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Cerebrovascular function in pre-symptomatic and symptomatic individuals with hereditary cerebral amyloid angiopathy: a case-control study

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Summary

Background—Previous work suggests that impairments of cerebrovascular flow or reactivity might be early markers of cerebral amyloid angiopathy (CAA). Hereditary cerebral hemorrhage with amyloidosis–Dutch type (HCHWA-D) is a genetic form of CAA that can diagnosed early by DNA testing, allowing study of CAA before onset of clinical symptoms. The aim of the present study was to investigate whether hemodynamic measures are decreased in HCHWA-D mutation carriers compared to healthy controls.

Methods—In this case-control study, we included pre-symptomatic and symptomatic HCHWA-D mutation carriers diagnosed through genetic testing and recruited through the HCHWA-D patient association (Katwijk, Netherlands) and the outpatient clinic of the Department of Neurology of the Leiden University Medical Center (Leiden, Netherlands), and healthy controls. Regional cerebral blood flow (rCBF) was measured using pseudo-continuous arterial spin labeling. Quantitative flow was determined by phase-contrast MR angiography of the cerebropetal vessels. Vascular reactivity was determined by measuring changes in the blood oxygen level-dependent (BOLD) signal after

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Contributors

AMvO and SvR collected the data. AMvO did the literature search, wrote the report and made part of the figures. AMvO, TvH, EG, PF and JvdG analyzed the data. AMvO and JvdG interpreted the data. PF and MEG prepared part of the figures. JvdG, MAvB, SvR, AMvO, GMT, MJHW and SMG designed the study. GL recruited all participants for the study. All authors critically appraised and edited the report, and approved the manuscript before submission.

Declaration of interests

SMG reports grants from the National Institutes of Health during the conduct of this study. The other authors declare no competing interests.

visual stimulation. Data from pre-symptomatic and symptomatic individuals were compared with healthy controls using mixed-model regression analysis.

Results—In the study done between May 15, 2012 and December 22, 2015, we investigated imaging data from 27 HCHWA-D mutation carriers (12 pre-symptomatic and 15 symptomatic) and 33 healthy controls. Compared with controls, symptomatic HCHWA-D carriers had significantly decreased cortical gray matter rCBF in the occipital lobe (mean difference −11.1 ml/100g/min, CI −2.8 to −19.3, p=0.010) and decreased flux in the basilar artery (mean difference −0.9ml/s, CI −1.5 to −0.2, p=0.019). However, no changes were observed in the rCBF and flux in pre-symptomatic carriers compared with controls. Vascular reactivity was significantly decreased in the occipital lobe in both pre-symptomatic (BOLD amplitude 1.1±0.5% change, mean difference −0.4% change, CI −0.7 to −0.2, p=0.001; time to baseline 10.1±7.6 s, mean difference 4.6 s, CI 0.4 to 8.8, p=0.032) and symptomatic carriers (BOLD amplitude 0.4±0.1% change, mean difference −0.9% change, CI −1.1 to −0.6, p<0.0001; TTP 14.8±8.6 s, mean difference 12.2 s, CI 8.6 to 15.9,p<0.0001; TTB 20.3±8.4 s, mean difference 13.1s, CI 9.4 to 16.9, p<0.0001) compared with controls.

Interpretation—Vascular reactivity in the occipital lobe was decreased in both symptomatic and pre-symptomatic individuals with HCHWA-D. This indicates that determination of vascular reactivity might be a useful biomarker for early detection of vascular amyloid pathology in sporadic CAA, and a biomarker of efficacy in future intervention trials.

Funding—National Institutes of Health.

Keywords

Cerebral Blood Flow; Vascular reactivity; Cerebral Amyloid Angiopathy; HCHWA-D; presymptomatic

Introduction

Cerebral amyloid angiopathy (CAA) is an increasingly recognized cause of intracerebral hemorrhages, loss of neurologic function and progressive cognitive decline. The disease is caused by excessive amyloid-β deposition in the vasculature of the brain, especially in the walls of the leptomeningeal and cortical vessels.[1–3] CAA is frequently found as co-morbidity in Alzheimer's disease but is also diagnosed as a standalone disease.[1–3] In the general population, sporadic CAA is found in older persons, and is typically diagnosed based on the presence and location of intracerebral hemorrhages using the Boston criteria.[4] However, for early diagnosis and subsequent determination of efficacy in intervention trials, sensitive biomarkers in the pre-symptomatic phase of the disease are needed.

Previous studies have shown decreased regional cerebral blood flow (rCBF) in symptomatic patients with CAA.[5] In addition, symptomatic patients with CAA have shown decreased vascular reactivity measured with transcranial Doppler or functional MRI (fMRI) in response to visual stimulation.[6;7] As CAA deposition of amyloid-β in cerebrovascular walls and loss of vascular smooth muscle cells are already present before overt signs or symptoms of the disease,[8–10] hemodynamic alterations in the pre-symptomatic stage of the disease may also be present. It is nonetheless difficult to identify these potential changes in persons with

asymptomatic CAA, because of the intrinsic difficulty in diagnosing sporadic CAA in the pre-symptomatic stages of the disease.

Hereditary cerebral hemorrhage with amyloidosis–Dutch type (HCHWA-D) is an autosomal dominant form of CAA that can be diagnosed before disease onset using genetic testing. In HCHWA-D, an E693Q point mutation in Amyloid Precursor Protein (APP) leads to accumulation of amyloid-β in vessel walls, while parenchymal depositions of amyloid-β and senile plaques as observed in Alzheimer's are mostly absent.[11;12] Mutation carriers develop symptoms relatively early in life, usually between the ages of 50 and 60 years, allowing CAA-related changes to be studied with minimal confounding factors caused by aging and other co-morbidities found in patients with sporadic CAA.[13]

The aim in the present study was to investigate whether rCBF and vascular reactivity are decreased in symptomatic and pre-symptomatic HCHWA-D mutation carriers compared to healthy controls.

