E4EX-cap	3	11	20.26	16.91				
	6m-E4NOEX-cap	4	12	21.91	14.61				

4E, I, M Vess Max Peak during Stim	3m-E3EX-pial	19	88	10.37	4.82	LMM with genotype, exercise, vessel type and age as fixed factors and anID and mouse cohort as random factors	genotype	5.2584	0.0222
	3m-E3NOEX-pial	5	33	12.05	4.22		exercise	5.7306	0.0170
	3m-E4EX-pial	19	73	9.68	5.41		age	0.2747	0.6004
	3m-E4NOEX-pial	6	30	9.27	4.26		vess_type	1.1078	0.3310
	6m-E3EX-pial	14	59	9.21	4.92		genotype:exercise	4.3979	0.0364
	6m-E3NOEX-pial	5	29	13.66	6.86		genotype:age	2.4947	0.1148
	6m-E4EX-pial	13	46	9.81	4.83		exercise:age	0.1433	0.7051
	6m-E4NOEX-pial	5	19	9.97	5.00		genotype:vess_type	0.2071	0.8130
	3m-E3EX-int	4	9	9.05	4.75		exercise:vess_type	1.4855	0.2273
	3m-E3NOEX-int	6	12	9.82	3.19		age:vess_type	2.2768	0.1035
	3m-E4EX-int	3	8	10.49	10.07		genotype:exercise:age	0.6848	0.4083
	3m-E4NOEX-int	6	17	7.09	2.83		genotype:exercise:vess_type	0.3048	0.7374
	6m-E3EX-int	3	13	16.12	8.13		genotype:age:vess_type	1.0614	0.3466
	6m-E3NOEX-int	5	8	10.08	8.98		exercise:age:vess_type	2.1762	0.1144
	6m-E4EX-int	3	5	11.81	6.90		genotype:exercise:age:vess_type	0.9721	0.3789
	6m-E4NOEX-int	4	12	7.67	4.61				
	3m-E3EX-cap	3	15	11.39	6.97				
	3m-E3NOEX-cap	7	21	10.84	7.39				
	3m-E4EX-cap	3	13	14.42	14.14				
	3m-E4NOEX-cap	7	33	9.42	8.52				
	6m-E3EX-cap	4	14	10.55	6.76				
	6m-E3NOEX-cap	4	15	12.13	8.18				
	6m-E4EX-cap	3	10	9.09	3.72				
	6m-E4NOEX-cap	4	11	8.43	4.11				
4O RBCV Responsiveness	3m-E3EX	15	47	43.41	29.52	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype	8.3474	0.0043
	3m-E3NOEX	4	47	35.50	30.14		exercise	2.1780	0.1415
	3m-E4EX	15	12	37.53	36.88		age	3.2197	0.0742
	3m-E4NOEX	7	21	27.85	27.03		genotype:exercise	1.9408	0.1651
	6m-E3EX	13	45	34.41	34.02		genotype:age	1.1276	0.2895
	6m-E3NOEX	3	22	27.91	27.20		exercise:age	0.0051	0.9431
	6m-E4EX	8	11	39.48	33.19		genotype:exercise:age	1.4596	0.2284
	6m-E4NOEX	4	13	7.93	11.24				
4Q RBCV peak response	3m-E3EX	14	39	43.97	22.43	LMM with genotype, exercise and age	genotype	0.6842	0.4143
	3m-E3NOEX	4	8	46.01	34.10		exercise	1.6623	0.2067
	3m-E4EX	12	35	44.50	29.89		age	1.3805	0.2419

	3m-E4NOEX	7	15	26.25	16.05	as fixed factors and anID and mouse cohort as random factors	genotype:exercise genotype:age exercise:age genotype:exercise:age	2.3120 0.7451 0.0025 0.0646	0.1383 0.3895 0.9606 0.7997
	6m-E3EX	12	31	34.96	20.21				
	6m-E3NOEX	2	9	34.49	17.75				
	6m-E4EX	7	14	38.48	26.05				
	6m-E4NOEX	2	5	25.71	15.00				

Supplementary Table 5: Statistical outputs for Figure 5

Figure Label	Experimental Groups	n mice	n data	Mean	SD	Test	Factor	F value	p-value
5D Neuronal Calcium Increase (AUC)	3m-E3EX	7	7	1.77	0.43	LMM with genotype, exercise and age as fixed factors and anID and mouse cohort as random factors	genotype	0.8026	0.3795
	3m-E3NOEX	6	6	2.71	1.32		exercise	0.1771	0.6874
	3m-E4EX	8	8	2.27	0.39		age	1.0257	0.3217
	3m-E4NOEX	5	5	1.21	0.44		genotype:exercise	13.5841	0.0011
	6m-E3EX	7	7	1.55	0.30		genotype:age	1.1627	0.2921
	6m-E3NOEX	3	3	1.90	0.02		exercise:age	1.2071	0.2833
	6m-E4EX	5	5	2.46	1.60		genotype:exercise:age	0.0519	0.8218
	6m-E4NOEX	3	3	1.02	0.42				
5E, F, G NVCi in pial, intermediate vessels and capillaries	3m-E3EX-pial	19	95	7.40	7.85	LMM with genotype, exercise, vessel type and age as fixed factors and anID as random factor	genotype	6.6727	0.0131
	3m-E3NOEX-pial	5	36	6.44	9.27		exercise	9.2030	0.0040
	3m-E4EX-pial	19	86	5.69	8.79		age	0.2457	0.6203
	3m-E4NOEX-pial	6	43	0.77	5.10		vess_type	1.4055	0.2460
	6m-E3EX-pial	14	66	4.19	10.94		genotype:exercise	0.4807	0.4916
	6m-E3NOEX-pial	5	34	6.53	10.36		genotype:age	12.3101	0.0005
	6m-E4EX-pial	13	51	5.71	10.48		exercise:age	0.1083	0.7422
	6m-E4NOEX-pial	5	30	-2.44	11.15		genotype:vess_type	0.9710	0.3793
	3m-E3EX-int	4	10	6.14	5.10		exercise:vess_type	0.6529	0.5209
	3m-E3NOEX-int	6	12	4.06	6.90		age:vess_type	1.3050	0.2719
	3m-E4EX-int	3	8	10.68	16.16		genotype:exercise:age	0.3694	0.5435
	3m-E4NOEX-int	6	20	1.76	4.87		genotype:exercise:vess_type	4.8643	0.0080
	6m-E3EX-int	3	17	10.23	18.35		genotype:age:vess_type	5.8695	0.0030
	6m-E3NOEX-int	5	8	6.58	17.00		exercise:age:vess_type	0.2788	0.7568
	6m-E4EX-int	3	6	5.82	10.21		genotype:exercise:age:vess_type	3.7671	0.0236
	6m-E4NOEX-int	4	13	-1.66	6.78				
	3m-E3EX-cap	3	17	6.46	4.98				
	3m-E3NOEX-cap	7	26	1.04	10.46				
	3m-E4EX-cap	3	15	5.53	21.39				
	3m-E4NOEX-cap	7	37	1.14	4.73				
	6m-E3EX-cap	4	15	14.38	14.43				
	6m-E3NOEX-cap	4	18	8.90	9.62				
	6m-E4EX-cap	3	11	-3.41	5.42				

	6m-E4NOEX-cap	4	12	0.00	6.42				
5H NVCi RBCV	3m-E3EX	15	47	22.60	29.41	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.9180	0.3443
	3m-E3NOEX	4	12	30.13	45.86		exercise	0.0864	0.7704
	3m-E4EX	15	47	19.90	35.05		age	7.5448	0.0065
	3m-E4NOEX	7	21	14.34	17.11		genotype:exercise	0.3603	0.5520
	6m-E3EX	13	45	13.71	29.35		genotype:age	0.3250	0.5692
	6m-E3NOEX	3	11	18.08	27.53		exercise:age	1.4345	0.2324
	6m-E4EX	8	22	15.00	24.52		genotype:exercise:age	0.5135	0.4744
	6m-E4NOEX	4	13	2.95	15.59				

Supplementary Table 6: Correlations between exercise level and neurovascular functional parameters

