Diffusion Weighted Functional MRI

Speaker: Allen W. Song, allen.song@duke.edu

Highlights

- Moderate diffusion weighting can modulate fMRI signal and help differentiate its vascular origin
- Heavy diffusion weighting may generate alternative and potential contrast arising from cellular origins
- Static diffusion weighting strategies can help improve fMRI signal localization closer to the neuronal source
- Dynamic diffusion weighting strategies can generate contrasts reflecting changes in cerebral blood flow and cerebral blood volume
- High resolution diffusion tensor tractography can connect activated brain regions and help confirm their neuronal relevance

Target Audience

Researchers and clinicians interested in the contrast mechanism of fMRI and its applications.

Outcome/Objectives

The objectives of this lecture are to discuss the various important roles diffusion weighting strategies play in functional MRI (fMRI). Specifically, the incorporation of diffusion weighting into fMRI acquisition can help characterize the origin of the fMRI signal, improve the spatial localization to small vessel networks that are close to the neuronal source, and improve the quantitative accuracy of the underlying brain physiology. In addition, diffusion tensor imaging (DTI) and fMRI activation-guided diffusion tensor tractography can link activated areas and construct active brain networks. By understanding these important roles, learners will be able to adopt diffusion weighting strategies to improve their fMRI acquisition.

Purpose

Because of its hemodynamic origin, fMRI signal is secondary to neuronal activation. The complexity in brain vasculature often makes it difficult to achieve accurate localization and quantify the underlying brain physiology. To address these limitations, various diffusion weighting strategies have been incorporated into fMRI acquisitions.

Methods

Diffusion weighting is a family of MRI techniques that generates imaging contrasts based on the diffusion characteristics of water molecules. Its basic principles, from the original use of bi-polar gradients in an isotropic medium to more advanced techniques such as DTI, have been well described in the literature (Stejskal & Tanner, 1965; Mosley 1990; Le Bihan, 1986; Basser et al., 1994) and are therefore not included in this syllabus. Rather, here we focus on specific applications of diffusion weighting in fMRI.

Based on the degrees of diffusion weighting, its primary effect can be on different proton pools, for example, those in the vasculature, cerebral spinal fluid, or intracellular space. As it pertains to fMRI, our attention will be focused on the effects of diffusion weighting in cerebral vasculature and intracellular space in activated brain areas, as well as connectivities among these activated regions in a network perspective.

Vascular Regime

Given that the predominant blood oxygenation level dependent (BOLD) contrast (Ogawa et al., 1993) in fMRI is based on the hemodynamic mechanism and arises from the cerebral vasculature with mobile proton pools, diffusion weighting would naturally play a critical role in modulating the BOLD signal.

In general, when a moderate amount of diffusion weighting (typically with a *b* factor under 200 s/mm^2, $b = \int_0^T (\gamma \cdot G(t) \cdot t)^2 \, dt$, where $G(t)$ is the time-varying diffusion weighting gradient, T the duration of diffusion weighting) is used, only proton pools in the vascular space are significantly attenuated due to their relatively high mobility. Such a selective attenuation would allow us, at least in principle, to probe the various vascular proton pools (e.g. venous, capillary). For example, a simple application would be the removal of large vein signal that is distant from neuronal sources. Going further, however, one needs to consider the anisotropic effect of diffusion weighting on smaller vessels, as diffusion weighting gradients are directional. To ensure equal effects along all directions, specialized diffusion weighting gradients have been developed (Wong et al., 1995). Further still, most of the diffusion weighting schemes have inherent flow moments, oftentimes manipulations to alter or even null the flow moment can be advantageous in applications where flow velocity dependence is undesired (e.g. where only cerebral blood volume contrast is of interest).

Assuming a simple case of isotropic weighting, the signal attenuation factor can be estimated using the intra-voxel incoherent motion (IVIM) model (Le Bihan et al. 1996; Song et al, 2002), and can be estimated as $F = \left| \; f \cdot J_o(cv) + (1-f) \cdot e^{-bD_{brain}} \; \right|$, [1], where f is the volume fraction of the vasculature, c the flow moment coefficient of the gradient waveform used for the IVIM weighting, v the blood velocity to the first order, J_o the Bessel function, b the inherent diffusion weighting factor, and D_{brain} the diffusion coefficient of the brain tissue. This equation was derived from a simplified two-compartment model (vasculature and parenchyma) for the human brain. Nevertheless, it can easily be seen that the functional signal using this method is dependent upon both blood velocity and volume changes. Consequently, the observed changes in the overall apparent diffusion coefficient (ADC) D, by fitting $F = e^{-bD}$ in a dynamic manner, are believed to reflect cerebral blood flow (CBF).