Methods

Study design and participants

This case-control study was done between May 15, 2012 and December 22, 2015 at the Departments of Radiology and Neurology of the Leiden University Medical Center (Leiden, Netherlands). Patients were identified and enrolled through the HCHWA-D patient association (Katwijk, Netherlands) and the outpatient clinic of the Department of Neurology of the Leiden University Medical Center (Leiden, Netherlands). The diagnosis of HCHWA-D was based on DNA analysis confirming the codon 693 mutation in the amyloid-β precursor protein (*APP*) gene. Both symptomatic and pre-symptomatic mutation carriers were included in the HCHWA-D cohort. Subjects were considered symptomatic if they previously had one or more intracerebral haemorrhages, and were only included if they did not experience new symptoms one month preceding the MRI examination. Pre-symptomatic mutations carriers were recruited blinded to mutation status from families at risk of HCHWA-D. Participants with a positive mutation status were included in the pre-symptomatic group; mutation negative participants were included in the control group. Other control subjects were recruited from participants' spouses, family, or friends. All control subjects underwent genetic testing.

After recruitment, all participants were assessed by SvR or AMvO for cognitive markers: Mini-Mental State Examination for global cognitive functioning; Wechsler Memory Scale and Hopkins Verbal Learning Test immediate and delayed recall for memory function; Trail making test part A for psychomotor speed; TMT part B, Digit symbol substitution test of the WAIS III15 and Clock drawing for executive function; and letter and animal naming (letter and category fluency) and Boston naming test for language function. The ethics committee of the Leiden University Medical Center approved the study, and written informed consent was obtained from all participants.

MRI acquisition

All individuals with HCHWA-D and controls were scanned using a whole body magnetic resonance system with a 3 Tesla field strength (Philips Medical Systems, Best, Netherlands). 3D T1-weighted images (echo time [TE] 4.6ms, repetition time [TR] 9ms, Flip 8°, field of view]FOV] = 224 × 177 × 168mm, scan duration ~5mins), T2-weighted images (TE/TR/Flip: 80ms/4.2s/90°, 40 slices, FOV 224 × 180 × 144mm, slice thickness 3.6mm, matrix size 448 × 320), fluid-attenuated inversion recovery (TE/TR/Flip angle: 125ms/11.0s/90 °, slices 25, FOV 252 × 179.76 × 250mm, matrix size 224 × 224, scan duration 293s), susceptibility-weighted images (TE/TR/Flip angle: 31ms/45ms/13°, 125 slices, matrix size: 250 × 175 × 112mm voxel size: 0.78 × 0.78 × 0.8mm), and pseudo continues arterial spin labeling (TE/TR/Flip angle: 14ms/4.0s/90°, FOV 240 × 133 × 240mm, matrix 80 × 80mm, 19 slices) were obtained. Phase-contrast quantitative flow scans were planned using 2 localizer angiograms in the sagittal and coronal planes and acquired (TR=11ms; TE 7.5ms; flip angle=10°; slice thickness=5mm; field of view 150×103mm; voxel size 1.17×1.17mm; velocity sensitivity=200cm/s, 20 signal averages). The visually stimulated blood-oxygen-level-dependent (BOLD) fMRI scans were acquired with a TE/TR: 31ms/1499ms, FOV 220 × 75 × 220mm, matrix 80 × 80mm, slices 25, 130 dynamics, scan duration 201sec. The visual stimulus consisted of 16 blocks of an 8Hz flashing radial black and white checkerboard pattern for 20 seconds alternated with 28 seconds of gray screen, as used in an earlier study in CAA.[6]

Microbleeds and intracerebral haemorrhages were scored on susceptibility weighted MRI according to criteria as described previously.[14]

Flow measurements in the internal carotid and basilar arteries were done using Philips Software on a PACS (Philips Medical Systems, Best, Netherlands) workstation with region of interest measurement tools. Flux and average flow velocity were measured for basilar artery and both internal carotid arteriesseparately. Total flux was calculated for all three vessels together; anterior flux was calculated as the sum of the flux of bothinternal carotid arteries.

Image processing and quantitative analysis

Structural MRI acquisitions were analyzed using FMRIB Software Library version 5.0.4 (Analysis Group, FMRIB, Oxford, UK) for white matter hyper intensities as described earlier.[15;16] Pseudo continues arterial spin labeling scans were motion corrected using FMRIB-MCFLIRT to reduce subtraction errors. Files were smoothed and after subtraction a mean rCBF map was calculated. This map was then translated to MNI152 space using FMRIB-FLIRT and FMRIB-FNIRT with the conversion matrix based on the 3D T1 scans. The perfusion was measured in the corrected supra-tentorial cortical gray matter volume with an erosion applied tothe locations of the white matter lesions and to areas of intracerebral haemorrhages to make sure we measured gray matter. This corrected cortical gray matter was segmented in four cortical areas based on the Harvard Oxford probabilistic cortical atlas threshold of 25 percent.[17] BOLD fMRI scans were analyzed for BOLD amplitude, time to peak and time to baseline as described before.[6]

Statistical analysis

Statistical analysis was performed with the SPSS software (version 23). Comparisons of baseline characteristics between control subjects and mutation carriers were done using mixed models with subject group as a fixed effect (three levels: pre-symptomatic, symptomatic, and control), and family history of HCHWA-D as a random factor to account for clustered data caused by familial relations between participants. Differences in rCBF and BOLD measurements between pre-symptomatic and symptomatic mutation carriers and controls were performed with a mixed model with subject group as a fixed effect (three levels: pre-symptomatic, symptomatic, and control), adjusted for age and sex; family history of HCHWA-D was used as a random factor to account for clustered data. Partial correlations adjusted for sex were used to determine the association of rCBF and BOLD measurements with age, for the controls and mutation carriers seperately. Uncorrected $p<0.05$ was considered statistically significant for all analysis, $p<0.0045$ was considered statistically significant after Bonferroni correction for multiple comparisons of the hemodynamic outcome measures (n=11).

