Cerebrovascular reactivity in the brain white matter: magnitude, temporal delays, and age effects

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INTRODUCTION: Structural studies using T2w, DTI, and magnetization transfer have revealed a wealth of information about the brain's white matter (WM) and its alteration due to aging and diseases. However, physiological properties of the WM are still poorly understood, partly due to limitations in SNR. Recent technical advances in several methodologies have provided the potential to examine vascular physiology in the WM (1, 4). We have recently demonstrated the feasibility of evaluating WM perfusion on a tract-by-tract basis and showed a strong relationship between WM perfusion and fractional anisotropy (FA) (2). The goal of the present study is to examine another important property of the WM microvasculature: its ability to dilate upon stimulation. This physiological property, known as Cerebrovascular Reactivity (CVR), forms the basis of the BOLD-response and is well understood in the gray matter (GM), but little is known about its characteristics in the WM. Note that vascular deficits in the WM may be responsible for many abnormalities observed on structural MRI (e.g. WM hyper-intensity, FA decrease) (3), and often precede these structural changes. In the present study, we used CO2 inhalation to determine CVR in the WM and compared it to that in the GM. The CVR responses were examined in the context of both amplitude and temporal shift. Age-related differences were investigated by including both younger and older participants. For completeness, baseline perfusion was also measured with ASL MRI.

METHODS: Experiment: 15 healthy young (27±5 years, age range: 20 to 35 years) and 15 healthy elderly volunteers (75±7 years, age range: 62 to 86 years) were recruited using criteria typical of normal aging. The participants had a minimal MMSE score of 26 and at least high school education. MRI was performed on a Philips 3T. For the CO2 inhalation task, the subject breathed room-air and 5% CO2 (mixed with 21% O2 and 74% N2) in an interleaved fashion (switching every 1 min) while single-shot BOLD EPI images (TE=25ms) were acquired continuously. This short-duration breathing paradigm has previously been shown to improve subject comfort yet maintaining data quality (4, 5). End-tidal CO2 (Etco2), the CO2 concentration in the lung and thus arterial blood, is recorded throughout the breathing task and a regression analysis between this signal and the MRI time course yields the CVR value in the unit of %BOLD/mmHg. For comparison, baseline cerebral blood flow (CBF) was measured using pseudocontinuous ASL and absolute CBF (in ml/100g/min) was quantified with an approach described previously (6). An MPRAGE image (resolution 1x1x1 mm^3) was also acquired for anatomic reference and for GM/WM segmentation. Data Analysis: Only ROI analysis was performed and no attempt was made for voxel-wise analysis, as the low sensitivity in WM (which contains 75% less blood compared to GM) precludes a reliable measurement on a voxel level. Extreme caution was taken to avoid any GM contribution in the WM ROI: BOLD EPI images were co-registered to the MPRAGE scan; an MPRAGE-derived WM mask (thresholded at 90% WM probability) was obtained. Recognizing that the BOLD resolution (3.4x3.4x3.5 mm^3) is considerably lower than MPRAGE and that there could be slight misregistration between BOLD and MPRAGE, we further eroded the WM mask three-dimensionally by six times (peeling off a 1mm layer each time), resulting in a rather small but minimally contaminated WM ROI. BOLD time-courses of the voxels within the ROI were subsequently averaged. From the averaged BOLD time-course, two measures were obtained: the temporal shift and the response amplitude. Previous studies have established that the trace of end-tidal CO2 and GM BOLD signal have a time shift of ~15 sec (4), which is the total time it takes for the blood to travel from the lungs to the brain tissue and for the vessels in the tissue to react to the change in CO2-concentration. This delay time is expected to be greater for WM, and was determined by shifting the traces relative to each other until maximal Cross-Correlation (CC) was observed. Next, the response amplitude was calculated using a linear regression between the WM BOLD time-course and the shifted end-tidal CO2 trace. A GM ROI was also identified from a single slice above the lateral ventricles. The BOLD time-course was extracted and the measures of temporal shift and response amplitude were calculated using procedures similar to those for the WM. GM samples from other regions and slices were also investigated, but no dependency of the results on sampling position was found. From the ASL data, baseline CBF was obtained for both GM and WM ROIs.

RESULTS and DISCUSSION: Averaged traces of Etco2, GM and WM BOLD time-courses are shown in Fig. 1. A clear temporal delay in the WM time-course can be observed relative to the GM. Table 1 summarizes CVR results for both young and old subjects. It can be seen that the BOLD response in the WM occurs as late as 21 seconds after the GM response. This is surprising considering that the WM ROI is just a few centimeters deeper located than the GM. Of course, it is well known that blood arrives later in the WM than the GM due to the known layout of the vasculature. However, evidence from ASL and DSC-MRI literature suggests that this should only be 2-3 seconds at most (7). Therefore, we could only speculate that this large delay is primarily due to a delayed reaction time of the WM vasculature compared to the GM. Elderly individuals manifested a smaller GM/WM time delay (Table 1), but the delay was nonetheless on the order of 10 seconds. For CVR amplitude, GM CVR showed an age-related decrease, consistent with the expected age effect and previous reports (5). WM CVR, on the other hand, was higher in the older subjects. Baseline CBF manifested similar patterns (Table 2): GM CBF was significantly higher in younger participants, whereas there was a trend for a higher WM CBF in the older participants.

The present study provided an unprecedented examination of cerebrovascular reactivity in the WM and its dependence on age. Our data suggested that vascular physiology in the WM is drastically different from that in the GM. Specifically, blood flow and reactivity decrease with age in the GM (which is more in line with traditional thoughts), but the opposite pattern is seen in the WM. We hypothesize that this may be associated with the unique mechanical properties of the WM. WM in young subjects is tightly packed with axons and myelin, which makes it difficult for blood to penetrate and for vessels to dilate. In older individuals, as age-related demyelination and axon loss takes place, WM becomes less densely packed, thus exhibiting less hindrance for blood to flow through loose white matter fibers. We also observed a surprisingly large difference between the GM and WM response time, which we have no clear explanation for at this point.

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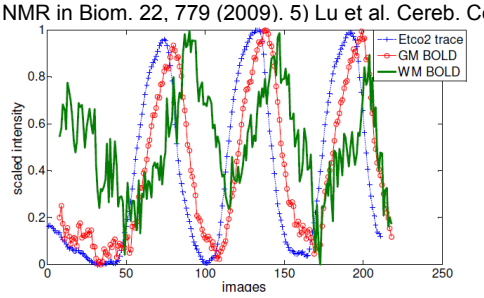

Fig. 1. Average time-course data for the young group

CVR	GM (% BOLD/mmHgCO2)	WM (% BOLD/mmHgCO2)	GM to WM delay (s)
young (N=15)	0.285 ± 0.051	0.046 ± 0.022	20.8 ± 9.25
old (N=15)	0.231 ± 0.045	0.061 ± 0.018	12.26 ± 4.89
p-value	0.005	0.048	0.003

Table 1. CVR results

CBF	GM (ml/100gm/min)	WM (ml/100gm/min)
young (N=15)	82.88 ± 11.57	20.36 ± 3.71
old (N=15)	69.29 ± 9.24	24.21 ± 7.10
p-value	0.001	0.072

Table 2. Baseline CBF results