Introduction and Purpose. In humans, white matter maturation continues until early adulthood and is thought to be important for the development of cognitive functions during childhood. One way to link white matter structure to neuronal function is to examine how white matter properties affect the timing and strength of the neural response during cognitive performance. For example, a recent study in healthy adults demonstrated that white matter integrity, as measured by Diffusion Tensor Imaging (DTI), contributed to inter-individual variability of the latency of neural activation in the primary visual cortex, as measured by Magnetoencephalography (MEG) [1]. Importantly, no one has yet investigated the relationship between the biophysical properties of white matter and the latency of neural activation in childhood, a time of ongoing brain development. We investigated age related changes in the latency of the P100m visual response in occipital cortex, as measured by MEG, and the biophysical properties of white matter, as measured with DTI, in eleven healthy children to determine the impact of white matter growth on the maturation of neuronal signaling.

Subjects and Methods. ***Subjects***. Eleven right-handed children were recruited for the study (6F/5M, mean age = 8.95 years +/- 2.15 SD). All participants were free from neurological or psychiatric symptoms. ***MEG recordings***. Neuromagnetic activity was recorded using a whole-head 151 channel CTF MEG system located in a magnetically shielded room. Prior to MEG data acquisition, each patient was fitted with three fiducial localization coils placed at the nasion and preauricular points in order to localize the position of the patient's head relative to the MEG sensors. Recordings were performed with participants lying supine on an adjustable bed with their eyes open and fixated on a cross shape projected, by LCD projector, onto a semi-transparent screen placed 50 cm from the subjects' eyes. MEG data were collected continuously at a sample rate of 625 samples /s and a bandpass of DC to 200 Hz. Upon completion of all MEG data collection, the MEG fiducial coils were replaced with MRI-visible fiducial markers. ***Visual Stimulation***. Participants were instructed to attend to the cross on the LCD screen and to abduct their right index finger as quickly as possible in response to a colour change (from a white "+" (2 cm x 2 cm) to green, 200 ms duration). Approximately 100 movements were recorded for each 400 second MEG recording. Head movement was monitored for each data recording. If the head motion tolerance was exceeded (0.5 cm, pre-post), the subject repeated the condition. ***P100m latency and localization.*** The continuously recorded MEG data were epoched into single trials of 1s duration (0.2s preceding and 0.8s following colour change onset). Responses were filtered from 1 and 55 Hz and averaged for each participant to create an averaged, evoked response for each individual. Latencies of the P100m response were determined by determining the peak response closest to 100ms following the colour change. Subsequent dipole source localization was performed using a single equivalent dipole best fit for each individual's P100m latency. ***MRI recordings.*** Whole-brain axial DTI images were acquired at 2.5 x 2.5 x 2.5 mm voxel resolution using a single-shot EPI sequence with 15 gradient directions, b=0 and 1000s/mm2, TE=82.4ms, TR=15s, and 2 repetitions with a GE LX 1.5T MRI Scanner. ***DTI Analyses.*** Fractional anisotropy (FA) maps were calculated using FSL [2]. Voxelwise statistical analysis of the relations between FA and P100m latency was carried out using TBSS (Tract-Based Spatial Statistics [3]). TBSS projects all subjects' FA data onto a mean FA tract skeleton, before applying cross-subject statistics. Data were processed for multiple comparisons using a family-wise model and results were thresholded to an alpha level of 0.05. Subsequently, the clusters of voxels where p100m latency was correlated with FA was delineated as a region of interest and applied to individual FA maps to extract mean FA for multiple regression analyses.