Role of the funding source

The funding source of the study had no role in the performance of this study, analyses, interpretation of results, or manuscript preparation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Demographic data and clinical characteristics of the cohorts are shown in Table 1. Symptomatic HCHWA-D mutation carriers had a significant increase in prevalence of intracerebral haemorrhages ($p<0.0001$), increased WMH volume ($p<0.0001$) and increased prevalence of microbleeds ($p=0.0001$) at enrolment, compared with controls. Symptomatic mutation carriers showed significantly lower scores on all cognitive test compared to controls. Pre-symptomatic carriers showed no differences in MRI and cognitive markers compared to controls. Only two (17%) out of twelve pre-symptomatic carriers presented with microbleeds, even though microbleeds are often seen as early markers of CAA. In contrast, all fifteen of the symptomatic patients presented with microbleeds; one of control subjects also presented with a microbleed.

Although total blood flow to the brain (total flux) in both pre-symptomatic (13.1 ± 1.8 ml/s) and symptomatic (10.0 ± 2.4 ml/s) HCHWA-D mutation carriers was not different from controls (11.7 ± 3.1 ml/s), flow in the posterior circulation (flux in the basilar artery) was significantly lower ($p = 0.019$) in symptomatic HCHWA-D mutation carriers (1.9 ± 1.2 ml/s) compared with control (3.1 ± 1.2 ml/s). Total flux ($p<0.0001$; Fig 1A) and flux in the basilar artery ($p=0.001$; Fig 1B) showed a significant negative association with age in the mutation carriers but not in the control subjects.

rCBF was not different between both pre-symptomatic (62.1 ± 7.9 ml/100g/min) and symptomatic (51.0 ± 14.8 ml/100g/min) HCHWA-D mutation carriers and controls (60.8

± 13.1 ml/100g/min) (table 2). However, rCBF in the occipital region was significantly lower (p=0.010) in symptomatic HCHWA-D mutation carriers (49.3 ± 17.9 ml/100g/min) than in controls (66.7 ± 14.9 ml/100g/min). Significant associations with age were found for total supra-tentorial cortical grey matter rCBF (p=0.021, Fig 1C) and occipital cortical grey matter rCBF (p=0.002, Fig 1D) in mutation carriers. In the control subjects, total supra-tentorial cortical grey matter rCBF, but not occipital cortical grey matter rCBF, showed a significant negative association with age (p=0.025).

Figure 2 shows the shape of the hemodynamic response curves in the occipital lobe after visual stimulation by checkerboard for the entire HCHWA-D group and for the pre-symptomatic and symptomatic HCHWA-D mutation carriers separately. In symptomatic HCHWA-D mutation carriers, the BOLD response after visual stimulation has a distinct pattern. Directly after the start of the checkerboard stimulus, only a very small hemodynamic response amplitude is observed with a subsequent long time to peak. In pre-symptomatic HCHWA-D mutation carriers, the overall hemodynamic response curve follows a more classic pattern. Nevertheless, hemodynamic response amplitude was clearly lower than in age-matched controls. The quantitative average hemodynamic response parameters, stratified by age, are shown in figure 3. When comparing the overall BOLD response of HCHWA-D mutation carriers to the overall response in controls, we found significant differences (table 3). Mutation carriers show a significantly lower average BOLD amplitude in the symptomatic stage p<0.0001) and pre-symptomatic stage (p=0.001) compared with controls. We also found a significantly increased time to baseline in both pre-symptomatic (p=0.032) and symptomatic carriers (p<0.0001) compared with controls. A significant increased time to peak (p<0.0001) was found only in the symptomatic mutation carriers compared with controls. The BOLD amplitude (Fig 3A) showed a significant positive association with age (p<0.0001) and time to baseline (Fig 3C) showed a significant negative association with age (p=0.028) in the mutation carriers but not in the controls.

Discussion

To investigate hemodynamic measures as possible biomarkers for early detection of vascular amyloid pathology, we assessed rCBF, quantitative flow, and vascular reactivity in both symptomatic and pre-symptomatic HCHWA-D mutation carriers compared with healthy controls. We found that the BOLD response in occipital cortex after visual stimulation was markedly disrupted in participants with HCHWA-D, including pre-symptomatic carriers as well as symptomatic carriers with past intracerebral haemorrhages. For measures of vascular flux and rCBF, however, differences between HCHWA-D mutation carriers compared with controls were seen only in the basilar artery and occipital brain regions, and were restricted to symptomatic HCHWA-D mutation carriers. These findings combined with the observation that no changes were found in the frontal, parietal, or temporal cortical grey matter in symptomatic HCHWA-D mutation carriers, indirectly confirms previous findings that the occipital lobe is preferentially affected by CAA and the area most affected by intracerebral haemorrhages.[9]

In contrary to our findings, a previous study found changes in perfusion in the parietal, temporal, and frontal lobes of sporadic CAA patients.[5] The regions found by Chung and

colleagues are concordant with areas affected by Alzheimer's disease, indicating that changes in resting CBF could be related to parenchymal instead of vascular amyloid deposition.[5] Moreover, the finding in our study that there were no changes in the pre-symptomatic mutation carriers without confounding tissue damage indicate that the flow changes observed are related to tissue damage and not to vascular amyloid deposition. However, because of the cross-sectional design of our study we cannot elucidate whether these flow changes are causative or secondary to hemorrhagic damage at tissue level.

In contrast to the non-significant changes in rCBF, we found significant changes in our vascular reactivity data in both pre-symptomatic and symptomatic mutation carriers. In HCHWA-D mutation carriers, all three BOLD parameters (BOLD amplitude, time to peak, and time to baseline) were altered. These changes indicate both a decreased and a delayed response to stimulation. This may suggest a decreased capability for vasodilation, but also a decreased reaction of the vessel wall to a stimulus. Mouse models of CAA have shown that the amyloid deposition indeed causes loss of vessel wall functions in the early phase of the disease.[18;19] Another study suggests that the decrease in hemodynamic function in CAA is mainly caused by vessel wall damage and not necessarily by changes in blood flow and metabolic demand,[7] which is in line with our finding of no significant changes in rCBF. Two additional studies found decreased vascular reactivity in symptomatic CAA patients or CAA mutation carriers,[7,20] which is also in line with our findings in pre-symptomatic HCHWA-D mutation carriers.