As mentioned earlier, flow moment manipulation strategies can be adopted to remove the velocity dependence. As a specific example with the flow moment nulled (c = 0), the signal attenuation factor F can be approximated as $F = \left| \; f \cdot e^{-bD_{static\_blood}} + (1-f) \cdot e^{-bD_{brain}} \; \right|$, [2], where D_{static_blood} is the ADC of static blood, and D_{brain} the ADC of brain tissue. As a result, this nulling strategy would generate signal changes mostly dependent upon changes in the blood volume fraction, f (Song et al., 2003a). For very small b factors ($bD << 1$), which is true for diffusion weighting in the vascular regime, we can further derive that $\Delta D \propto \Delta f$, that is, the observed changes in the overall ADC is proportional to the changes in cerebral blood volume (CBV).

Cellular Regime

In addition to modulating the BOLD signal, diffusion weighting also has the potential to generate new contrasts that are more closely tied to neuronal sources. For example, when a large *b* factor (*b* of 1500 s/mm^2 or larger) is used, most of the fluid and vascular signal would already have been removed, leaving the remaining signal largely sensitive to diffusion changes in the intracellular space where diffusion is more restricted. Indeed, it has long been known that diffusion weighting can generate contrast reflecting cell swelling. For example, it was found that water diffusion was decreased in infarcted areas immediately after acute ischemic stroke, when the brain cells (e.g. astrocytes) swell through cytotoxic edema.

More recently, and more relevant to fMRI, Le Bihan et al. have shown that water diffusion is modulated by brain activity (Le Bihan *et al*, 2006), based on the convergent evidence that brain cells can swell during activation. If proven true, such an application of diffusion weighting can open a new avenue to investigate brain activation in a more direct and precise manner, both spatially and temporally.

Network Perspective

Although the incorporation of diffusion weighting strategies has provided evidence for improved spatial localizations for fMRI, it has remained difficult to truly validate the neuronal relevance of the activated brain regions, largely because of the lack of a gold standard for noninvasive neuronal localization. Encouragingly, advances in DTI and tractography (Basser et al., 1994; Mori et al., 1999) have opened yet another avenue for diffusion MRI to contribute. Specifically, DTI tractography can link areas of neuronal relevance through noninvasive nerve fiber tracking algorithms, based on the general knowledge that functionally connected neuronal populations are connected by neural pathways. Reduced or lack of neuronal connectivities in some regions may suggest that they are distant from the neuronal source. For example, activation arising from large draining veins will likely lead to few or no neuronal fiber pathways to other activated regions.

Moving forward, it is expected that parallel uses of fMRI and DTI tractography will allow us to image and track the neural pathways among activated regions, construct active brain networks, and ultimately bridge the gap between neuroimaging and neuroanatomy.

Results and Discussions

Vascular Regime

As it is generally known, the spatial specificity of BOLD contrast is compromised by the diversity of the participating vasculature, including large draining veins. A direct and perhaps simplest application of diffusion weighting is the removal of large vein signals (Song et al., 1996). Shown in Fig. 1 is an example of various mobile proton pools within the BOLD activated area. It is evident that highly mobile proton pools (with ADC much larger than that of water at 2.2 x 10^{-3} mm^2/s) are contributing to the BOLD signal at the pial surface, likely arising from the large veins.

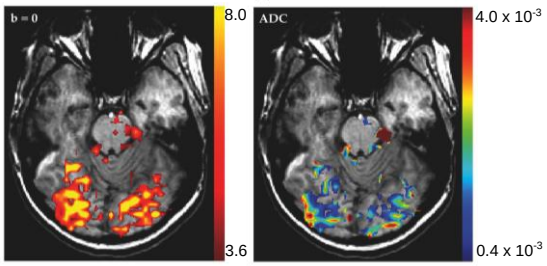

Fig. 1 BOLD activation map (left) and the corresponding ADC values (left) within the activated region, illustrating venous signal near surface brain areas.