Correlation between (timepoint of haemodynamic data collection vs. timepoint of exercise measurement)	**variable**	**Pearson's r**	**Lower CI**	**Upper CI**	**p.value**	**FDR adjusted p**
3m data vs. 2m distance travelled	calcium.AUC	0.04	-0.64	0.68	0.92	0.95
	cap.NVCi	0.20	-0.35	0.65	0.47	0.65
	cap.resp.maxpk	0.10	-0.44	0.58	0.73	0.82
	cap.VessRespRate	0.64	0.20	0.87	0.01	0.13
	cmro2.maxpk	0.14	-0.38	0.60	0.60	0.73
	cmro2.norm	-0.28	-0.68	0.25	0.29	0.48
	flux.maxpk	0.26	-0.27	0.67	0.34	0.52
	flux.norm	-0.43	-0.76	0.09	0.10	0.38
	hbt.maxpk	0.14	-0.38	0.60	0.60	0.73
	hbt.norm	-0.19	-0.63	0.34	0.48	0.65
	int.NVCi	0.41	-0.15	0.77	0.14	0.42
	int.resp.maxpk	0.67	0.19	0.89	0.01	0.13
	int.VessRespRate	0.16	-0.40	0.64	0.58	0.73
	ls_RBCV.VessRespRate	0.22	-0.35	0.67	0.45	0.65

	pia.NVCi	-0.07	-0.60	0.50	0.83	0.86
	pia.resp.maxpk	0.42	-0.20	0.80	0.17	0.42
	pia.VessRespRate	-0.08	-0.60	0.50	0.81	0.86
	RBCV.NVCi	0.31	-0.26	0.72	0.27	0.47
	so2.maxpk	0.26	-0.27	0.67	0.33	0.52
	so2.norm	-0.64	-0.86	-0.21	0.01	0.13
	speed.maxpk	0.39	-0.13	0.74	0.13	0.42
	speed.norm	-0.55	-0.82	-0.07	0.03	0.24
	vasomotion.Param	0.41	-0.19	0.78	0.17	0.42
6m data vs. 2m distance travelled	calcium.AUC	0.01	-0.88	0.88	0.99	1.00
	cap.NVCi	0.14	-0.57	0.74	0.71	0.82
	cap.resp.maxpk	0.41	-0.35	0.84	0.27	0.47
	cap.VessRespRate	0.36	-0.40	0.83	0.34	0.52
	cmro2.maxpk	0.20	-0.42	0.70	0.53	0.69
	cmro2.norm	-0.38	-0.77	0.22	0.20	0.44
	flux.maxpk	0.42	-0.20	0.80	0.17	0.42
	flux.norm	-0.07	-0.60	0.50	0.82	0.86
	hbt.maxpk	0.46	-0.16	0.82	0.14	0.42
	hbt.norm	0.20	-0.40	0.67	0.52	0.69
	int.NVCi	0.61	-0.09	0.91	0.08	0.35
	int.resp.maxpk	0.65	-0.03	0.92	0.06	0.29
	int.VessRespRate	0.45	-0.31	0.86	0.23	0.45
	ls_RBCV.VessRespRate	0.49	-0.26	0.87	0.18	0.43
	pia.NVCi	0.27	-0.40	0.75	0.43	0.64
	pia.resp.maxpk	0.42	-0.29	0.83	0.23	0.45
	pia.VessRespRate	0.63	0.04	0.89	0.04	0.28
	RBCV.NVCi	0.45	-0.31	0.86	0.23	0.45
	so2.maxpk	0.12	-0.49	0.65	0.71	0.82
	so2.norm	0.41	-0.18	0.78	0.17	0.42

	speed.maxpk	0.43	-0.19	0.81	0.16	0.42
	speed.norm	-0.22	-0.69	0.37	0.46	0.65
	vasomotion.Param	0.59	-0.06	0.89	0.07	0.34
6m data vs. 6m distance travelled	calcium.AUC	0.24	-0.56	0.81	0.56	0.72
	cap.NVCi	0.41	-0.18	0.78	0.17	0.42
	cap.resp.maxpk	0.55	0.00	0.85	0.05	0.28
	cap.VessRespRate	0.57	0.03	0.85	0.04	0.28
	cmro2.maxpk	0.31	-0.24	0.71	0.26	0.47
	cmro2.norm	0.18	-0.33	0.61	0.48	0.65
	flux.maxpk	0.65	0.21	0.87	0.01	0.13
	flux.norm	0.35	-0.15	0.71	0.16	0.42
	hbt.maxpk	0.77	0.42	0.92	0.00	0.06
	hbt.norm	0.27	-0.24	0.67	0.29	0.48
	int.NVCi	0.49	-0.09	0.82	0.09	0.37
	int.resp.maxpk	0.34	-0.25	0.75	0.25	0.46
	int.VessRespRate	0.72	0.29	0.91	0.01	0.13
	ls_RBCV.VessRespRate	0.11	-0.47	0.63	0.71	0.82
	pia.NVCi	0.35	-0.19	0.73	0.20	0.44
	pia.resp.maxpk	0.09	-0.46	0.59	0.76	0.85
	pia.VessRespRate	0.00	-0.51	0.51	1.00	1.00
	RBCV.NVCi	0.56	0.02	0.85	0.05	0.28
	so2.maxpk	0.06	-0.47	0.56	0.83	0.86
	so2.norm	0.48	0.00	0.78	0.05	0.28
	speed.maxpk	0.35	-0.19	0.73	0.20	0.44
	speed.norm	0.30	-0.22	0.68	0.25	0.46
	vasomotion.Param	0.61	0.11	0.86	0.02	0.22

Supplementary Table 6A: Statistical outputs for Figure 6A.

Comparison	Variable	Pearson's R	Lower 95th CI	Upper 95th CI	p value	FDR adjusted p value
Data at 3 months vs distance run at 2 months	Calcium response size	0.03782046	-0.6424376	0.68474321	0.92304457	0.96500114
	Capillary NVCi	0.20094528	-0.3470408	0.6466446	0.4726851	0.6470411
	Cap. response size	0.09908809	-0.4352686	0.58181833	0.72533363	0.80722614
	Cap. responsiveness	0.64471292	0.19776416	0.86973495	0.0094641	0.1618284
	CMRO2 - stimulus	0.14205389	-0.3804409	0.59580453	0.59972406	0.72598176
	CMRO2 baseline	-0.2795347	-0.6808911	0.25094297	0.29439626	0.49544737
	Flux - stimulus	0.25768143	-0.27288	0.66805357	0.33528591	0.52845522
	Flux baseline	-0.4283412	-0.7622064	0.08552343	0.0978638	0.35540011
	HbT - stimulus	0.14275153	-0.3798317	0.59626364	0.59791479	0.72598176
	HbT baseline	-0.1911408	-0.6274002	0.33644231	0.47824777	0.6470411
	Intermediate vessel NVCi	0.41260559	-0.1510395	0.77378748	0.14260449	0.39321366
	Intermediate vessel resp. size	0.67285459	0.19366864	0.8928361	0.0117267	0.1618284
	Intermediate vessel responsiveness	0.16146516	-0.4036993	0.6374355	0.58131788	0.72598176
	RBCV responsiveness	0.22046885	-0.3511918	0.6723942	0.44880853	0.64516226
	Pia NVCi	-0.0672362	-0.5961369	0.50235958	0.82724054	0.87814765
	Pia response size	0.42273628	-0.1995869	0.80205267	0.17096246	0.39321366
	Pia responsiveness	-0.0752927	-0.6013317	0.49628088	0.80687174	0.87814765
	RBCV NVCi	0.31420507	-0.2596631	0.72407369	0.27393471	0.48491146
	sO2 - stimulus	0.25932375	-0.2712503	0.6690269	0.33210542	0.52845522
	sO2 baseline	-0.6414295	-0.8627992	-0.2136593	0.00740352	0.1618284
	Speed - stimulus	0.39261233	-0.1280054	0.7435985	0.1325229	0.39321366
	Speed baseline	-0.5492213	-0.8213205	-0.0735364	0.0275579	0.31691582
	Vasomotion	0.40654685	-0.1861323	0.78229665	0.16803176	0.39321366
	Calcium response size	0.0093143	-0.8801852	0.88431371	0.98814083	0.99518912

Data at 6 months vs. distance run at 2 months	Capillary NVCi	0.1449978	-0.5744403	0.73804827	0.70973934	0.80722614
	Cap. response size	0.40922911	-0.3500204	0.8439766	0.27408039	0.48491146
	Cap. responsiveness	0.36030706	-0.3993818	0.82662705	0.34083064	0.52845522
	CMRO2 - stimulus	0.20226642	-0.4204403	0.69544058	0.52840708	0.67518683
	CMRO2 baseline	-0.3765455	-0.7681599	0.22010524	0.20473715	0.42737792
	Flux - stimulus	0.42328611	-0.1989439	0.80229142	0.17034752	0.39321366
	Flux baseline	-0.0719023	-0.5991509	0.49884586	0.81543072	0.87814765
	HbT - stimulus	0.45610993	-0.1595579	0.81632777	0.13613788	0.39321366
	HbT baseline	0.19704279	-0.3970492	0.67476989	0.51877362	0.67518683
	Intermediate vessel NVCi	0.60820094	-0.0938141	0.90626471	0.08225323	0.35471704
	Intermediate vessel resp. size	0.64700485	-0.0300133	0.91707054	0.05963254	0.35471704
	Intermediate vessel responsiveness	0.4462761	-0.3096076	0.8565362	0.22854752	0.42737792
	RBCV responsiveness	0.49127619	-0.2565491	0.87116526	0.17925397	0.39615578
	Pia NVCi	0.26669479	-0.3966354	0.74705353	0.4279238	0.62822855
	Pia response size	0.41874308	-0.2863906	0.82963479	0.22842371	0.42737792
	Pia responsiveness	0.62669272	0.04297278	0.89144159	0.0390804	0.33706848
	RBCV NVCi	0.44574096	-0.3102115	0.85635817	0.22917367	0.42737792
	sO2 - stimulus	0.12023986	-0.4872874	0.64933366	0.70972758	0.80722614
	sO2 baseline	0.40815064	-0.1842754	0.78304163	0.16619804	0.39321366
	Speed - stimulus	0.43112076	-0.1897221	0.80568024	0.16173622	0.39321366
	Speed baseline	-0.223433	-0.6895313	0.37353793	0.46308151	0.6470411
	Vasomotion	0.58922571	-0.0642291	0.88902926	0.07305501	0.35471704
Data at 6 months vs. distance run at 6 months	Calcium response size	0.22150327	-0.8212573	0.92332835	0.72029676	0.80722614
	Capillary NVCi	0.35766373	-0.4019291	0.82566369	0.34464471	0.52845522
	Cap. response size	0.58653922	-0.1270872	0.90005818	0.09689339	0.35540011
	Cap. responsiveness	0.62261582	-0.0707679	0.91032486	0.0733187	0.35471704
	CMRO2 - stimulus	0.49068043	-0.1158428	0.8306649	0.10529281	0.36326018
	CMRO2 baseline	0.27647466	-0.3238427	0.71807335	0.36050336	0.54075503

