Supplementary Text 1

CAA-related disease markers

The CAA-related MRI markers: intracerebral hemorrhage (ICH), cerebral microbleeds (CMB), cortical superficial siderosis (cSS), white matter hyperintensities (WMH), and perivascular spaces in the centrum semiovale (CSO-PVS) were scored in accordance with the STRIVE criteria[1], by a single observer (EAK) with > 5 years' experience in the field under the supervision of an experienced neuroradiologist (MAAvW). Additionally, 10% of all the scans were scored by another observer (SV) to assure interrater reliability. Both the number of CMBs and ICHs were counted on susceptibility weighted imaging (SWI). Presence and focality of cSS was also scored on SWI (0-4 focality score point scale ranging from no cSS to more than 3 adjacent affected sulci in both hemispheres)[2]. Deep and periventricular WMH were rated on the Fazekas scale on FLAIR sequences (0-3 point scale for both periventricular and deep WMH)[3]. CSO-PVS were scored on one slice of one hemisphere, using a validated visual rating scale on T2 weighted sequences (0-4 point scale ranging from 0 till more than 40 PVS)[1].

Supplementary Text 2

Uncorrected PSMD in relation to BOLD parameters

Linear regression modeling showed that decreasing blood-oxygen-level-dependent (BOLD) amplitude significantly predicted increasing uncorrected Peak Width of Skeletonized Mean Diffusivity (PSMD) (unstandardized B = -1.15×10^{-4} mm^2/s/percentage, 95% CI [-1.74×10^{-4}, -0.56×10^{-4}], $p < 0.001$, Adjusted $R^2 = 0.39$). Linear regression modeling showed that increasing BOLD time-to-peak (TTP) significantly predicted increasing uncorrected PSMD (unstandardized B = 1.08×10^{-05} $mm^2/s/s$, 95% CI [3.02×10^{-06}, 1.86×10^{-05}], $p = 0.009$, Adj. $R^2 = 0.28$). Linear regression modeling showed that increasing BOLD time-to-baseline (TTB) significantly predicted increasing uncorrected PSMD (unstandardized B = 8.64×10^{-06} $mm^2/s/s$, 95% CI [3.15×10^{-06}, 1.41×10^{-05}], $p = 0.004$, Adj. $R^2 = 0.34$).

Addition of the independent variables as quadratic components to the regression models, was only statistically significant for increasing BOLD amplitude as predictor of increasing uncorrected PSMD. The quadratic regression models with increasing timing parameters TTP and TTB as predictors for increasing PSMD where not significant and are reported in Supplementary Table 3. Adding BOLD amplitude as quadratic effect to the model, leads to increase explained variance, while the relation remains significant (unstandardized B = 8.13×10^{-5} mm^2/s/percentage, 95% CI [1.66×10^{-5}, 14.61×10^{-5}], $p = 0.02$, Adj. $R^2 = 0.51$). A t-test comparing the linear and quadratic regression models revealed a statistically significant difference between the two models ($p = 0.02$).

Supplementary Figure 1 shows the quadratic regression modeling with decreasing BOLD amplitude as predictor of increasing uncorrected PSMD and the linear regression

modeling with increasing BOLD timing parameters as predictors of increasing uncorrected PSMD.

These results show that without correcting for age, all effects remain statistically significant. Also, the explained variance remains similar to the explained variance of the linear and quadratic regression analyses where the BOLD parameters predict increasing healthy age corrected PSMD.