Shown in Fig. 2 are BOLD activations compared with ADC activations, derived from a high-resolution diffusion weighted acquisition in the vascular regime (Truong et al., 2009). The corresponding cortical depth dependence of the ADC and BOLD activations are also illustrated. Note that the ADC activation is more restricted in the gray matter, while the BOLD activation is more concentrated in the pial surface. More importantly, the average functional ADC changes increase by a factor of 5.1 from the cortical surface to its peak value at a cortical depth of about 1 mm, whereas the average BOLD signal change is the highest at the pial surface. Both of these observations confirm the improved spatial localization of the

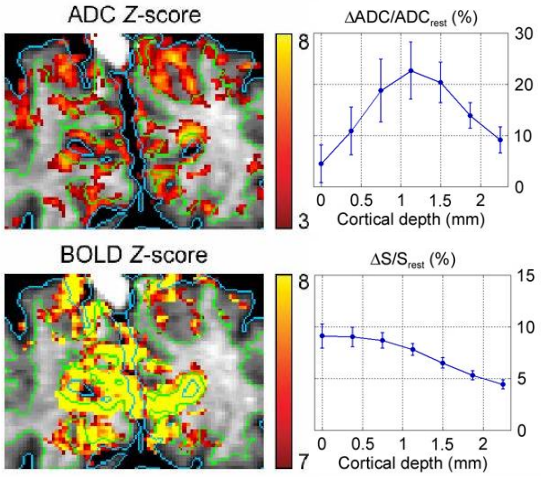

Fig. 2 ADC activation map and cortical depth dependence (top) and BOLD activation map and cortical depth dependence (bottom).

functional diffusion contrast in the small vessels, which is consistent with findings in animal models in that activations in mid-cortical layers are true to the neuronal origins using functional CBV contrast (Zhao et al., 2006).

Cellular Regime

Fig. 3 illustrates the impact of heavy diffusion weighting on fMRI signal. When a large *b* factor at 1600 s/mm^2 is applied, most vascular signals are removed resulting in little BOLD contrast, at which point the negative ADC changes are revealed (as opposed the positive ADC changes in the vascular regime). These negative activations are thought to be the result of reduced diffusion during brain cell swelling. Interestingly, the diffusion signal response is characterized by a sharp rise and early onset, generally on the order of 2-3 seconds faster than the BOLD signal. This observation is consistent with other reports (Darquie et al., 2001; Le Bihan et al., 2006; Aso *et al*, 2009; Aso et al., 2013; Tsurugizawa et al., 2013).

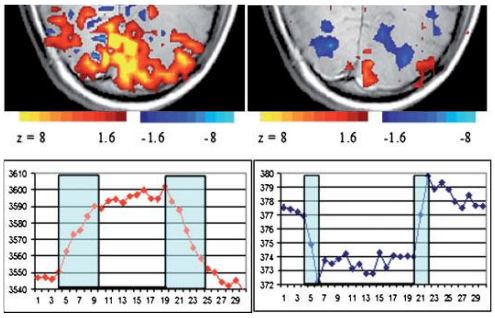

Fig. 3 BOLD activation map (top left) and ADC activation map (top right) under heavy diffusion weighting (b = 1600 s/mm^2). The negative activation (reduction of ADC) with diffusion weighting exhibits a faster onset (bottom right) than the positive BOLD activation (bottom left).

If proven consistent, this diffusion contrast would allow direct investigations of functional neuronal responses at a cellular level, and provide a new neuroimaging method to study brain activation at its neuronal source.

Network Perspective

The prospect of applying non-invasive neural fiber pathway tracking among activated brain regions is exciting in that it could provide an alternative approach to confirm the neuronal relevance of these activated regions (Song et al., 2003b; Kim et al., 2006). Using these regions as seed points, researchers can carry out DTI tractography, for example, in the occipitotemporal area during visual stimulation, as illustrated in Fig. 4. While connected fiber pathways are visible among V1, V2 and PPA, it can also be seen that these fiber pathways (in orange) do not fully cover and connect the entire volumes of these ROIs. This can be due to the vascular nature of some parts of these activated regions, or potentially due to the lack of sufficient characterization at the boundaries of gray/white matters at the current spatial resolution. Nevertheless, the joint use of DTI and fMRI provides a new means to construct active brain networks, which are key to understanding human brain functions.

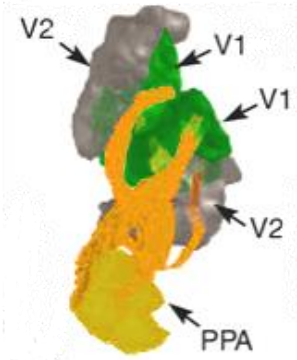

Fig. 4 Connecting fiber pathways (in orange) in the occipitotemporal regions. V1: primary visual area; V2: secondary visual area; PPA: parahippocampal place area. After Kim et al., 2006.