	Flux - stimulus	0.71541135	0.24008128	0.91403314	0.00890108	0.1618284
	Flux baseline	0.5050953	-0.063586	0.82616016	0.07830738	0.35471704
	HbT - stimulus	0.77067647	0.35282805	0.93225065	0.00334866	0.1618284
	HbT baseline	0.40726056	-0.1853065	0.78262831	0.16721413	0.39321366
	Intermediate vessel NVCi	0.51077316	-0.2320705	0.8773008	0.1599714	0.39321366
	Intermediate vessel resp. size	0.24458399	-0.5009008	0.78172702	0.52591265	0.67518683
	Intermediate vessel responsiveness	0.69613955	0.05954829	0.93020677	0.0372498	0.33706848
	RBCV responsiveness	-0.021341	-0.6758834	0.6520218	0.95654089	0.98509434
	Pia NVCi	0.53215277	-0.0994782	0.85810052	0.09197719	0.35540011
	Pia response size	0.42167098	-0.2831231	0.83073988	0.22484788	0.42737792
	Pia responsiveness	-0.0020664	-0.6011962	0.5985506	0.99518912	0.99518912
	RBCV NVCi	0.61834686	-0.0776711	0.90912819	0.07589827	0.35471704
	sO2 - stimulus	0.11740759	-0.4894751	0.64766901	0.71631222	0.80722614
	sO2 baseline	0.54609712	-0.006992	0.84333123	0.05351267	0.35471704
	Speed - stimulus	0.33319548	-0.2976169	0.76148488	0.28990344	0.49544737
	Speed baseline	0.3932586	-0.2013566	0.77608256	0.18372442	0.39615578
	Vasomotion	0.60026826	-0.0471952	0.89255728	0.06653429	0.35471704

Supplementary Table 6B: Statistical outputs for Figure 6B&C

Figure Label	**Test**	**Factor/ comparison**	**Test statistic (d.f.)**	**p-value**
6B – Comparison of average correlations (Fisher's Z	One way ANOVA with Tukey HSD post hoc tests	Age at correlation	F = 5.49 (2,66)	0.0062

transformed from Pearson's R) of neurovascular function with distance travelled with age		2 month distance/3 month data vs 2 month distance/6 month data	Diff = 0.22	0.068
		2 month distance/3 month data vs 6 month distance/6 month data	Diff = 0.31	0.0055
		2 month distance/6 month data vs 6 month distance/6 month data	Diff = 0.092	0.60
	One way t tests vs. 0 correlation	2 month distance/3 month data	t = 1.45 (22)	0.16
		2 month distance/6 month data	T = 5.33 (22)	2.4e-5
		6 month distance/ 6 month data	T = 7.62 (22)	1.3e-7
6C – Compare correlations between distance run and neurovascular function across APOE genotype	LMM with genotype as a fixed factor and the exact parameters correlated (e.g. RBCV at 3m/ distance at 2m) as a random factor (to enable paired comparison across genotypes)	genotype	F = 0.076 (1,135)	0.78

Supplementary Table 7:
Summary of the main sex effects observed when sex was added as a factor to the LMMs presented in the tables above.
Complete results of the anova test on LMM are shown in Supplementary Table S7.

Measure	**Figure**	**Most significant sex effect or interaction**	**Summary of the effect**
Capillary Density	2C	sex: p = 0.0381	male have lower density
Resting Flux	2D	sex: p = 0.0028	male have lower flux
Resting HBT	2E	sex: p = 0.0055	male have lower hbt
Resting CMRO2	2F	sex: p = 0.0222	male have lower cmro2
Vasomotion	2K	genotype*exercise*sex: p = 0.0327	E4NOEX male have lower vasomotion
Max Peak Vessel	4E,I,M	age*sex*vess_type: p = 0.0265	older male have higher max peak in int vessels
Vess Responsiveness	4C, G,K	sex*genotype: p = 0.0237	E4 females have lower responsiveness
RBCV Responsiveness	4O	exercise * age *sex: p = .0239	young E3NOEX female and young E4EX female have lower

			RBCV responsiveness than male
NVCi vessels	5E-H	exercise * age * sex: p = 0.009	Old EX female have higher NVCi than male and old NOEX female have lower NVCi than male

Supplementary Table S1: Statistical outputs for Supplementary Figure 1.

	Experimental Groups	n mice	n data	Mean	SD	Test	Test Statistic	F-value	p-value
S1A Locomotion percentage	3m-E3EX	19	19	13.78	3.32	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.3198	0.5743
	3m-E3NOEX	7	7	13.19	4.26		exercise	0.2235	0.6385
	3m-E4EX	19	19	14.47	3.23		age	0.5996	0.4434
	3m-E4NOEX	7	7	15.35	3.24		genotype:exercise	0.4518	0.5046
	6m-E3EX	11	11	13.50	3.45		genotype:age	1.1996	0.2802
	6m-E3NOEX	6	6	16.46	7.86		exercise:age	0.2289	0.6351
	6m-E4EX	9	9	15.18	4.11		genotype:exercise:age	3.7391	0.0605
	6m-E4NOEX	6	6	14.20	2.81				
S1B Speed of CBF	3m-E3EX	19	19	1.01	0.13	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	1.3811	0.2458
	3m-E3NOEX	7	7	0.99	0.21		exercise	0.0057	0.9400
	3m-E4EX	19	19	1.03	0.19		age	0.0117	0.9142
	3m-E4NOEX	7	7	1.02	0.23		genotype:exercise	1.0795	0.3041
	6m-E3EX	11	11	1.01	0.16		genotype:age	0.6469	0.4253
	6m-E3NOEX	6	6	0.90	0.26		exercise:age	0.0376	0.8471
	6m-E4EX	9	9	1.00	0.24		genotype:exercise:age	1.1569	0.2877
	6m-E4NOEX	6	6	1.12	0.48				

Supplementary Table S2: Statistical outputs for Supplementary Figure 2.

	Experimental Groups	n mice	n data	Mean	SD	Test	Test Statistic	F-value	p-value
S2A CMRO2 AUC	3m-E3EX	19	19	8.74	8.82	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	1.2539	0.2662
	3m-E3NOEX	7	7	18.69	11.14		exercise	0.0944	0.7651
	3m-E4EX	19	19	9.06	8.66		age	0.1248	0.7248
	3m-E4NOEX	7	7	8.87	18.65		genotype:exercise	0.3602	0.5501
	6m-E3EX	14	14	13.73	11.50		genotype:age	0.3368	0.5634
	6m-E3NOEX	6	6	8.66	18.27		exercise:age	2.0723	0.1539
	6m-E4EX	11	11	10.47	12.20		genotype:exercise:age	1.4821	0.2271
	6m-E4NOEX	5	5	8.88	11.40				