Sensitivity analyses

Sensitivity analyses in the pre-symptomatic Dutch-type Cerebral Amyloid Angiopathy (D-CAA) mutation carriers showed that the effect size as estimated by unstandardized B collapses in the linear (unstandardized B = -0.98×10^{-5} mm^2/s/percentage, 95% CI [-4.93×10^{-5}, 2.97×10^{-5}], $p = 0.60$, Adj. $R^2 = -0.05$) and quadratic regression modeling (unstandardized B = 0.52×10^{-5} mm^2/s/percentage, 95% CI [-4.16×10^{-5}, 5.40×10^{-5}], $p = 0.78$, Adj. $R^2 = -0.13$) of BOLD amplitude as predictor of uncorrected PSMD. Sensitivity analysis shows that the effect size in the linear regression modeling, as estimated by unstandardized B, collapses for increasing BOLD TTP as predictor of increasing uncorrected PSMD (unstandardized B = 1.21×10^{-7} $mm^2/s/s$, 95% CI [-5.48×10^{-6}, 5.72×10^{-6}], $p = 0.96$, Adj. $R^2 = -0.08$). Sensitivity analysis shows that the sign of the effect size in the linear regression modeling, as estimated by unstandardized B, turns around for BOLD TTB as predictor of increasing uncorrected PSMD (unstandardized B = -2.70×10^{-6} $mm^2/s/s$, 95% CI [-7.35×10^{-6}, 1.95×10^{-6}], $p = 0.23$, Adj. $R^2 = 0.04$). In addition, the regression models no longer show statistically significant effects.

Supplementary Table 1. Complete MRI protocol with parameters

	3D T1 weighted sequence	DTI sequence	Visually stimulated BOLD fMRI sequence	T2 weighted sequence	3D FLAIR sequence	SWI sequence
TR [ms]	9.7	8194	1500	4744	4800	31
TE [ms]	4.6	76	38	80	280	7.2
Flip angle [degrees]	8	90	78	90	TI: 1650 ms	17
Number of slices	130	48	18	48	321	130
Slice thickness [mm]	1.20	2.50	2.81	3.00	0.60	1.00
Interslice gap [mm]	0	0	0.5	0	0	0
FOV [mm]	217x172x156	220x220x120	210x177x59	220x176x144	250x250x180	230x190x130
Voxel size [mm]	1.2x1.2x1.2	1.72x1.72x2.5	2.5x2.5x2.81	0.5x0.6x3.0	1.0x1.0x0.6	0.6x0.6x1.0
Scan duration [min]	2:48	6:33	5:41	2:13	4:43	3:31
b-value [s/mm^2]		1200				
Directions		45				

Abbreviations. DTI; Diffusion Tensor Imaging. BOLD; Blood-Oxygen-Level-Dependent. FLAIR; Fluid Attenuated Inversion Recovery. SWI; Susceptibility Weighted Imaging. TR; repetition time. TE; echo time. TI; inversion time. FOV; Field of View.

Supplementary Table 2. Additional descriptive statistics of the current study cohort

	Study cohort (n = 25)	Pre-symptomatic mutation carriers (n = 15)	Symptomatic mutation carriers (n = 10)
Median number of ICH (IQR)[A]	0 (0—9)	0 (0—0)	19 (7—37)
Median number of CMB (IQR)[A]	0 (0—129)	0 (0—0)	154 (108—353)
Median cSS multifocality score (IQR)[B]	0 (0—0)	0 (0—0)	1 (0—2)
0	15	11	4
1	1	0	1
2	3	0	3
3	1	0	1
4	0	0	0
Median periventricular WMH Fazekas score (IQR)[B]	1 (0—3)	0 (0—1)	3 (3—3)
0	7	7	0
1	3	2	1
2	3	2	1
3	7	0	7
Median deep WMH Fazekas score (IQR)[B]	1 (0—2)	0 (0—1)	3 (2—3)
0	6	6	0
1	5	5	0
2	4	0	4
3	5	0	5
Median CSO-PVS visual rating score (IQR)[B]	3 (3—4)	3 (2—4)	4 (3—4)
0	1	0	1
1	2	2	0
2	2	2	0
3	5	3	2
4	10	4	6

Abbreviations. ICH; intracerebral hemorrhage. IQR; interquartile range. CMB; cerebral microbleeds. cSS; cortical superficial siderosis. WMH; white matter hyperintensity. CSO-PVS; perivascular spaces in the centrum semiovale.

A. 1 missing value in the pre-symptomatic D-CAA mutation carriers.

B. 5, 4, and 1 missing values in the total study cohort, pre-symptomatic, and symptomatic D-CAA mutation carriers, respectively.