Stratification for symptomatology showed significant changes in all parameters in symptomatic mutation carriers, whereas in the pre-symptomatic group, the BOLD amplitude and time to baseline were still significantly different from control subjects. Our findings in symptomatic mutation carriers are in line with previous reports showing similar BOLD changes after a visual stimulus in symptomatic persons diagnosed with sporadic CAA that are shown to decrease over time.[6;20;21] Using the same methods to assess the vascular reactivity as previously published,[6] we found that the BOLD response values for symptomatic HCHWA-D mutation carriers were very similar to the older sporadic CAA patients. Compared with this previous study,[6] the values we obtained in the older controls were similar, although the younger controls in our study have higher amplitude and a faster time to peak. In addition, the pre-symptomatic mutation carriers in our study showed an average BOLD response that falls between the older sporadic CAA patients and the controls. Taken together, our data are the first to show similar, although less severe, vascular reactivity changes in pre-symptomatic CAA compared to symptomatic stages of sporadic CAA. Moreover, since no intracerebral haemorrhages were present in our pre-symptomatic mutation carriers, these changes in vascular reactivity may be indicative for very early changes on tissue level, even before more manifest tissue damage occurs.

A limitation of our study is the small number of mutation carriers in our study population, which limits the power of our analyses. Additionally, the heterogeneity of our control group which included participants with familial relations to the carriers or a family history of HCWA-D and participants without such a background (ie, friends and spouses of carriers) could confound our findings. A further limitation of the study is the cross-sectional design of study which, as mentioned before, does not allow us to determine whether hemodynamic

changes are causative or secondary to structural damage in the form of microbleeds, and whether any of the markers found in this study are predictive for disease progression. Longitudinal follow up studies are necessary to further investigate whether vascular reactivity and change in rCBF over time have predictive value.

In conclusion, our data clearly demonstrate changes in rCBF and in vascular reactivity in symptomatic HCHWA-D mutation carriers with hemorrhagic lesions compared with healthy controls. More importantly, vascular reactivity is already affected in the pre-symptomatic stage of HCHWA-D indicating that vascular amyloid pathology causes changes in vascular reactivity that can be detected at an early phase of the disease process.

Acknowledgments

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Research in context

Evidence before this study

We searched PubMed for articles on hereditary cerebral hemorrhage with amyloidosis - Dutch type (HCHWA-D), cerebral amyloid angiopathy (CAA) and cortical atrophy published between Jan 1, 1980, and Jan 1, 2016, with different combinations of the terms “cerebral amyloid angiopathy”, “HCHWA-D”, “cerebral blood flow”, “vascular reactivity” and” vascular function”. We found seven articles showing decreased regional cerebral blood flow (rCBF) and decreased vascular reactivity in symptomatic patients with CAA and in mouse models of the disease. However, we found no human studies investigating cerebrovascular function in the pre-symptomatic stage of the disease, which is imperative to understanding the pathophysiology of CAA.

Added value of this study

To our knowledge this is the first study to use individuals with HCHWA-D as a model to examine cerebrovascular function in pre-symptomatic and symptomatic stages of CAA using MRI techniques. Our data show that vascular amyloid pathology causes a decrease in vascular reactivity that can already be detected in pre-symptomatic individuals. In contrast, rCBF was not affected in individuals in the pre-symptomatic stage of the disease.

Implications of all the available evidence

CAA is an increasingly recognized cause of intracerebral hemorrhages, loss of neurologic function and progressive cognitive decline. As CAA deposition of amyloid-β in cerebrovascular walls and loss of vascular smooth muscle cells are most likely present before overt signs or symptoms of the disease, hemodynamic alterations may also be present in the pre-symptomatic stage of the disease. Our study is the first to show that CAA pathology causes vascular dysfunction before the onset of clinical symptoms of the disease. These new findings are important to understand the pathophysiology of CAA and, in the context of earlier pathology studies, suggest that changes in vascular reactivity might be a cause of the cerebral damage seen in symptomatic CAA. Additionally, our findings indicate that changes in vascular reactivity might be a possible biomarker for early diagnosis of CAA and that vascular reactivity could be a biomarker of efficacy in future intervention trials.