S2B CMRO2 time to peak	3m-E3EX	19	19	2.56	1.41	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	5.4770	0.0246
	3m-E3NOEX	7	7	2.49	0.74		exercise	0.0367	0.8498
	3m-E4EX	19	19	2.85	1.17		age	0.2435	0.6248
	3m-E4NOEX	7	7	2.53	1.06		genotype:exercise	1.2988	0.2616
	6m-E3EX	14	14	2.44	1.22		genotype:age	3.9533	0.0547
	6m-E3NOEX	6	6	1.24	0.73		exercise:age	0.2639	0.6107
	6m-E4EX	11	11	2.85	1.22		genotype:exercise:age	2.9461	0.0950
	6m-E4NOEX	5	5	3.22	0.90				
S2C Flux AUC	3m-E3EX	19	19	23.78	14.33	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	2.7953	0.1024
	3m-E3NOEX	7	7	37.83	22.25		exercise	1.1454	0.2934
	3m-E4EX	19	19	21.59	16.49		age	0.3512	0.5569
	3m-E4NOEX	7	7	19.05	15.76		genotype:exercise	1.5646	0.2183
	6m-E3EX	14	14	26.36	18.58		genotype:age	0.6108	0.4393
	6m-E3NOEX	6	6	25.26	30.07		exercise:age	1.1952	0.2811
	6m-E4EX	11	11	24.45	19.48		genotype:exercise:age	0.4488	0.5069
	6m-E4NOEX	5	5	18.42	11.81				
S2D Flux time to peak	3m-E3EX	19	19	2.24	0.78	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.6452	0.4279
	3m-E3NOEX	7	7	2.18	0.67		exercise	0.4075	0.5279
	3m-E4EX	19	19	2.79	1.09		age	0.5181	0.4784
	3m-E4NOEX	7	7	2.45	0.96		genotype:exercise	0.5245	0.4743
	6m-E3EX	14	14	2.25	0.56		genotype:age	1.7030	0.2038
	6m-E3NOEX	6	6	2.38	0.89		exercise:age	0.0876	0.7697
	6m-E4EX	11	11	2.29	0.76		genotype:exercise:age	0.0176	0.8955
	6m-E4NOEX	5	5	2.07	0.33				
S2E Speed AUC	3m-E3EX	19	19	16.53	15.35	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	2.6972	0.1073
	3m-E3NOEX	7	7	22.54	16.04		exercise	3.1252	0.0842
	3m-E4EX	19	19	9.51	8.99		age	0.3432	0.5611
	3m-E4NOEX	7	7	13.61	8.73		genotype:exercise	1.1050	0.2986
	6m-E3EX	14	14	14.05	11.18		genotype:age	0.9649	0.3315
	6m-E3NOEX	6	6	17.81	22.38		exercise:age	1.1673	0.2860
	6m-E4EX	11	11	16.40	16.08		genotype:exercise:age	0.8528	0.3610
	6m-E4NOEX	5	5	9.43	10.43				
S2F Speed time to peak	3m-E3EX	19	19	1.99	0.33	LMM with genotype, exercise and age	genotype	1.3428	0.2500
	3m-E3NOEX	7	7	2.46	0.54		exercise	5.3573	0.0232
	3m-E4EX	19	19	2.08	0.88		age	0.3291	0.5678

	3m-E4NOEX	7	7	2.71	1.06	as fixed factors and anID as random factors	genotype:exercise	0.4135	0.5221
	6m-E3EX	14	14	2.21	0.79		genotype:age	0.0545	0.8160
	6m-E3NOEX	6	6	2.36	0.62		exercise:age	0.4057	0.5260
	6m-E4EX	11	11	2.31	0.88		genotype:exercise:age	0.0520	0.8201
	6m-E4NOEX	5	5	2.78	1.18				
S2G HbT AUC	3m-E3EX	19	19	9.35	6.07	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	2.1142	0.1536
	3m-E3NOEX	7	7	10.54	7.14		exercise	1.5273	0.2517
	3m-E4EX	19	19	7.30	5.28		age	0.5204	0.4758
	3m-E4NOEX	7	7	4.19	2.39		genotype:exercise	0.5063	0.4808
	6m-E3EX	14	14	8.27	5.16		genotype:age	3.5046	0.0701
	6m-E3NOEX	6	6	6.49	6.26		exercise:age	0.1586	0.6931
	6m-E4EX	11	11	7.57	6.74		genotype:exercise:age	0.7670	0.3875
	6m-E4NOEX	5	5	5.89	0.97				
S2H HbT time to peak	3m-E3EX	19	19	1.98	0.73	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.8576	0.3603
	3m-E3NOEX	7	7	1.85	0.21		exercise	0.0192	0.8905
	3m-E4EX	19	19	2.30	1.03		age	0.5880	0.4487
	3m-E4NOEX	7	7	2.01	0.58		genotype:exercise	0.1549	0.6961
	6m-E3EX	14	14	2.11	0.79		genotype:age	0.1257	0.7253
	6m-E3NOEX	6	6	2.12	0.58		exercise:age	1.9746	0.1695
	6m-E4EX	11	11	1.92	0.40		genotype:exercise:age	0.8759	0.3563
	6m-E4NOEX	5	5	2.48	0.82				
S2I SO2 AUC	3m-E3EX	19	19	18.51	11.52	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	2.5951	0.1112
	3m-E3NOEX	7	7	20.99	23.50		exercise	1.3193	0.2585
	3m-E4EX	19	19	18.61	12.60		age	1.3248	0.2532
	3m-E4NOEX	7	7	12.17	5.54		genotype:exercise	3.5183	0.0644
	6m-E3EX	14	14	20.10	12.16		genotype:age	0.0652	0.7992
	6m-E3NOEX	6	6	28.88	17.29		exercise:age	0.3107	0.5788
	6m-E4EX	11	11	21.63	15.94		genotype:exercise:age	0.2373	0.6275
	6m-E4NOEX	5	5	15.28	7.02				
S2J SO2 time to peak	3m-E3EX	19	19	2.24	0.72	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	5.6457	0.0224
	3m-E3NOEX	7	7	2.06	0.27		exercise	0.2565	0.6153
	3m-E4EX	19	19	2.54	0.96		age	0.0490	0.8263
	3m-E4NOEX	7	7	3.06	1.10		genotype:exercise	0.3651	0.5491
	6m-E3EX	14	14	2.30	0.80		genotype:age	0.6383	0.4307
	6m-E3NOEX	6	6	2.39	0.61		exercise:age	0.1631	0.6893

	6m-E4EX	11	11	2.52	0.72		genotype:exercise:age	1.9132	0.1770
	6m-E4NOEX	5	5	2.67	0.81				

Supplementary Table S3: Statistical outputs for Supplementary Figure 3.

	Experimental Groups	**n mice**	**n data**	**Mean**	**SD**	**Test**	**Test Statistic**	**F-value**	**p-value**
S3A pial baseline diameter	3m-E3EX	19	93	25.57	8.93	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.4092	0.5228
	3m-E3NOEX	6	39	28.08	12.36		exercise	0.2931	0.5910
	3m-E4EX	19	79	26.13	8.93		age	0.0675	0.7997
	3m-E4NOEX	7	43	22.95	10.28		genotype:exercise	1.5840	0.2089
	6m-E3EX	13	61	24.07	10.22		genotype:age	0.0094	0.9229
	6m-E3NOEX	5	34	27.53	12.18		exercise:age	0.4372	0.5120
	6m-E4EX	11	41	23.36	7.95		genotype:exercise:age	3.7356	0.0540
	6m-E4NOEX	5	42	23.30	8.11				
S3B Intermediate vessel baseline diameter	3m-E3EX	4	12	9.30	1.45	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.1572	0.8017
	3m-E3NOEX	5	15	9.26	1.50		exercise	0.5277	0.5312
	3m-E4EX	3	3	8.83	2.83		age	0.9772	0.2937
	3m-E4NOEX	7	33	9.07	1.49		genotype:exercise	0.5297	0.7369
	6m-E3EX	3	16	8.53	1.23		genotype:age	0.0826	0.3109
	6m-E3NOEX	5	12	9.74	1.39		exercise:age	0.2541	0.5951
	6m-E4EX	3	4	8.82	1.46		genotype:exercise:age	0.7174	0.3272
	6m-E4NOEX	4	19	9.09	1.34				
S2C Capillary baseline diameter	3m-E3EX	3	19	5.68	0.98	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	2.0209	0.1572
	3m-E3NOEX	6	22	4.97	1.41		exercise	0.4326	0.5277
	3m-E4EX	3	23	5.29	1.33		age	0.0009	0.9772
	3m-E4NOEX	6	30	5.28	0.97		genotype:exercise	0.3968	0.5297
	6m-E3EX	3	21	5.31	1.20		genotype:age	3.0527	0.0826
	6m-E3NOEX	3	16	5.28	0.95		exercise:age	1.4897	0.2541
	6m-E4EX	3	16	5.46	0.72		genotype:exercise:age	0.1315	0.7174
	6m-E4NOEX	5	19	5.87	0.89				
S3D Pial AUC	3m-E3EX	19	88	22.22	12.69	LMM with genotype, exercise and age as fixed factors	genotype	0.8271	0.3692
	3m-E3NOEX	5	33	22.86	13.74		exercise	0.0781	0.7815
	3m-E4EX	19	73	21.74	14.10		age	0.7255	0.3949
	3m-E4NOEX	6	30	17.71	11.96		genotype:exercise	3.0415	0.0898