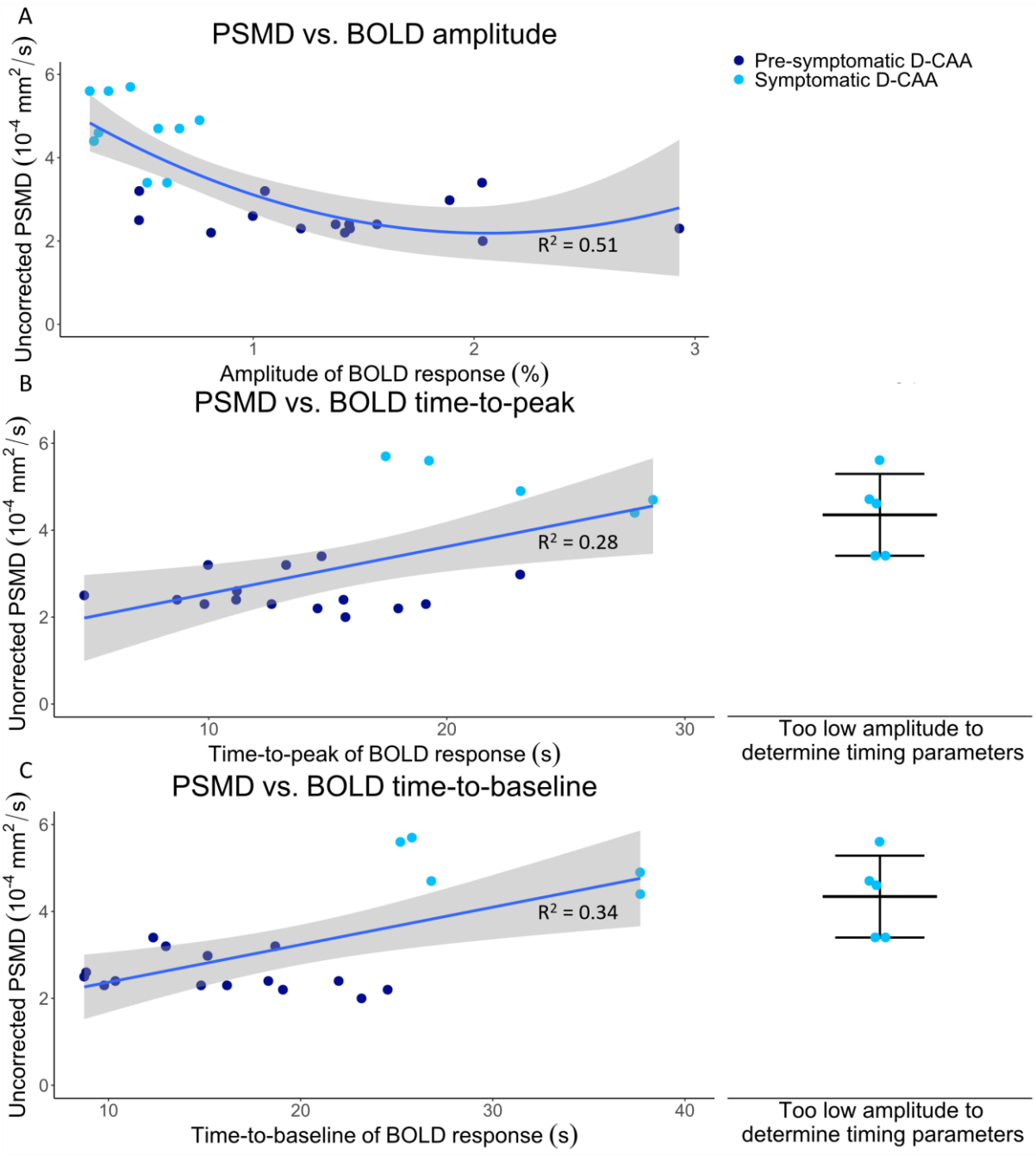
Supplementary Table 3. Statistics of the regression analyses performed on PSMD versus the BOLD parameters, including the standardized and unstandardized beta