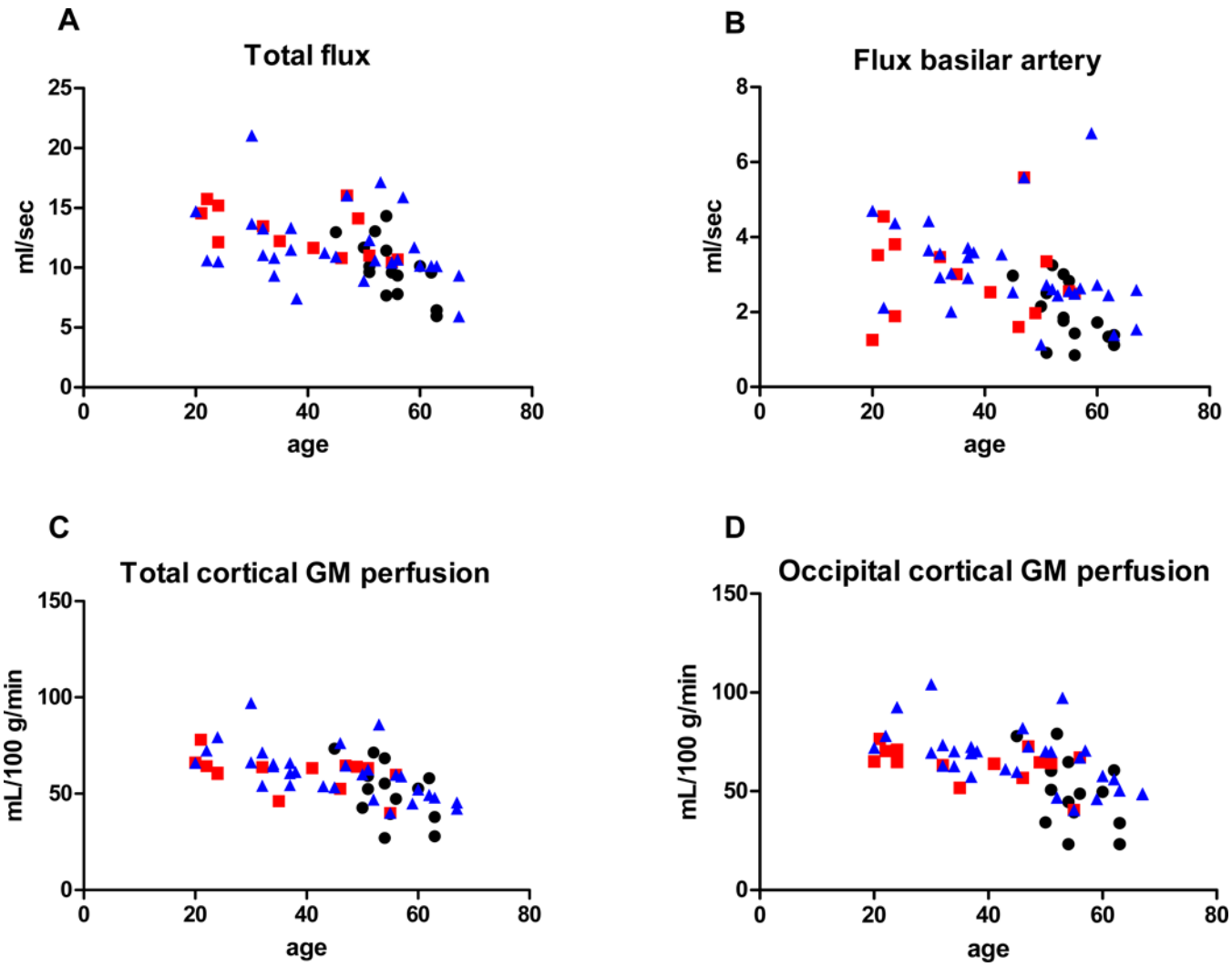
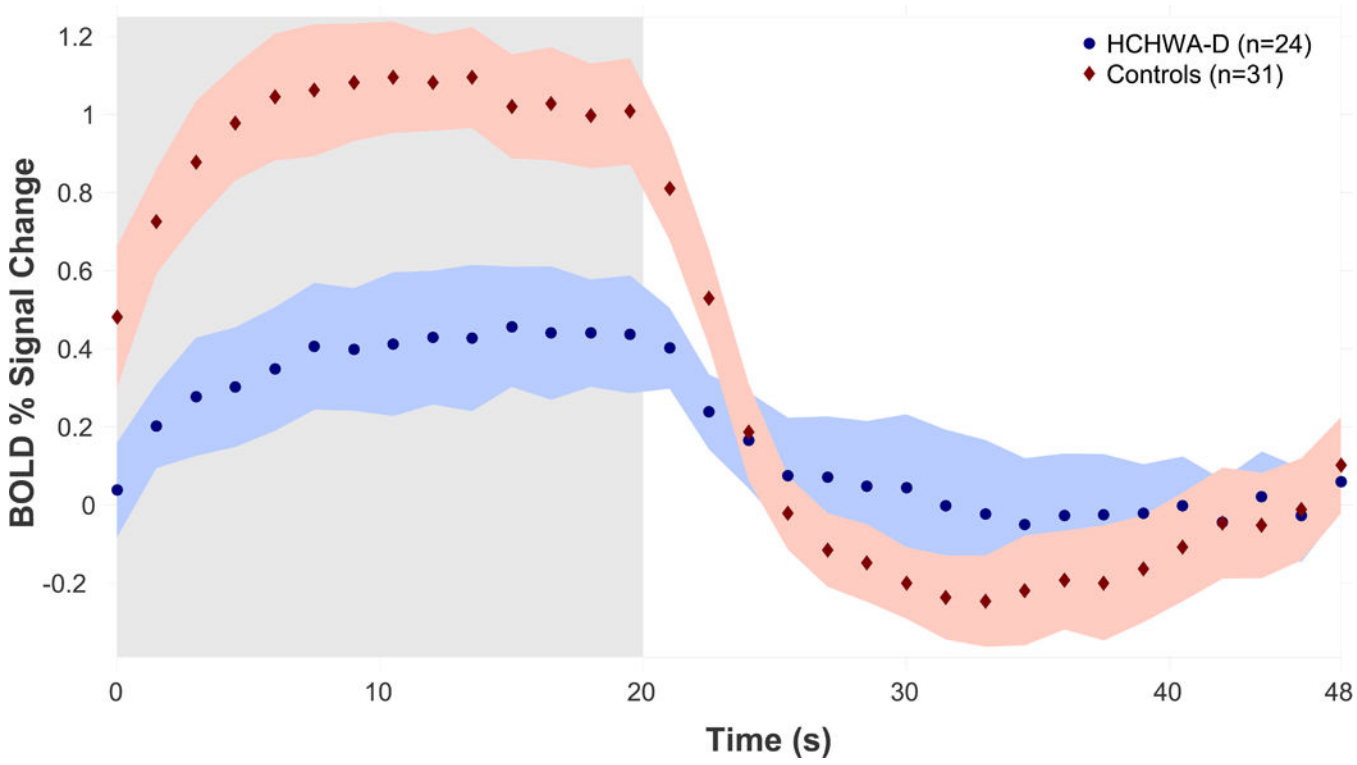
