BOLD Signal Fractal Dimension Mapping in AD Demonstrates Increase Microvascular Activity and Metabolism When Combined With Spectroscopy

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Introduction

MR imaging using T2* weighted blood oxygen level dependent (BOLD) signal can be used to noninvasively assess the tissue microvascular environment. The periodicity or temporal complexity can be quantified using a frequency based fractal dimension (FD) and thus allow insight into the underlying microvascular processes **[1]**. Alzheimer's Disease (AD) is associated with regional hypermicrovascularity, especially in the deep grey matter. This increase in vascular microstructure has been related to neurofibrillary tangles and amyloid plaques. Another reason for increased microvascularity is related to a compensatory hyperperfusion secondary to neurotransitter depletion. An increase in regional microvascularity is hypothesized to be associated with decreased BOLD FD **[2]**.

Creatine (Cr) in the brain plays a crucial role in energy metabolism. Although creatine has been presumed constant, recent studies suggest there may be subtle variations, where for example higher metabolism is associated with higher levels **[3]**. There has not been any comparisons of creatine levels and microvascularity as measured by BOLD FD mapping. Any correlation may allow us to detect subtle changes in energy metabolism in disease states, such as Alzheimer's disease. Here we compare BOLD FD and [Cr] in AD vs. normal age/gender matched controls (NC) in the basal ganglion.

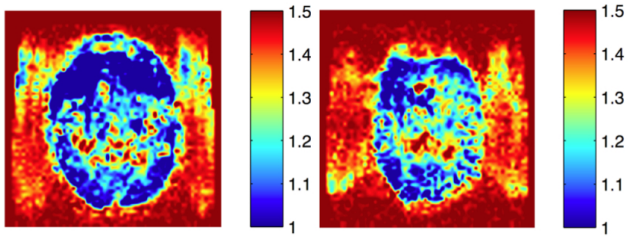

Fig 1. BOLD FD maps of representative AD subject (left) and NC (right). The AD subject showed lower FD (dark blue) around the deep grey matter as well as the frontal and occipital lobes. FD approach 1 indicates approaching periodicity.

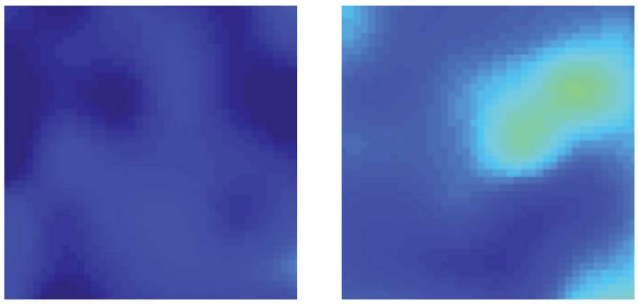

Fig 2. Comparison of BOLD FD over the putamen in images averaged for all subjects in AD (left) and NC (right) groups. The AD shows lower FD in this area.

Materials and Methods

14 subjects (7 AD and 7 NC) were scanned using a 3T GE Signa HD MRI system and 8 channel phased array head RF coil. Standard T1 and T2-weighted images were used to prescribe T2* (BOLD) weighted ($\alpha=70^o$, TE/TR = 35/250ms, FOV24cm, 64x64 matrix) image acquisition through large volume, basal ganglion slices. 2400 temporally contiguous BOLD images were acquired over 10 minutes at a sampling rate of 4Hz (1/250ms). BOLD data, spatially correlated with anatomical slices, was assessed for nonlinear microvascular characteristics using in-house programs written in Matlab (The Mathworks, Natick MA). This FD analysis used Fourier transformed 4D BOLD on a pixel-by-pixel basis. Spectroscopy data was obtained using a STEAM sequence (TE/TM/TR=72/6/3000ms, NEX=512, $8cm^3$) and analyzed using LCmodel.

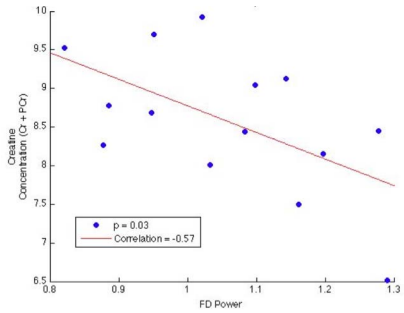

Fig 3. Plot of total Creatine (PCr+Cr) compared to BOLD FD values for 14 subjects (7 AD + 7 NC). (P<0.03 with r=-0.57)

Results and Discussion

BOLD FD maps through the basal ganglion are shown for a representative AD and NC (**Fig.1**). **Figure 2** shows a comparison of a voxel placed over the putamen based on the average for all subjects of each group. Qualitatively a difference between AD and NC is evident. The areas around the basal ganglion, frontal and occipital lobes show more complex FD (dark blue) in AD versus NC. Comparisons of all subjects showed an average lower FD for AD within the MRS voxel placed in the putamen (**Fig.2**). Lower FD values around the basal ganglion is consistent with increase microvasculature in these structures. Early AD is usually associated with microvascular pathology in the temporal and parietal lobes with relative sparing of the frontal and occipital lobes (as represented here).

A comparison of BOLD FD power maps to [Cr] from MRS showed a strong negative correlation (**Fig.3**). This correlation was also seen in the AD and NC groups individually. The mean [Cr] was not significantly different between the two groups. The strong negative correlation of [Cr] and FD suggests that an increase in microvasculature (low FD) is associated with an increase in metabolic activity (high Cr). Creatine acts as an energy shuttle with ATP. Areas of increased metabolism are often associated with increased vasculature secondary to the oxygen demand. An FD mapping approach may provide a measure of energy metabolism at the microstructure level distinct from perfusion. Small brain [Cr] changes are difficult to detect using spectroscopy. This was also true for our MRS comparison of AD to NC. However, [Cr] correlated strongly with FD and we noted a measurable difference in FD between the two groups. It is possible that FD may provide a more accurate measure of local metabolism than [Cr]. This may explain the relative sparing of the frontal and occipital lobes compared to the temporal and pariatal lobes in AD.

References: **[1]** Wardlaw G, Wong R, Noseworthy MD. (2008) Phys Med.24:87-91. **[2]** Moody DM, et al. (1997) Ann N Y Acad Sci. 826:103-116. **[3]** Slosman DO et al. (2001) Brain Res Brain Res Rev. 36:230-240.