	6m-E3EX	14	59	18.18	13.23	and anID as random factors	genotype:age	0.0160	0.8993
	6m-E3NOEX	5	29	24.77	13.94		exercise:age	0.5085	0.4762
	6m-E4EX	13	46	21.35	14.15		genotype:exercise:age	0.6978	0.4041
	6m-E4NOEX	5	19	16.41	12.42				
S3E Pial time to peak	3m-E3EX	19	88	2.50	0.76	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.2842	0.5994
	3m-E3NOEX	5	33	2.18	0.70		exercise	4.8763	0.1246
	3m-E4EX	19	73	2.50	0.86		age	0.0297	0.8633
	3m-E4NOEX	6	30	2.31	0.99		genotype:exercise	0.0685	0.7960
	6m-E3EX	14	59	2.42	0.67		genotype:age	0.0157	0.9004
	6m-E3NOEX	5	29	2.26	0.76		exercise:age	0.2191	0.6400
	6m-E4EX	13	46	2.47	0.89		genotype:exercise:age	0.1787	0.6728
	6m-E4NOEX	5	19	2.29	1.15				
S3F Intermediate vessel AUC	3m-E3EX	4	9	17.81	11.87	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.0408	0.8476
	3m-E3NOEX	6	12	24.80	11.50		exercise	3.7333	0.1088
	3m-E4EX	3	8	32.08	30.07		age	0.0004	0.9849
	3m-E4NOEX	6	17	15.85	8.79		genotype:exercise	2.4796	0.1737
	6m-E3EX	3	13	28.02	22.16		genotype:age	0.1635	0.6871
	6m-E3NOEX	5	8	18.17	23.88		exercise:age	0.8104	0.3709
	6m-E4EX	3	5	29.09	22.93		genotype:exercise:age	1.4014	0.2402
	6m-E4NOEX	4	12	15.49	11.22				
S3G Intermediate vessel time to peak	3m-E3EX	4	9	2.03	1.57	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	4.1047	0.0463
	3m-E3NOEX	6	12	2.25	1.00		exercise	0.0029	0.9572
	3m-E4EX	3	8	3.30	1.44		age	0.2390	0.6263
	3m-E4NOEX	6	17	2.53	1.45		genotype:exercise	1.3459	0.2496
	6m-E3EX	3	13	1.96	0.30		genotype:age	0.3723	0.5436
	6m-E3NOEX	5	8	2.39	1.22		exercise:age	0.7767	0.3809
	6m-E4EX	3	5	2.56	1.07		genotype:exercise:age	0.2915	0.5908
	6m-E4NOEX	4	12	2.62	1.52				
S3H capillaries AUC	3m-E3EX	3	15	26.59	18.91	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	2.9178	0.1230
	3m-E3NOEX	7	21	22.93	22.12		exercise	4.1638	0.0729
	3m-E4EX	3	13	36.61	50.08		age	0.5973	0.4413
	3m-E4NOEX	7	33	14.83	13.69		genotype:exercise	1.1103	0.3205
	6m-E3EX	4	14	32.75	21.57		genotype:age	4.8285	0.0301
	6m-E3NOEX	4	15	28.00	15.84		exercise:age	0.8733	0.3521
	6m-E4EX	3	10	15.37	6.13		genotype:exercise:age	1.2854	0.2593

	6m-E4NOEX	4	11	10.90	9.84				
S3I capillary time to peak	3m-E3EX	3	15	2.65	1.07	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	1.2002	0.2754
	3m-E3NOEX	7	21	2.48	1.32		exercise	0.0079	0.9292
	3m-E4EX	3	13	2.05	1.53		age	2.6082	0.1089
	3m-E4NOEX	7	33	2.89	1.17		genotype:exercise	4.6206	0.0335
	6m-E3EX	4	14	3.53	1.17		genotype:age	0.4900	0.4853
	6m-E3NOEX	4	15	2.71	1.17		exercise:age	1.7453	0.1889
	6m-E4EX	3	10	2.57	1.29		genotype:exercise:age	0.0035	0.9530
	6m-E4NOEX	4	11	2.80	1.71				
S3J RBCV AUC	3m-E3EX	14	39	91.60	64.49	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	0.0684	0.7953
	3m-E3NOEX	4	8	101.34	99.24		exercise	0.7906	0.3805
	3m-E4EX	12	35	99.79	92.48		age	1.0952	0.2971
	3m-E4NOEX	7	15	64.34	31.09		genotype:exercise	1.6183	0.2125
	6m-E3EX	12	31	68.77	60.26		genotype:age	0.5487	0.4601
	6m-E3NOEX	2	9	74.59	36.06		exercise:age	0.0006	0.9802
	6m-E4EX	7	14	91.43	75.02		genotype:exercise:age	0.0380	0.8457
	6m-E4NOEX	2	5	62.59	36.78				
S3K RBCV time to peak	3m-E3EX	14	39	2.027	0.778	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	4.1116	0.0444
	3m-E3NOEX	4	8	2.239	1.022		exercise	0.7916	0.3751
	3m-E4EX	12	35	2.383	0.896		age	7.3660	0.0074
	3m-E4NOEX	7	15	1.824	1.075		genotype:exercise	1.4820	0.2254
	6m-E3EX	12	31	2.401	0.997		genotype:age	4.7738	0.0305
	6m-E3NOEX	2	9	2.065	0.821		exercise:age	3.2771	0.0723
	6m-E4EX	7	14	2.349	1.039		genotype:exercise:age	10.6771	0.0013
	6m-E4NOEX	2	5	3.702	1.003				

Supplementary Table S4: Statistical outputs for Supplementary Figure 4.

	Experimental Groups	**n mice**	**n data**	**Mean**	**SD**	**Test**	**Test Statistic**	**F-value**	**p-value**
S4B Neuronal calcium peaks per minute at baseline	3m-E3EX	8	8	6.74	1.79	LMM with genotype, exercise and age as fixed factors	genotype	2.2216	0.1743
	3m-E3NOEX	6	6	7.26	2.40		exercise	0.0845	0.7787
	3m-E4EX	7	7	5.77	0.55		age	3.6086	0.1071
	3m-E4NOEX	5	5	7.22	0.67		genotype:exercise	0.4118	0.5389
	6m-E3EX	7	7	6.56	1.27		genotype:age	0.0234	0.8835

	6m-E3NOEX	4	4	6.22	2.10	and anID as random factors	exercise:age	0.0822	0.7842
	6m-E4EX	5	5	5.87	1.41		genotype:exercise:age	1.1146	0.3324
	6m-E4NOEX	3	3	5.15	2.32				
S4C ΔF/F neuronal calcium peaks at baseline	3m-E3EX	8	8	1.96	0.63	LMM with genotype, exercise and age as fixed factors and anID as random factors	genotype	1.5030	0.2349
	3m-E3NOEX	6	6	1.57	0.54		exercise	1.3888	0.2529
	3m-E4EX	7	7	1.90	0.48		age	0.9632	0.3395
	3m-E4NOEX	5	5	1.88	0.95		genotype:exercise	0.4284	0.5205
	6m-E3EX	7	7	1.61	0.57		genotype:age	0.4792	0.4977
	6m-E3NOEX	4	4	1.29	0.43		exercise:age	0.0331	0.8577
	6m-E4EX	5	5	1.93	0.91		genotype:exercise:age	0.0779	0.7834
	6m-E4NOEX	3	3	1.70	0.38				
S4E, G, I AUC of neuronal calcium responses to visual stim	3m-E3EX-ON	7	7	1.27	0.23	LMM with genotype, exercise, cell type and age as fixed factors and anID and experimenter as random factors	cell-type	98.0290	3.0074e-23
	3m-E3NOEX-ON	6	6	1.80	0.77		genotype	1.0035	0.3264
	3m-E4EX-ON	8	8	1.19	0.15		exercise	0.0067	0.9357
	3m-E4NOEX-ON	5	5	0.95	0.28		age	2.8464	0.0945
	6m-E3EX-ON	7	7	1.07	0.14		cell-type:genotype	0.1384	0.8710
	6m-E3NOEX-ON	3	3	1.54	0.06		cell-type:exercise	2.3900	0.0975
	6m-E4EX-ON	5	5	1.63	0.73		genotype:exercise	17.1651	0.0004
	6m-E4NOEX-ON	3	3	0.96	0.29		cell-type:age	2.9244	0.0589
	3m-E3EX-OFF	7	7	1.03	0.31		genotype:age	0.3501	0.5554
	3m-E3NOEX- OFF	6	6	1.07	0.50		exercise:age	0.8405	0.3613
	3m-E4EX- OFF	8	8	1.02	0.25		cell-type:genotype:exercise	10.9405	5.6302e-05
	3m-E4NOEX- OFF	5	5	0.73	0.16		cell-type:genotype:age	0.1079	0.8978
	6m-E3EX- OFF	7	7	1.01	0.46		cell-type:exercise:age	0.0898	0.9142
	6m-E3NOEX- OFF	3	3	0.97	0.31		genotype:exercise:age	0.5696	0.4521
	6m-E4EX- OFF	5	5	1.00	0.18		cell-type:genotype:exercise:age	1.0535	0.3530
	6m-E4NOEX- OFF	3	3	0.58	0.26				
	3m-E3EX-BOTH	7	7	3.97	0.96				
	3m-E3NOEX- BOTH	6	6	6.19	2.91				
	3m-E4EX-BOTH	8	8	6.37	2.34				
	3m-E4NOEX- BOTH	5	5	2.60	0.86				
	6m-E3EX- BOTH	7	7	3.56	1.34				
	6m-E3NOEX- BOTH	3	3	4.07	0.38				
	6m-E4EX- BOTH	5	5	5.08	3.47				
	6m-E4NOEX- BOTH	3	3	1.96	0.56				

Supplementary Table S5: Statistical outputs for Supplementary Figure 5.