Conclusion

In this lecture, we learned that diffusion weighting strategies already play several important roles in fMRI practice today. In particular, diffusion weighting can improve the BOLD localization in small vessel networks that are close to the neuronal source and generate dynamic contrasts reflecting CBF and CBV changes during brain activation. In addition, DTI and tractography can help connect activated brain regions via fiber pathways and provide convergent evidence on the neuronal relevance of these activated areas. With both research fields in diffusion and functional MRI constantly evolving (for example, ultrahigh resolution diffusion MRI techniques are now able to generate unprecedented and exquisite details in both gray and white matters), it is expected that diffusion weighting techniques will continue to complement fMRI investigations and improve our understanding of the functional brain.

References

Aso T, Urayama S, Poupon C, Sawamoto N, Fukuyama H, Le Bihan D. An intrinsic diffusion response function for analyzing diffusion functional MRI time series, NeuroImage 47:1487–1495, 2009.

Aso, T, Urayama, S, Fukuyama, H, Le Bihan, D, Comparison of diffusion-weighted fMRI and BOLD fMRI response in a verbal working memory task, NeuroImage 67:25-32, 2013.

Basser, PJ, Mattiello, J, LeBihan, D, Estimation of the effective selfdiffusion tensor from the NMR spin echo. J. Magn. Reson. 103:247–254, 1994.

Darquie, A, Poline, JB, Poupon, C, Saint-Jalmes, H, Le Bihan, D, Transient decrease in water diffusion observed in human occipital cortex during visual stimulation, Proc Natl Acad Sci U S A 98(16):9391-9395, 2001.

Kim, M, Ducros, M, Carlson, T, Ronen, I, He, S, Ugurbil, K, and Kim, DS, Anatomical correlates of the functional organization in the human occipitotemporal cortex, Magn. Reson. Imag. 24: 583-590, 2006.

Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 161(2):401-7, 1986.

Le Bihan D, Urayama SI, Aso T, Hanakawa T, Fukuyama H. Direct and fast detection of neuronal activation in the human brain with diffusion MRI. Proc Natl Acad Sci U S A 103:8263–8268, 2006.

Mori, S, Crain, BJ, Chacko, VP, van Zijl, PC, Three dimensional tracking of axonal projections in the brain by magnetic resonance imaging, Ann Neurol. 45(2):265-9, 1999.

Moseley, ME, Cohen, Y, Kucharczyk, J, Mintorovitch, J, Asgari, HS, Wendland, MF, Tsuruda, J, Norman, D, Diffusion-weighted MR imaging of anisotropic water diffusion in cat central-nervous-system. Radiology 176, 439–445, 1990.

Ogawa, S, Menon, R. S., Tank, D. W., Kim, S.-G., Merkle, H., Ellerman, J. M., and Ugurbil, K., Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging, Biophys. J. 64, 803-812, 1993.

Song, A. W., Wong, E. C., Tan, S. G., and Hyde, J. S., Diffusion weighted fMRI at 1.5 T, Magn. Reson. Med. 35, 155-158, 1996.

Song AW, Woldorff, MG, Gangstead, S, Mangun, GR, McCarthy, G, Enhanced spatial localization of neuronal activation using simultaneous apparent-diffusion-coefficient and blood-oxygenation functional magnetic resonance imaging. NeuroImage 17(2):742-50, 2002.

Song AW, Li T. Improved spatial localization based on flow-moment-nulled and intra-voxel incoherent motion-weighted fMRI, NMR Biomed. 16(3):137-43, 2003a.

Song AW, Harshbarger T, Li T, Kim KH, Ugurbil K, Mori S, Kim DS. Functional activation using apparent diffusion coefficient-dependent contrast allows better spatial localization to the neuronal activity: evidence using diffusion tensor imaging and fiber tracking. NeuroImage 20(2):955-61, 2003b.

Stejskal, EO, Tanner, JE, Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient, J. Chem. Phys. 42(1): 288-293, 1965.

Truong TK, Song AW. Cortical depth dependence and implications on the neuronal specificity of the functional apparent diffusion coefficient contrast, NeuroImage. 47(1):65-8, 2009.

Tsurugizawa T, Ciobanu L, Le Bihan D. Water diffusion in brain cortex closely tracks underlying neuronal activity. Proc Natl Acad Sci U S A. 110:11636–11641, 2013.

Wong, EC, Cox, RW, Song, AW, Optimized isotropic diffusion weighting, Magn. Reson. Med. 34(2):139-143, 1995.

Zhao, F, Wang, P, Hendrich, K, Ugurbil, K, Kim, SG, Cortical layer-dependent BOLD and CBV responses measured by spin-echo and gradient-echo fMRI: insights into hemodynamic regulation, NeuroImage 30(4): 1149-60, 2006.