	Standardized β [95% CI]	Unstandardized B [95% CI]	*p*-value	Adjusted R^2
Linear model of healthy age corrected PSMD vs. BOLD amplitude	-0.63 [-0.96, -0.29]	$-0.90x10^{-4}$ [$-1.39x10^{-4}$, $-0.42x10^{-4}$]	< 0.001	0.36
Linear model of healthy age corrected PSMD vs. BOLD TTP	0.54 [0.12, 0.95]	$8.34x10^{-6}$ [$1.84x10^{-6}$, $1.48x10^{-5}$]	0.02	0.25
Linear model of healthy age corrected PSMD vs. BOLD TTB	0.57 [0.17, 0.98]	$6.57x10^{-6}$ [$1.92x10^{-6}$, $1.12x10^{-5}$]	0.008	0.29
Quadratic model of healthy age corrected PSMD vs. BOLD amplitude	1.25 [0.19, 2.31]	$6.38x10^{-5}$ [$0.97x10^{-5}$, $11.79x10^{-5}$]	0.02	0.48
Quadratic model of healthy age corrected PSMD vs. BOLD TTP	0.47 [-1.60. 2.55]	$0.21x10^{-6}$ [$-0.70x10^{-6}$, $1.12x10^{-6}$]	0.64	0.21
Quadratic model of healthy age corrected PSMD vs. BOLD TTB	0.25 [-1.75, 2.25]	$0.62x10^{-7}$ [$-4.36x10^{-7}$, $5.60x10^{-7}$]	0.80	0.25
Linear model of uncorrected PSMD vs. BOLD amplitude	-0.64 [-0.97, -0.31]	$-1.15x10^{-4}$ [$-1.74x10^{-4}$, $-0.56x10^{-4}$]	< 0.001	0.39
Linear model of uncorrected PSMD vs. BOLD TTP	0.57 [0.16, 0.98]	$1.08x10^{-5}$ [$3.02x10^{-6}$, $1.86x10^{-5}$]	0.009	0.28
Linear model of uncorrected PSMD vs. BOLD TTB	0.62 [0.23, 1.01]	$8.64x10^{-6}$ [$3.15x10^{-6}$, $1.41x10^{-5}$]	0.004	0.34
Quadratic model of uncorrected PSMD vs. BOLD amplitude	1.29 [0.26, 2.31]	$8.13x10^{-5}$ [$1.66x10^{-5}$, $14.61x10^{-5}$]	0.02	0.51
Quadratic model of uncorrected PSMD vs. BOLD TTP	0.41 [-1.62, 2.44]	$0.22x10^{-6}$ [$-0.87x10^{-6}$, $1.31x10^{-6}$]	0.68	0.25
Quadratic model of uncorrected PSMD vs. BOLD TTB	0.41 [-1.50, 2.32]	$1.25x10^{-7}$ [$-4.60x10^{-7}$, $7.11x10^{-7}$]	0.66	0.31

Note. Units in the regression modeling of PSMD vs. BOLD amplitude is mm^2/s/percentage and of PSMD vs. BOLD TTP and TTB is $mm^2/s/s$.

Abbreviations. PSMD; Peak Width Skeletonised Mean Diffusivity. BOLD; Blood-Oxygen-Level-Dependent. TTP; time-to-peak. TTB; time-to-baseline.