Comparison	Variable	APOE3 r	APOE3 p value	APOE3 FDR adjusted p value	APOE4 r	APOE4 p value	APOE4 FDR adjusted p value
Data at 3 months vs distance run at 2 months	Calcium response size	0.02765432	-0.690474	0.71832899	-0.5431999	-0.9024389	0.26161265
	Capillary NVCi	-0.0974428	-0.7505771	0.65199988	-0.6495354	-0.9289971	0.10167539
	Cap. response size	-0.321701	-0.8366992	0.49523981	-0.1021917	-0.752664	0.64923368
	Cap. responsiveness	-0.527023	-0.8981442	0.28260249	-0.7657885	-0.9550743	-0.1327534
	CMRO2 - stimulus	-0.2413806	-0.8085275	0.55824702	-0.7307907	-0.9475205	-0.0538476
	CMRO2 baseline	-0.1088466	-0.8457022	0.77080421	0.66544184	-0.1756247	0.94496335
	Flux - stimulus	0.25628314	-0.5472144	0.81395857	0.10432282	-0.6479858	0.75359628
	Flux baseline	0.53000231	-0.2787942	0.89894049	0.13100084	-0.6320151	0.76504991
	HbT - stimulus	0.54553162	-0.2585231	0.90305205	-0.2040586	-0.7944884	0.5846895
	HbT baseline	0.35770047	-0.4639053	0.84849915	0.29591617	-0.5164488	0.82794301
	Intermediate vessel NVCi	0.63531405	-0.1255793	0.92560442	0.41790038	-0.4064715	0.86719813
	Intermediate vessel resp. size	0.69352543	-0.0218026	0.93920218	0.71355927	-0.0853755	0.95398956
	Intermediate vessel responsiveness	0.06834529	-0.6685245	0.73749945	0.205644	-0.727298	0.87172134
	RBCV responsiveness	0.20893111	-0.7256761	0.87254356	-0.3182245	-0.8641874	0.57187976
	Pia NVCi	-0.0885312	-0.7466255	0.65713759	0.36420675	-0.5358064	0.87678896
	Pia response size	0.69580126	-0.0174061	0.93971859	0.67138693	-0.5172953	0.97570322
	Pia responsiveness	-0.4424061	-0.9226864	0.57594075	0.82689767	0.04662623	0.98048016
	RBCV NVCi	-0.5479667	-0.9410396	0.47469593	0.44290913	-0.3805293	0.87461074
	sO2 - stimulus	-0.7779976	-0.9845012	0.33249107	0.70629914	-0.7932747	0.99319237
	sO2 baseline	-0.1042809	-0.7535779	0.64801039	0.42526136	-0.4822289	0.89249959
	Speed - stimulus	0.01644578	-0.6962965	0.71285748	0.56519582	-0.4551291	0.9438305
	Speed baseline	0.23443891	-0.7127269	0.87879861	-0.2992263	-0.858773	0.58584249

	Vasomotion	-0.2881034	-0.891273	0.68319912	0.52926922	-0.2797336	0.89874478
Data at 6 months vs. distance run at 2 months	Calcium response size	0.40544497	-0.6052796	0.91570088	-0.645459	-0.9410855	0.20936456
	Capillary NVCi	0.59784948	-0.4151287	0.94897579	-0.3092148	-0.8616353	0.57856638
	Cap. response size	-0.1275675	-0.8510233	0.76298469	0.23416773	-0.6299827	0.83923376
	Cap. responsiveness	0.59986148	-0.4125289	0.94928682	0.35242493	-0.5453733	0.87362584
	CMRO2 - stimulus	0.68337451	-0.2878016	0.96162068	-0.4618949	-0.9014117	0.44645543
	CMRO2 baseline	0.82100128	0.02828827	0.97975729	0.52917401	-0.8789123	0.98785534
	Flux - stimulus	0.74946088	-0.1585138	0.97064402	-0.4415406	-0.9225263	0.5766591
	Flux baseline	0.82334503	0.03551408	0.98004512	0.13561263	-0.7595423	0.85326527
	HbT - stimulus	0.67900432	-0.2952623	0.96100198	0.43217891	-0.5843301	0.92078453
	HbT baseline	-0.2212139	-0.875583	0.7195222	0.33112976	-0.6569843	0.9006559
	Intermediate vessel NVCi	-0.0358815	-0.8234635	0.79894509	0.57592299	-0.4424275	0.9455413
	Intermediate vessel resp. size	0.50811338	-0.6781715	0.96001387	0.26194863	-0.9343716	0.97705644
	Intermediate vessel responsiveness	0.49836104	-0.6851626	0.95897738	0.76107639	-0.7448097	0.99463042
	RBCV responsiveness	-0.446276	-0.9234	0.57270932	0.84442347	-0.1484075	0.98950343
	Pia NVCi	0.57556743	-0.6231235	0.96685911	0.33033734	-0.9241524	0.98022098
	Pia response size	0.65362212	-0.5401075	0.97413515	0.66524599	-0.8203209	0.99205406
	Pia responsiveness	0.5372364	-0.4863919	0.93927398	0.45264536	-0.8999472	0.9851577
	RBCV NVCi	-0.5603626	-0.9653637	0.63666317	0.97668008	0.25426667	0.99953192
	sO2 - stimulus	-0.9948208	-0.9948208	-0.9948208			
	sO2 baseline	0.30450883	-0.7899964	0.93545726	-0.3059593	-0.9791298	0.9280134
	Speed - stimulus	0.6513752	-0.542873	0.97393459	0.61942947	-0.8442779	0.99071719
	Speed baseline	0.29255318	-0.6805993	0.8922679	0.14634889	-0.8450262	0.91098952
	Vasomotion	0.39364875	-0.7486134	0.94701422	0.53112016	-0.878295	0.98792052
Data at 6 months vs. distance run at 6 months	Calcium response size	0.45636795	-0.4520453	0.90009052	0.02939007	-0.6115529	0.64704299
	Capillary NVCi	0.68303276	-0.1441929	0.94831327	0.24264843	-0.4567608	0.75667202
	Cap. response size	0.22188881	-0.6377311	0.83536197	0.26992586	-0.4333492	0.76887927
	Cap. responsiveness	0.67847051	-0.1525083	0.9474501	0.46381825	-0.2342028	0.84629824

	CMRO2 - stimulus	0.75518286	0.00492636	0.96146125	0.22825098	-0.4687391	0.75008102
	CMRO2 baseline	0.70638929	-0.0997095	0.95267164	0.81646787	0.16463557	0.97193434
	Flux - stimulus	0.50122803	-0.4045163	0.91058307	-0.6546437	-0.9302043	0.09287197
	Flux baseline	0.86031356	0.30458711	0.97906721	-0.1251268	-0.762562	0.63558813
	HbT - stimulus	0.80567865	0.13380015	0.97013419	0.53021803	-0.2785175	0.89899805
	HbT baseline	-0.2154986	-0.8333226	0.64169583	0.30888096	-0.5059079	0.83237837
	Intermediate vessel NVCi	0.2048449	-0.6482055	0.82988488	0.52775423	-0.2816702	0.89833985
	Intermediate vessel resp. size	0.24780814	-0.7056719	0.88199091	0.64514678	-0.209876	0.94102424
	Intermediate vessel responsiveness	0.66184399	-0.3234522	0.95854494	0.70482305	-0.1027968	0.95238251
	RBCV responsiveness	-0.5975431	-0.9314589	0.28274672	-0.0314934	-0.7201836	0.68845818
	Pia NVCi	0.46335902	-0.558056	0.92651113	0.25571885	-0.6159543	0.84588409
	Pia response size	0.56391185	-0.4566221	0.94362436	0.20592818	-0.6475492	0.83023661
	Pia responsiveness	-0.1059131	-0.7955214	0.70323408	0.29206167	-0.5909752	0.85669811
	RBCV NVCi	-0.5718555	-0.944895	0.4472922	0.44436483	-0.4639441	0.89719298
	sO2 - stimulus	-0.7809058	-0.7809058	-0.7809058	-0.1924085	-0.9187175	0.83090941
	sO2 baseline	0.33273508	-0.6559577	0.90099599	-0.7415452	-0.9590463	0.02607242
	Speed - stimulus	0.48868884	-0.5350894	0.93101049	0.58389015	-0.3019256	0.92862768
	Speed baseline	0.1239202	-0.6938912	0.80212474	0.41492561	-0.4094714	0.86630295
	Vasomotion	0.59391627	-0.4201637	0.94836577	0.35379049	-0.5442763	0.87399473

Supplementary Table S6: Statistics outputs for Supplementary Figure 6

Figure Label	Test	Factor	Test statistic (d.f.)	p-value (Bonferroni corrected)
Supp. 6F – 1st principal component of cluster 1	LMM with genotype, exercise, vessel type and age as fixed factors and anID as random factor	genotype	F = 1.79 (1, 85)	0.18
		exercise	F = 0.80 (1, 85)	0.37
		age	F = 0.0002 (1, 85)	0.99
		genotype:exercise	F = 0.042 (1, 85)	0.83
		genotype:age	F = 0.018 (1,85)	0.89
		exercise:age	F = 3.20 (1, 85)	0.077
		genotype:exercise:age	F = 0.38 (1, 85)	0.54
Supp. 6H – 2nd principal component of cluster 2	LMM with genotype, exercise, vessel type and age as fixed factors and anID as random factor	genotype	F = 5.81 (1, 85)	0.018 (0.072)
		exercise	F = 1.07 (1, 85)	0.30 (1)
		age	F = 9.33 (1, 85)	0.003 (0.012)
		genotype:exercise	F = 1.62 (1, 85)	0.21 (0.84)
		genotype:age	F = 3.07 (1,85)	0.083 (0.33)
		exercise:age	F = 0.40 (1, 85)	0.40 (1)
		genotype:exercise:age	F = 1.13 (1, 85)	0.29 (1)

Supplementary Table S7: Statistic outputs for sex analysis.
Sex was added as a factor to the LMMs presented in the tables above. Significant main effects of sex or interactions with other factors are shown in bold type.