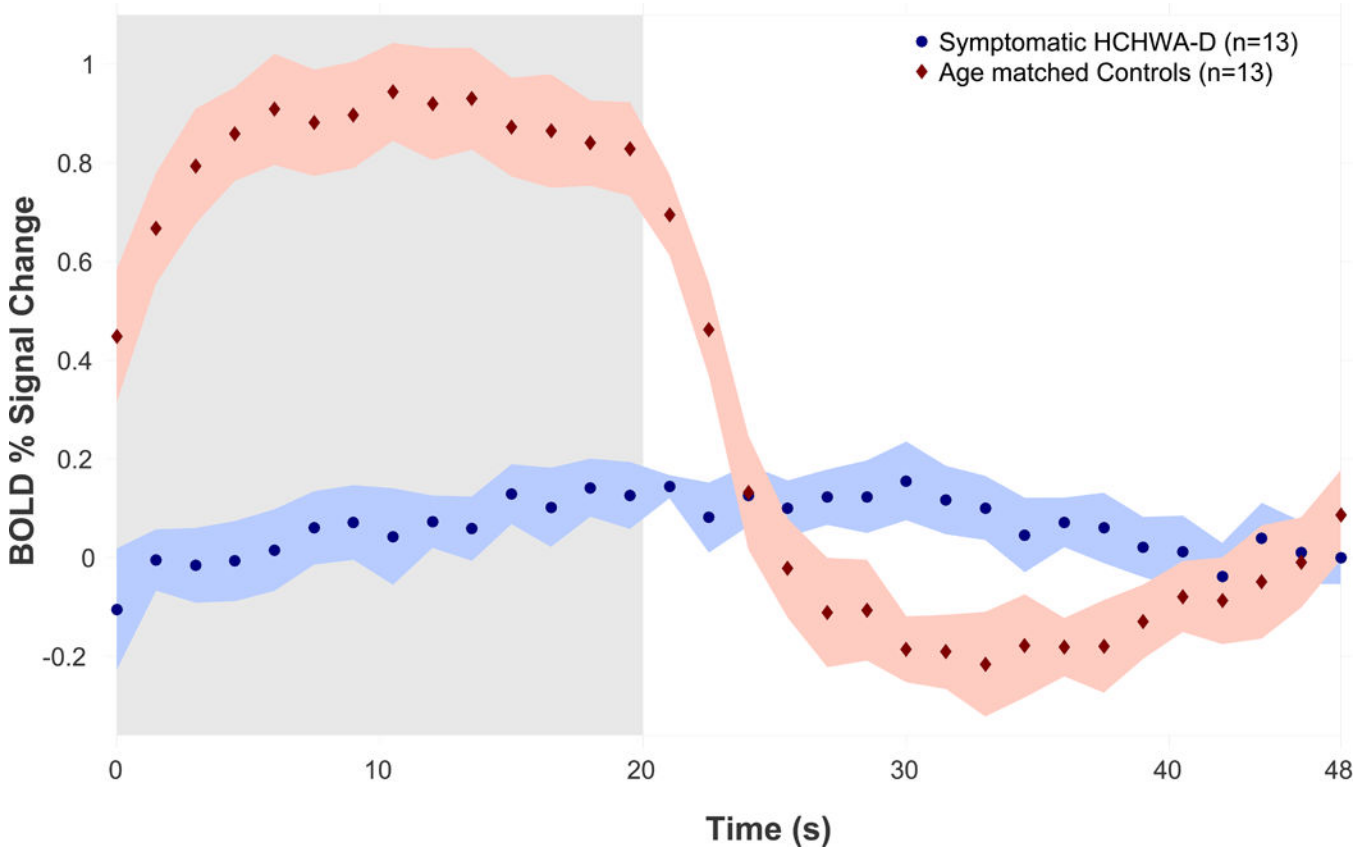