Figure 1 (subject example)

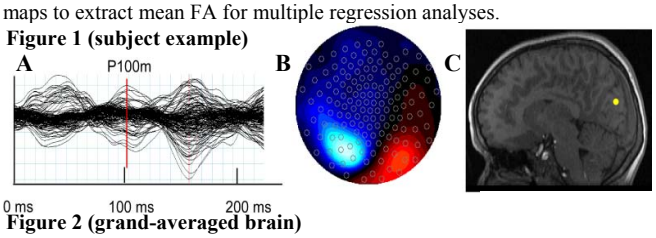
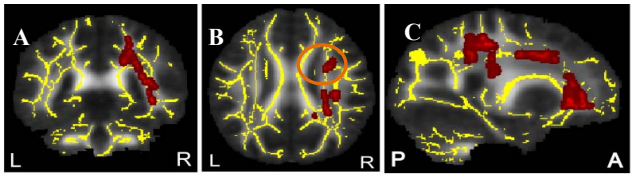


Figure 2 (grand-averaged brain)



Results. Latencies of the P100m (Fig.1A) were localized to the occipital region on a contour map (Fig. 1B). Subsequent dipole fits determined that, over all subjects, the P100m was localized to primary visual cortex (Fig. 1C). Using TBSS, we found a significant relationship between FA and P100m latency along an anterior-posterior dorsal pathway in the right hemisphere, consistent with the location of the extrastriate, dorsal processing stream (note that regions of significance have been inflated for the purposes of visualization) (Figures 2A-C). Figure 2B depicts a significant correlation between FA and latency in the right Frontal Eye Field (FEF) (orange circle). Correlation analyses were then conducted for age, P100m latency, and mean FA of the ROI created from the cluster of significant voxels produced by TBSS. The latency of the P100m was inversely related to FA across subjects ($r = -0945$, $p< 0.00012$) (Fig. 3). Moreover, FA values reliably increased with increases in age ($r = 0.549$, $p< 0.01$)(Fig. 4). After removing one outlier in the latency x age relation, regression analyses showed that age did not contribute any variance to the model predicting P100m latency when FA from the right dorsal stream and FEF regions were included ($F=-45.46$, $p<0.000$, FA beta=-7.23, $p<0.000$, age beta=0.247, $p=0.161$).

Figure 3. FA Value Predicts Latency

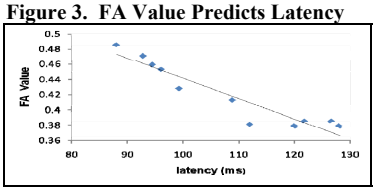
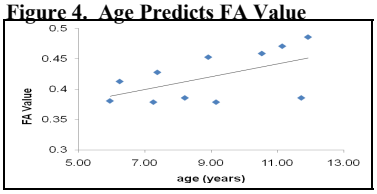


Figure 4. Age Predicts FA Value



Conclusions. In this study, we provide evidence that in children the speed of the P100m visual response was related to the diffusion properties of white matter. Specifically, significant white matter clusters where FA was related to P100m were found within the right dorsal processing stream and FEF region. It is generally purported that these regions both modulate early visual responses. The dorsal stream, in particular, is involved in spatial awareness and guidance of actions and therefore its activation corresponds well with our visuomotor reaction time task. Children with damage to this tract have shown deficits in visual attention and impaired visuomotor performance [4]. Further, our findings suggest that growth in the integrity of white matter found in visual-association regions predicts age related increases in speed of processing the primary visual cortex in children: with increasing age, greater FA predicted shorter latencies of the P100m originating in the primary visual cortex. This finding is significant as it suggests that development of neural signaling is supported by increased white matter organization with age. Our study is a novel investigation of spatio-temporal dynamics in the developing cortex and suggests that simple measures of evoked latency on a visuomotor-attention task may reflect dorsal stream integrity that is related to stage of cortical maturation in healthy children and may serve as an index of neural integrity in clinical populations with white matter injury.

Refs

[1] Stufflebeam, SM. et al. (2008) Neuroimage, 42(2): 710-6.
[2] Smith, SM. et al. (2004) Neuroimage, 23(S1): 208-19.
[3] Smith, SM. et al. (2006) Neuroimage, 31: 1487-1505.
[4] Dutton. GN & Jacobsen. LK (2001) Semin Neonatol 6(6): 477-85. Review.