Figure Label	Test	Factor	F value	p-value
1H. Exercise Distance	LMM with genotype, exercise, age and sex as fixed factors and anID as random factor	genotype	0.0172	0.8980
		exercise	12.0008	0.0051
		age	433.0177	2.11e-43
		sex	0.5569	0.4708
		genotype:exercise	0.1140	0.7418
		genotype:age	0.6447	0.4235
		exercise:age	38.0556	7.92e-09
		genotype:sex	1.9957	0.1847
		exercise:sex	0.1529	0.7030
		age:sex	0.0301	0.8625
		genotype:exercise:age	10.5440	0.0015
		genotype:exercise:sex	0.0367	0.8514
		genotype:age:sex	0.0664	0.7971
		exercise:age:sex	1.1665	0.2821
		genotype:exercise:age:sex	1.1207	0.2917
2C. Capillary Density	LMM with genotype, exercise and sex as fixed factors and anID as random factor	genotype	2.8075	0.1415
		exercise	6.2538	0.0439
		sex	**6.7646**	**0.0381**
		genotype:exercise	0.5859	0.4711
		genotype:sex	1.4159	0.2761
		exercise:sex	2.1743	0.1875
		genotype:exercise:sex	0.6766	0.4402
2D. Flux baseline	LMM with genotype, exercise, age and sex as fixed factors and anID and exp as random factors	genotype	0.0201	0.8879
		exercise	0.0063	0.9372
		age	0.3588	0.5508
		sex	**9.8038**	**0.0028**
		genotype:exercise	0.1062	0.7457
		genotype:age	0.2292	0.6334
		exercise:age	0.1275	0.7219

		genotype:sex	0.2141	0.6455
		exercise:sex	1.1817	0.2819
		age:sex	**5.5528**	**0.0208**
		genotype:exercise:age	0.2375	0.6272
		genotype:exercise:sex	0.4464	0.5069
		genotype:age:sex	1.5081	0.2228
		exercise:age:sex	0.5864	0.4460
		genotype:exercise:age:sex	0.2637	0.6089
2E. hbt baseline	LMM with genotype, exercise, age and sex as fixed factors and anID and exp as random factors	genotype	0.2562	0.6150
		exercise	0.0530	0.8234
		age	3.4737	0.0660
		sex	**8.4534**	**0.0055**
		genotype:exercise	0.7151	0.4019
		genotype:age	0.0561	0.8133
		exercise:age	0.0257	0.8731
		genotype:sex	1.2466	0.2697
		exercise:sex	1.7038	0.1979
		age:sex	0.4043	0.5266
		genotype:exercise:age	2.1236	0.1489
		genotype:exercise:sex	2.5472	0.1169
		genotype:age:sex	0.0449	0.8328
		exercise:age:sex	1.23e-05	0.9972
		genotype:exercise:age:sex	1.0847	0.3007
2F. CMRO2 baseline	LMM with genotype, exercise, age and sex as fixed factors and anID and exp as random factors	genotype	0.1057	0.7463
		exercise	0.1878	0.6666
		age	0.0536	0.8175
		sex	**5.5507**	**0.0222**
		genotype:exercise	0.2702	0.6054
		genotype:age	0.1079	0.7434
		exercise:age	0.8041	0.3725
		genotype:sex	0.1066	0.7453

		exercise:sex	1.6064	0.2106
		age:sex	2.3474	0.1293
		genotype:exercise:age	0.1767	0.6753
		genotype:exercise:sex	0.6106	0.4381
		genotype:age:sex	1.5398	0.2181
		exercise:age:sex	1.0303	0.3131
		genotype:exercise:age:sex	1.0011	0.32
2G. sO2 baseline	LMM with genotype, exercise, age and sex as fixed factors and anID and exp as random factors	genotype	0.0069	0.9341
		exercise	0.0010	0.9750
		age	2.0271	0.1580
		sex	2.2413	0.1399
		genotype:exercise	0.0067	0.9353
		genotype:age	0.5437	0.4629
		exercise:age	3.8064	0.0542
		genotype:sex	0.0641	0.8011
		exercise:sex	0.3211	0.5731
		age:sex	**3.0714**	**0.0832**
		genotype:exercise:age	0.0120	0.9131
		genotype:exercise:sex	0.1076	0.7441
		genotype:age:sex	0.0003	0.9867
		exercise:age:sex	0.0660	0.7978
		genotype:exercise:age:sex	0.5975	0.4416
2K. vasomotion	LMM with genotype, exercise, age and sex as fixed factors and anID and exp as random factors	genotype	3.0336	0.0917
		exercise	9.6650	0.0041
		age	0.1701	0.6803
		sex	0.0961	0.7587
		genotype:exercise	0.0710	0.7917
		genotype:age	1.5335	0.2165
		exercise:age	0.4697	0.4936
		genotype:sex	2.90e-05	0.9957
		exercise:sex	0.8981	0.3508

		age:sex	0.9191	0.3384
		genotype:exercise:age	0.4569	0.4996
		genotype:exercise:sex	**5.0078**	**0.0327**
		genotype:age:sex	0.3931	0.5311
		exercise:age:sex	0.3344	0.5635
		genotype:exercise:age:sex	2.9209	0.0884
3C. CMRO2 stim	LMM with genotype, exercise, age and sex as fixed factors, anID and exp as random factors	genotype	2.3699	0.1306
		exercise	0.8055	0.3742
		age	0.0622	0.8043
		sex	0.7514	0.3905
		genotype:exercise	1.6890	0.2003
		genotype:age	0.4964	0.4854
		exercise:age	1.8472	0.1822
		genotype:sex	0.0285	0.8668
		exercise:sex	0.0182	0.8932
		age:sex	0.1119	0.7399
		genotype:exercise:age	0.0550	0.8158
		genotype:exercise:sex	0.2349	0.6302
		genotype:age:sex	1.7392	0.1951
		exercise:age:sex	0.6019	0.4427
		genotype:exercise:age:sex	**3.0880**	**0.0869**
3D Flux Stim	LMM with genotype, exercise, age and sex as fixed factors, anID and exp as random factors	genotype	2.6183	0.1129
		exercise	1.0980	0.4438
		age	0.3887	0.5370
		sex	0.0122	0.9127
		genotype:exercise	3.0471	0.0880
		genotype:age	0.3847	0.5391
		exercise:age	3.1718	0.0835
		genotype:sex	0.6930	0.4097
		exercise:sex	0.5667	0.4556
		age:sex	0.0431	0.8368

		genotype:exercise:age	0.1648	0.6872
		genotype:exercise:sex	0.0009	0.9765
		genotype:age:sex	2.2259	0.1446
		exercise:age:sex	0.0617	0.8053
		genotype:exercise:age:sex	0.1980	0.6590
3E Speed stim	LMM with genotype, exercise, age and sex as fixed factors, anID and exp as random factors	genotype	5.8205	0.0203
		exercise	4.2392	0.0461
		age	0.3047	0.5840
		sex	**2.8485**	**0.0989**
		genotype:exercise	1.7275	0.1958
		genotype:age	0.0114	0.9157
		exercise:age	0.4115	0.5248
		genotype:sex	1.4294	0.2385
		exercise:sex	0.4689	0.4973
		age:sex	0.5576	0.4595
		genotype:exercise:age	3.9189	0.0546
		genotype:exercise:sex	0.7219	0.4003
		genotype:age:sex	**3.4214**	**0.0716**
		exercise:age:sex	2.0392	0.1609
		genotype:exercise:age:sex	1.1490	0.2901
3F HbT stim	LMM with genotype, exercise, age and sex as fixed factors, anID and exp as random factors	genotype	3.9224	0.0543
		exercise	2.0688	0.1578
		age	0.6344	0.4309
		sex	0.9648	0.3316
		genotype:exercise	0.7286	0.3982
		genotype:age	1.2221	0.2762
		exercise:age	0.4733	0.4958
		genotype:sex	**3.6128**	**0.0643**
		exercise:sex	0.1796	0.6739
		age:sex	0.3539	0.5556
		genotype:exercise:age	0.0911	0.7645

