Functional magnetic resonance imaging of the mouse

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With the advances of genetic manipulations and transgenic models of human diseases, mouse has become one of the most important lab animals for basic science research and drug development. Currently, there are two major ways to detect neural activation in mouse by MRI. One approach relies on hemodynamic responses that coupled with neural activity (for review, see 1) and the other utilizes a Ca^{2+} analog – Mn^{2+} – to detect activity (for review, see 2).

The underlying mechanism for the hemodynamic-based methods is that when neurons are activated, the metabolic rate of oxygen and glucose increase. This will induce large increase in the cerebral blood flow (CBF) and cerebral blood volume (CBV), which will over-compensate the consumed oxygen and hence increase the blood oxygenation in the downstream venous vessel. Since the oxy-hemoglobin is diamagnetic while deoxy-hemoglobin is paramagnetic, the blood oxygenation change will cause a T_2 or T_2* change which can be detected by T_2-weighted or T_2*-weighted MRI. This blood oxygenation level dependent (BOLD) functional MRI (3-5) has been applied to study the visual (6) and somatosensory (7, 8) responses in the cortex, as well as odor activation in the olfactory bulb (9) and hippocampus (10) in mice. The functional roles of nicotine receptor (11) and dopamine-D2-receptor (12) were studied in knock-out mice.

Although BOLD contrast doesn't need exogenous contrast agent, the signal change is very low. For example, the BOLD signal change in somatosensory cortex under electrical hind-paw stimulation in mouse is about 7% at 11.7T (7). Besides, the spatial localization is limited by the large vein artifact. Therefore, CBV-based method using exogenous contrast agent such as iron oxide nanoparticle provides a good alternative with higher signal change and better localization especially at a lower field such as 4.7T (13).

Besides the hemodynamic-based methods, the other method uses Mn^{2+} as an exogenous T_1 contrast agent to detect the accumulation of Mn^{2+} into activated neurons via voltage-gated calcium channels (14, 15). Compared to hemodynamic-based methods, this so-called activity induced manganese (AIM) method has advantages such as the detected area is more localized to the activated neurons and doesn't affected by alteration of neuro-vascular coupling in diseased conditions. Furthermore, Mn^{2+} has high relaxivity and could stay in neurons for a while to allow high-resolution images to be taken. However, this property also prohibits repeating experiments in the same animal in the same imaging session. Especially, this AIM method requires disruption of the blood-brain barrier (BBB) to allow fast access of Mn^{2+} in

the brain. To overcome this limitation, three techniques have been proposed. One approach utilizes the fact that certain regions in the brain, such as nuclei in the hypothalamus, don't have BBB and can take up Mn^{2+} easily. This allows detection of differential uptake of Mn^{2+} in appetite regulating nuclei under fasting and stimulation by gut-peptide (16, 17).

Since Mn^{2+} can slowly distribute in the brain through ventricular-blood junction (18), another way to map activation is by injecting Mn^{2+} intraperitoneally and stimulate continuously for a long period of time to enhance Mn^{2+} uptake and transport into activated neural areas. This was demonstrated in mapping tonotopic organization in the inferior colliculus (19) and detection of auditory pathway (20) in mice. The major advantage of this approach is that stimulation can be applied in awake, normal behaving animals outside the magnet and hence allows more flexible task designs. However, excess Mn^{2+} has neurotoxicity and hence systemic administration of large dose may damage cells and alter behavior.

Another interesting property of Mn^{2+} is that once it gets in neurons, it can be transported anterogradely along axons and can cross synapses (21-23). Mn^{2+} transport across a synapse relies on presynaptic release and postsynaptic uptake, therefore, the amount of Mn^{2+} transported may change depending on stimulations. Based on this property, the third technique detects Mn^{2+} movement through a neural system after an activity-based representation is initiated, and hence maps the strongest functional connections through that system. It was demonstrated that Mn^{2+} can be transported from the nose of a mouse to the olfactory bulb and the tracing could be modulated by odorants (24). A recent study further showed that the stimulus-elicit tracing allows generating odorant-specific mapping in the glomerular and mitral cell layers in the olfactory bulb at glomerular resolution (25). This would provide unique information about neural circuits.