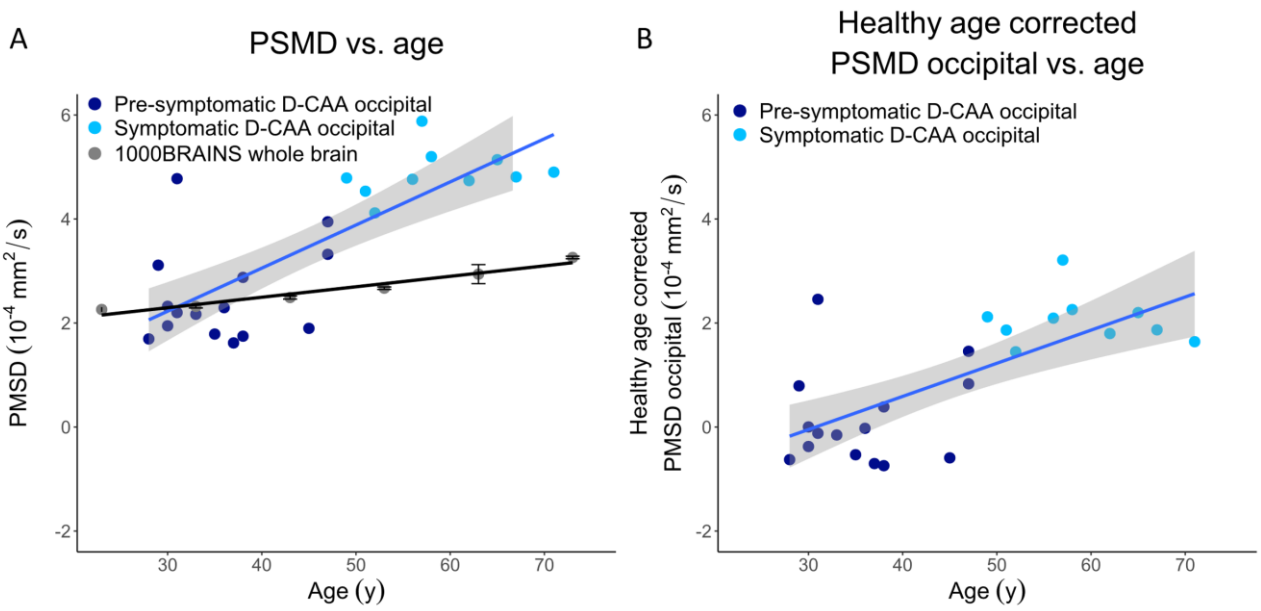
Supplementary Figure 1



Graphs showing the relations between uncorrected PSMD and BOLD parameters with corresponding adjusted R^2 values; A) quadratic relationship between uncorrected PSMD and BOLD amplitude, B) linear relationship between uncorrected PSMD and BOLD time-to-peak, and C) linear relationship between uncorrected PSMD and BOLD time-to-baseline. In B and C, the uncorrected PSMD values, of symptomatic D-CAA mutation carriers of whom no timing parameter could be calculated due to minimal