		genotype:exercise:sex	0.1984	0.6583
		genotype:age:sex	0.2888	0.5943
		exercise:age:sex	0.3426	0.5619
		genotype:exercise:age:sex	0.1228	0.7281
3G sO2 stim	LMM with genotype, exercise, age and sex as fixed factors, anID and exp as random factors	genotype	4.0903	0.0468
		exercise	2.1120	0.1505
		age	1.2987	0.2582
		sex	0.2136	0.6454
		genotype:exercise	7.4682	0.0079
		genotype:age	0.3355	0.5643
		exercise:age	0.1066	0.7450
		genotype:sex	**3.3795**	**0.0701**
		exercise:sex	**2.9240**	**0.0916**
		age:sex	0.0141	0.9058
		genotype:exercise:age	1.1126	0.2950
		genotype:exercise:sex	0.6012	0.4406
		genotype:age:sex	1.0280	0.3140
		exercise:age:sex	**3.1151**	**0.0818**
		genotype:exercise:age:sex	0.0011	0.9739
4C, G, K vessel responsiveness	LMM with genotype, exercise, age, sex and vess_type as fixed factors and anID, exp and n trials as random factors	genotype	22.8747	1.33e-05
		exercise	5.0157	0.0301
		age	1.3876	0.2393
		sex	0.0747	0.7856
		vess_type	3.2825	0.0396
		genotype:exercise	0.5975	0.4428
		genotype:age	6.6447	0.0102
		exercise:age	0.5277	0.4679
		genotype:sex	**5.4086**	**0.0237**
		exercise:sex	0.3414	0.5613
		age:sex	0.1096	0.7407
		genotype:vess_type	0.5583	0.5731

		exercise:vess_type	0.2989	0.7419
		age:vess_type	0.1862	0.8302
		sex:vess_type	0.4157	0.6604
		genotype:exercise:age	0.5747	0.4487
		genotype:exercise:sex	0.6599	0.4201
		genotype:age:sex	2.7742	0.0964
		exercise:age:sex	0.0444	0.8332
		genotype:exercise:vess_type	0.9488	0.3889
		genotype:age:vess_type	4.8657	0.0080
		exercise:age:vess_type	1.1958	0.3032
		genotype:sex:vess_type	**3.0744**	**0.0484**
		exercise:sex:vess_type	0.4018	0.6697
		age:sex:vess_type	0.7455	0.4749
		genotype:exercise:age:sex	3.1099	0.0784
		genotype:exercise:age:vess_type	1.9132	0.1485
		genotype:exercise:sex:vess_type	0.0904	0.9136
		genotype:age:sex:vess_type	1.2390	0.2904
		exercise:age:sex:vess_type	0.0475	0.9536
		genotype:exercise:age:sex:vess_type	1.3578	0.2580
4C, G, K Vess Max Peak during Stim	LMM with genotype, exercise, age, sex and vess_type as fixed factors and anID and exp as random factors	genotype	2.4605	0.1173
		exercise	4.7754	0.0293
		age	0.0010	0.9746
		sex	0.1304	0.7181
		vess_type	1.4884	0.2267
		genotype:exercise	3.1047	0.0786
		genotype:age	2.2573	0.1336
		exercise:age	0.1361	0.7123
		genotype:sex	0.0151	0.9022
		exercise:sex	1.0580	0.3041
		age:sex	**3.2533**	**0.0718**
		genotype:vess_type	1.3903	0.2499

		exercise:vess_type	1.0602	0.3471
		age:vess_type	1.1537	0.3162
		sex:vess_type	**3.7776**	**0.0235**
		genotype:exercise:age	1.2571	0.2627
		genotype:exercise:sex	**3.1251**	**0.0777**
		genotype:age:sex	0.3889	0.5331
		exercise:age:sex	1.7594	0.1853
		genotype:exercise:vess_type	1.1903	0.3049
		genotype:age:vess_type	1.1190	0.3273
		exercise:age:vess_type	1.4932	0.2256
		genotype:sex:vess_type	0.7413	0.4770
		exercise:sex:vess_type	1.6853	0.1863
		age:sex:vess_type	**3.6538**	**0.0265**
		genotype:exercise:age:sex	0.6020	0.4381
		genotype:exercise:age:vess_type	2.1932	0.1125
		genotype:exercise:sex:vess_type	2.0319	0.1321
		genotype:age:sex:vess_type	0.4158	0.6600
		exercise:age:sex:vess_type	0.0061	0.9940
		genotype:exercise:age:sex:vess_type	0.9358	0.3929
4O RBCV responsiveness	LMM with genotype, exercise, age and sex as fixed factors and anID and exp as random factors	genotype	10.3259	0.0015
		exercise	1.5795	0.2103
		age	2.6549	0.1048
		sex	1.3880	0.2401
		genotype:exercise	2.1099	0.1479
		genotype:age	1.6108	0.2058
		exercise:age	0.1160	0.7338
		genotype:sex	1.0760	0.3008
		exercise:sex	0.0454	0.8314
		age:sex	0.6524	0.4202
		genotype:exercise:age	1.0748	0.3011
		genotype:exercise:sex	0.0401	0.8416

		genotype:age:sex	**4.0457**	**0.0456**
		exercise:age:sex	**5.1777**	**0.0239**
		genotype:exercise:age:sex	0.1674	0.6828
4Q RBCV max peak	LMM with genotype, exercise, age and sex as fixed factors and anID and exp as random factors	genotype	0.9728	0.3337
		exercise	1.5887	0.2194
		age	3.0038	0.0859
		sex	1.5502	0.2249
		genotype:exercise	3.3885	0.0779
		genotype:age	0.9101	0.3422
		exercise:age	0.0051	0.9432
		genotype:sex	0.1355	0.7159
		exercise:sex	2.5570	0.1227
		age:sex	1.0200	0.3147
		genotype:exercise:age	0.2093	0.6482
		genotype:exercise:sex	2.1247	0.1577
		genotype:age:sex	0.5244	0.4705
		exercise:age:sex	0.0334	0.8554
		genotype:exercise:age:sex	1.7257	0.1917
5D Neuronal Calcium Increase (AUC)	LMM with genotype, exercise, age and sex as fixed factors and anID as random factor	genotype	0.6201	0.4417
		exercise	0.1023	0.7565
		age	0.6786	0.4207
		sex	8.786e-05	0.9926
		genotype:exercise	13.3769	0.0019
		genotype:age	0.8348	0.3728
		exercise:age	1.4819	0.2389
		genotype:sex	0.6926	0.4166
		exercise:sex	1.6650	0.2142
		age:sex	0.3319	0.5715
		genotype:exercise:age	0.0005	0.9832
		genotype:exercise:sex	0.4075	0.5316
		genotype:age:sex	0.2206	0.6441

		exercise:age:sex	0.2106	0.6517
		genotype:exercise:age:sex	0.9658	0.3385
5E, F, G NVCi in pia, intermediate vessels and capillaries	LMM with genotype, exercise, age, sex and vess_type as fixed factors and anID and exp as random factors	genotype	5.3228	0.0257
		exercise	6.3354	0.0155
		age	0.0907	0.7634
		vess_type	0.3216	0.7251
		sex	2.0870	0.1555
		genotype:exercise	0.0018	0.9667
		genotype:age	3.8477	0.0503
		exercise:age	0.1346	0.7138
		genotype:vess_type	0.5028	0.6051
		exercise:vess_type	0.1797	0.8356
		age:vess_type	2.0921	0.1243
		genotype:sex	0.1611	0.6900
		exercise:sex	1.6129	0.2106
		age:sex	2.0035	0.1574
		vess_type:sex	**3.7777**	**0.0234**
		genotype:exercise:age	0.0338	0.8541
		genotype:exercise:vess_type	5.9206	0.0028
		genotype:age:vess_type	1.7564	0.1735
		exercise:age:vess_type	0.0605	0.9413
		genotype:exercise:sex	**3.8404**	**0.0562**
		genotype:age:sex	**3.3166**	**0.0691**
		exercise:age:sex	**6.8574**	**0.0090**
		genotype:vess_type:sex	0.8340	0.4348
		exercise:vess_type:sex	1.7191	0.1801
		age:vess_type:sex	1.3336	0.2643
		genotype:exercise:age:vess_type	1.2536	0.2862
		genotype:exercise:age:sex	0.0427	0.8364
		genotype:exercise:vess_type:sex	1.8249	0.1621
		genotype:age:vess_type:sex	1.9626	0.1414

		exercise:age:vess_type:sex	1.4983	0.2243
		genotype:exercise:age:vess_type:sex	1.6953	0.1844
5H RBCV NVCi	LMM with genotype, exercise, age and sex as fixed factors and anID as random factor	genotype	0.6971	0.4104
		exercise	0.0745	0.7867
		age	7.1680	0.0081
		sex	1.2472	0.2730
		genotype:exercise	0.1518	0.6996
		genotype:age	0.3465	0.5568
		exercise:age	1.5401	0.2161
		genotype:sex	0.0003	0.9853
		exercise:sex	0.0028	0.9584
		age:sex	0.3057	0.5810
		genotype:exercise:age	0.7658	0.3826
		genotype:exercise:sex	0.0956	0.7594
		genotype:age:sex	0.1859	0.6668
		exercise:age:sex	0.0874	0.7679
		genotype:exercise:age:sex	0.2477	0.6193