In practice, imaging the brain function of the mouse is challenging because the size of the brain is only about 1/1000 of the human brain. That means the voxel size of the image also needs to be reduced by a similar factor to resolve enough details. Since signal-to-noise ratio is proportional to voxel size, high magnetic field and dedicated receiver coils are needed to compensate the reduced voxel volume. Conventional gradient echo or fast spin echo sequences are usually used to achieve high resolution and good image quality of the mouse brain. High performance shim system is also desirable to optimize magnetic field homogeneity in such small volume especially when echo planar imaging is used. Besides, maintaining physiological conditions of anesthetized mouse in MRI for hemodynamic-based functional imaging is more difficult than in the rat. Therefore, anesthetics other than α-chloralos are usually considered and noninvasive monitoring of blood gas may be needed to avoid large change of blood volume due to blood withdraw.

1. Logothetis, N. K. & Wandell, B. A. (2004) *Annu Rev Physiol* **66,** 735-69.
2. Koretsky, A. P. & Silva, A. C. (2004) *NMR Biomed* **17,** 527-531.

3. Ogawa, S., Lee, T. M., Kay, A. R. & Tank, D. W. (1990) *Proc Natl Acad Sci U S A* **87,** 9868-72.
4. Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., Turner, R. & et al. (1992) *Proc Natl Acad Sci U S A* **89,** 5675-9.
5. Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H. & Ugurbil, K. (1992) *Proc Natl Acad Sci U S A* **89,** 5951-5.
6. Huang, W., Plyka, I., Li, H., Eisenstein, E. M., Volkow, N. D. & Springer, C. S., Jr. (1996) *Proc Natl Acad Sci U S A* **93,** 6037-42.
7. Ahrens, E. T. & Dubowitz, D. J. (2001) *NMR Biomed* **14,** 318-24.
8. Nair, G. & Duong, T. Q. (2004) *Magn Reson Med* **52,** 430-4.
9. Xu, F., Liu, N., Kida, I., Rothman, D. L., Hyder, F. & Shepherd, G. M. (2003) *Proc Natl Acad Sci U S A* **100,** 11029-34.
10. Kent, K., Hess, K., Tonegawa, S. & Small, S. A. (2007) *Hippocampus* **17,** 1003-11.
11. Suarez, S. V., Amadon, A., Giacomini, E., Wiklund, A., Changeux, J. P., Le Bihan, D. & Granon, S. (2008) *Psychopharmacology (Berl).*
12. Kuriwaki, J., Nishijo, H., Kondoh, T., Uwano, T., Torii, K., Katsuki, M. & Ono, T. (2004) *Neurosignals* **13,** 227-40.
13. Mueggler, T., Baumann, D., Rausch, M. & Rudin, M. (2001) *Magn Reson Med* **46,** 292-8.
14. Lin, Y. J. & Koretsky, A. P. (1997) *Magn Reson Med* **38,** 378-88.
15. Aoki, I., Tanaka, C., Takegami, T., Ebisu, T., Umeda, M., Fukunaga, M., Fukuda, K., Silva, A. C., Koretsky, A. P. & Naruse, S. (2002) *Magn Reson Med* **48,** 927-33.
16. Kuo, Y. T., Parkinson, J. R., Chaudhri, O. B., Herlihy, A. H., So, P. W., Dhillo, W. S., Small, C. J., Bloom, S. R. & Bell, J. D. (2007) *J Neurosci* **27,** 12341-8.
17. Kuo, Y. T., Herlihy, A. H., So, P. W. & Bell, J. D. (2006) *NMR Biomed* **19,** 1028-34.
18. Lee, J. H., Silva, A. C., Merkle, H. & Koretsky, A. P. (2005) *Magn Reson Med* **53,** 640-8.
19. Yu, X., Wadghiri, Y. Z., Sanes, D. H. & Turnbull, D. H. (2005) *Nat Neurosci* **8,** 961-8.
20. Watanabe, T., Frahm, J. & Michaelis, T. (2008) *Magn Reson Med* **60,** 210-2.
21. Sloot, W. N. & Gramsbergen, J. B. (1994) *Brain Res* **657,** 124-32.
22. Tjalve, H., Mejare, C. & Borg-Neczak, K. (1995) *Pharmacol Toxicol* **77,** 23-31.
23. Pautler, R. G., Silva, A. C. & Koretsky, A. P. (1998) *Magn Reson Med* **40,** 740-8.
24. Pautler, R. G. & Koretsky, A. P. (2002) *Neuroimage* **16,** 441-8.
25. Chuang, K. H., Lee, J. H., Silva, A. C., Belluscio, L. & Koretsky, A. P. (2009) *Neuroimage* **44,** 363-72.