Figure 1. Cerebral blood flow measurements by age

Blue triangles, ▲: control subjects, red squares, ■: pre-symptomatic mutation carriers, black circles, ●; symptomatic mutation carriers. (A) Total flux measured in ml/sec. (B) Flux in the basilar artery measured in cm/sec. (C) Mean total supra-tentorial cortical gray matter perfusion and (D) mean occipital cortical grey matter perfusion both measured in mL/100 g/min.





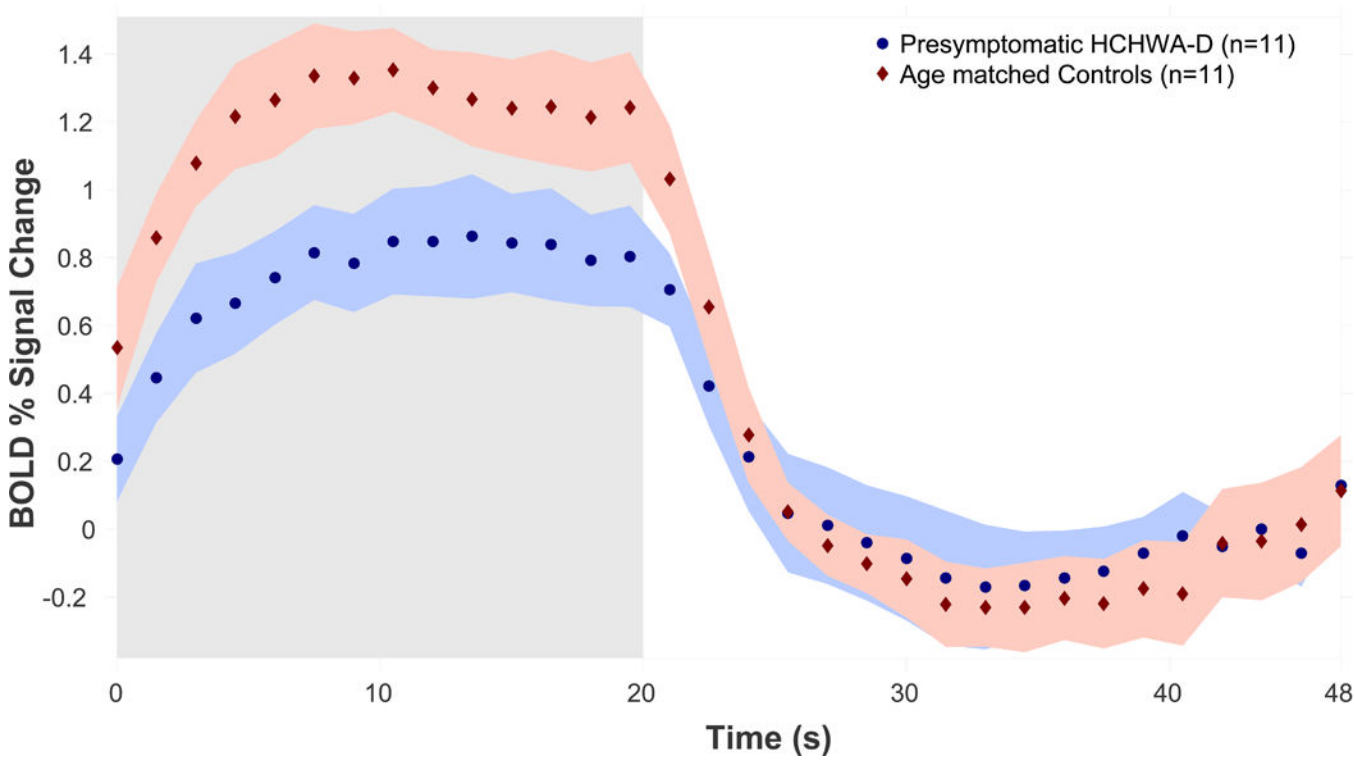


Figure 2. Blood oxygen level-dependent (BOLD) response within the occipital lobe

(Top panel) Average group block responses relative to baseline (set at 0%) for all HCHWA-D mutation carriers and all controls; and (middle panel) for symptomatic and (bottom panel) pre-symptomatic mutation carriers and age-matched control subjects. BOLD amplitude measured in percentage BOLD change. Grey boxes indicate the time of activation of the visual stimulus.

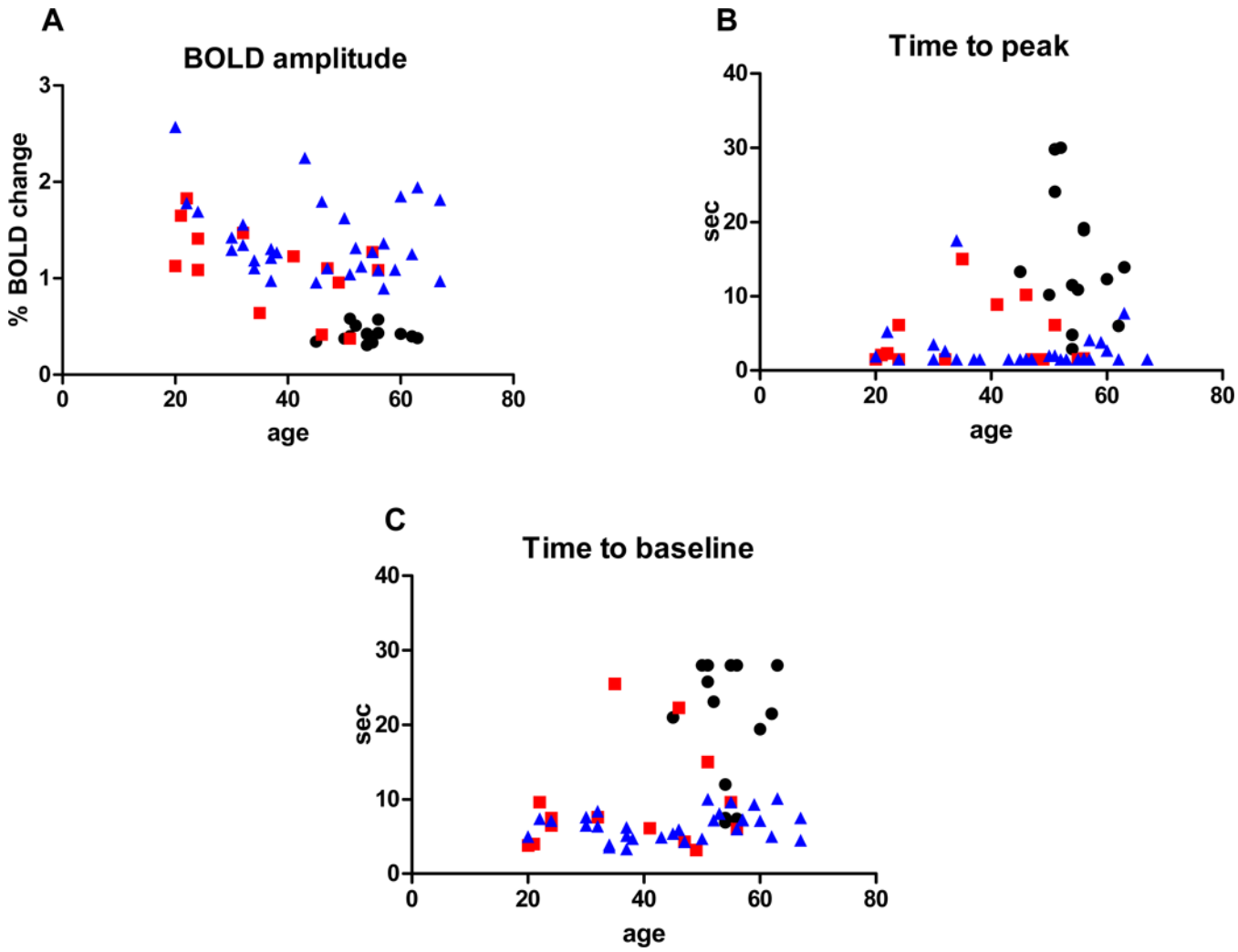


Figure 3. Blood oxygen level-dependent (BOLD) fMRI measurements by age

Blue triangles, ▲: control subjects, red squares, ■: pre-symptomatic mutation carriers, black circles, ●; symptomatic mutation carriers.(A) BOLD amplitude measured in percentage BOLD change, (B) time to peak, and (C) time to baseline in seconds.