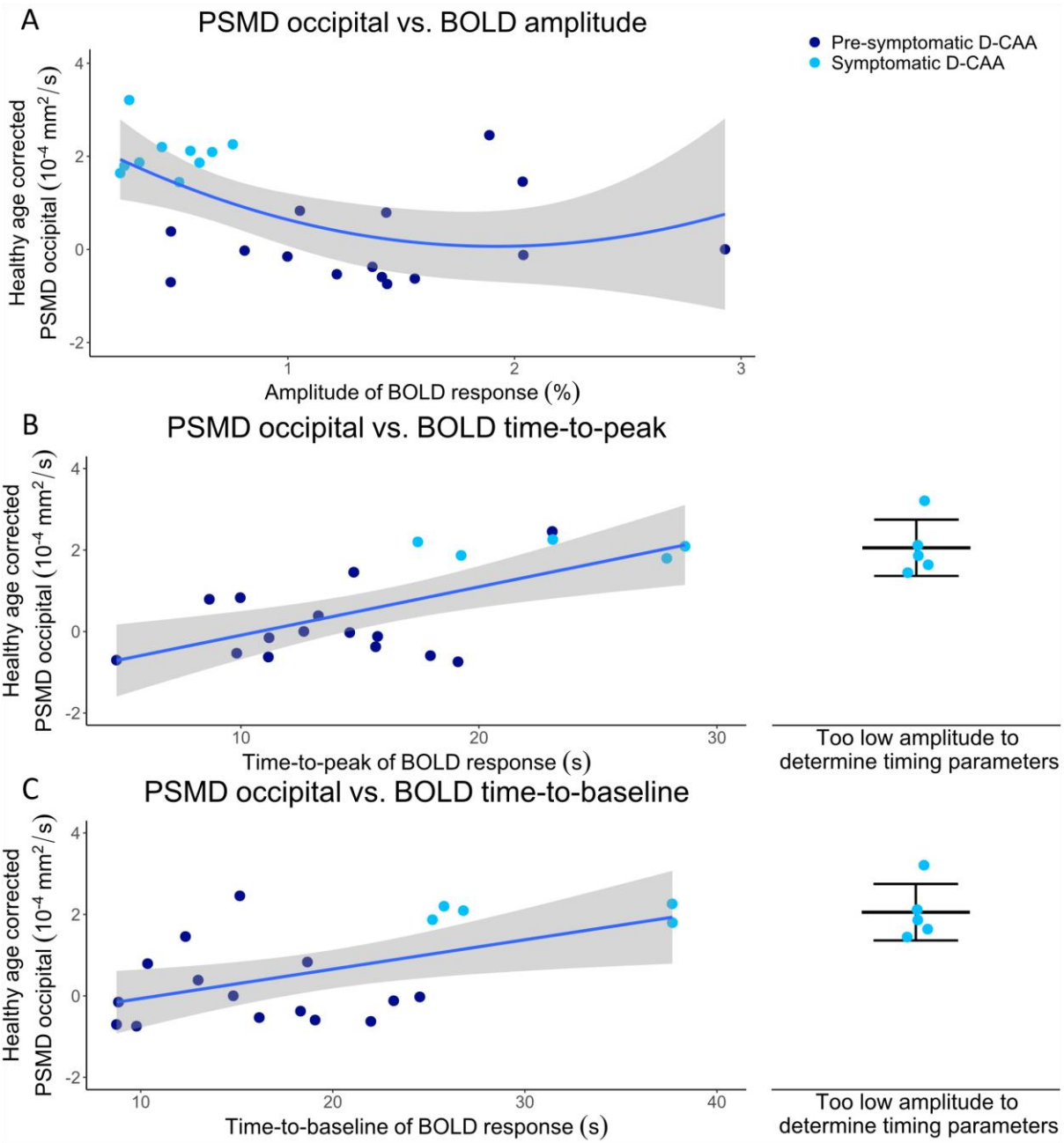
BOLD response to the visual stimulus, are jittered on the right side of the plot, presenting the mean and standard deviation. *Abbreviations.* PSMD; Peak Width Skeletonised Mean Diffusivity. BOLD; Blood-Oxygen-Level-Dependent. D-CAA; Dutch-type Cerebral Amyloid Angiopathy.

Supplementary Figure 2



A) occipital PSMD as a function of age in the D-CAA study cohort and PSMD in the 1000BRAINS cohort, and B) healthy age corrected occipital PSMD as a function of age in the D-CAA study cohort. All graphs include linear regression trends. The standard error for the D-CAA dataset is indicated by the shaded error bar and for the 1000BRAINS cohort it is indicated with standard error bars per age group. Abbreviations. PSMD; Peak Width Skeletonized Mean Diffusivity. D-CAA; Dutch-type Cerebral Amyloid Angiopathy.

Supplementary Figure 3



Graphs showing the relations between occipital PSMD and BOLD; A) quadratic relationship between occipital PSMD and BOLD amplitude, B) linear relationship between occipital PSMD and BOLD time-to-peak, and C) linear relationship between occipital PSMD and BOLD time-to-baseline. In B and C, the occipital PSMD values, of symptomatic D-CAA mutation carriers of whom no timing parameter could be calculated due to minimal BOLD response to the visual stimulus, are jittered on the

right side of the plot, presenting the mean and standard deviation. *Abbreviations.* PSMD; Peak Width Skeletonised Mean Diffusivity. BOLD; Blood-Oxygen-Level-Dependent. D-CAA; Dutch-type Cerebral Amyloid Angiopathy.

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