Table 1

Characteristics of participants at baseline

	Pre-symptomatic HCHWA-D mutation carriers N = 12	Symptomatic HCHWA-D mutation carriers N = 15	Controls N = 33
Age, years	34±12**	55 ± 5*	46 ± 14
Sex			
Men	3 (25%)	7 (47%)	13 (39%)
Women	9 (75%)	8 (53%)	20 (61%)
Systolic blood pressure	125 ± 14	144 ± 20	130 ± 26
Diastolic blood pressure	80 ± 9	89 ± 10*	81 ± 12
Hypertension	0	7 (40%)*	6 (18%)
Diabetes	1(8%)	1 (7%)	0
Epilepsy	0	3 (20%)*	0
MMSE	30 (28–30)	27 (16–30) ***	29 (27–30)
WMS (mean MQ)	122 (103–137)	111 (72–143) **	125 (105–143)
HVLT immediate recall	28 (24–32)	21 (7–31) ***	28 (1–35)
HVLT delayed recall	10 (7–12)	7 (0–12) ***	10 (6–19)
TMT A (sec)	27 (16–44)	55 (29–96) ***	30 (15–53)
TMT B (sec)	55 (39–85)	161 (67–540) ***	60 (30–105)
DSST (number correct symbols)	84 (6–101)	47 (18–79) ***	77 (46–110)
Clock drawing (points)	3 (2–3)	2 (1–3) ***	3 (2–3)
Letter fluency (number correct words)	33 (19–54)	24 (12–38) **	34 (13–50)
Category fluency (number correct words)	23 (14–32)	15 (3–23) **	22 (14–40)
BNT (number of correct items)	28 (26–30)	23 (4–29) ***	29 (27–30)
Age of onset	–	49 (44–60)	–
ICH Total	0 (0–7)	20 (1–46) ***	0 (0–0)
Frontal	0 (0–1)	3 (0–17) ***	0 (0–0)
Parietal	0 (0–1)	2 (0–7) ***	0 (0–0)
Temporal	0 (0–1)	7 (0–14) ***	0 (0–0)
Occipital	0 (0–4)	9 (0–17) ***	0 (0–0)
WMH volume (cm^3)	5.8 (0.0–37.3)	92.4 (2.1–180.6) ***	2.3 (0.0–23.3)
Microbleeds	0 (0–32)	42 (2–468) ***	0 (0–1)

Mean age in years with SD, mean blood pressure in mm/Hg with SD, median MMSE score with range, mean Wechsler Memory Scale (WMS) Memory Quotient (MQ) with range, Mean Hopkins Verbal Learning Test (HVLT) immediate and delayed recall score with range, mean Trail making test (TMT) A/B time in seconds with range, Mean Digit symbol substitution test (DSST) score with range, median Clock drawing points with range, mean letter and category fluency score with range, mean number of correct BNT items, mean Age of onset of clinical symptoms with range, median number of ICH with range of number of ICH, mean WMH volume in cm^3 with range, median number of microbleeds with range. Significantly different from control subjects at uncorrected *p<0.05, **p<0.01 and ***p<0.001

Table 2

CBF measurements in pre-symptomatic and symptomatic HCHWA-D mutation carriers compared to controls.

	Pre-symptomatic HCHWA-D mutation carriers	Symptomatic HCHWA-D mutation carriers	Controls
Flux (ml/sec)			
Total	13.1 ± 1.8	10.0 ±2.4	11.7 ± 3.1
Anterior	10.1 ± 1.8	8.0 ± 1.9	8.7 ± 2.8
Basilar	2.8 ± 1.0	1.9 ± 0.8*	3.1 ± 1.2
pCASL signal (ml/100g/min)			
Total cortical GM	62.1 ±7.9	51.0 ± 14.8	60.8 ± 13.1
Frontal cortical GM	69.7 ± 9.8	56.3 ± 17.1	66.0 ± 14.5
Parietal cortical GM	72.4 ± 7.9	58.9 ± 17.6	69.8 ± 14.5
Temporal cortical GM	58.2 ± 8.4	49.3 ± 12.6	58.5 ± 12.6
Occipital cortical GM	64.8 ± 6.7	49.3 ± 17.9*	66.7 ± 14.9

Mean total flux, anterior flux and posterior ± SD measured in ml/sec. Mean flow velocity in the left internal carotid artery, right internal carotid artery and basilar artery ± SD measured in cm/sec. Mean pCASL signal ± SD, measured in total supratentorial cortical gray matter (GM) and respective cortical gray matter areas in mutation carriers and controls in mL/100 g/min. Significantly different from control subjects at uncorrected $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$, significantly different at Bonferroni corrected $^{*}p<0.0045$

Table 3

Vascular reactivity measurements in pre-symptomatic and symptomatic HCHWA-D mutation carriers compared to controls.

	Pre-symptomatic HCHWA-D mutation carriers	Symptomatic HCHWA-D mutation carriers	Controls
BOLD amplitude (% BOLD change)	$1.1 \pm 0.5^{**\dagger}$	$0.4 \pm 0.1^{***\dagger}$	1.4 ± 0.4
Time to peak (sec)	5.2 ± 4.6	$14.8 \pm 8.6^{***\dagger}$	2.7 ± 3.1
Time to baseline (sec)	$10.1 \pm 7.6^{*}$	$20.3 \pm 8.4^{***\dagger}$	6.4 ± 1.9

Blood oxygen level dependent (BOLD) amplitude measured in % BOLD change. Time to peak and time to baseline measured in seconds. All values reported as means with standard deviations. significantly different from control subjects at $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$, significantly different at Bonferroni corrected $^{\dagger}p<0.0045$