

Functional MRI in Animal Models

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Objectives: To understand the role of animal models in determining the basis of the functional MRI signal; to identify good practices in fMRI of animals; to explore fMRI as a tool for basic science; to examine fMRI applications to clinical problems in animal models and drug development.

Overview: Why do fMRI in animal models? One reason is to learn something about the fMRI signal in humans. Animal models, particularly the rodent and the nonhuman primate, have played a key role in understanding the neural basis of the fMRI signal. The availability of invasive recording measurements combined with MR imaging made it possible to determine that the BOLD signal is closely linked to local field potentials. Further studies have examined the limits of spatial and temporal resolution in fMRI studies, using well-defined cortical areas (whisker barrels, somatotopic maps) and precise stimulation. These studies have played a key role in the interpretation of the fMRI signal widely observed in humans, and will doubtless provide further insight into still-controversial issues such as the negative BOLD signal and the BOLD response to inhibition. A second reason to use fMRI in animal models is that it makes an excellent tool for studying alterations in brain function. fMRI has been used to assess changes in animal models of clinical conditions and to examine the effects of various drugs. We will discuss several examples of these applications.

Methods: Both stimulus-based fMRI and non-stimulus resting state functional connectivity have been mapped in animals. In addition to the standard acquisition and postprocessing methods required for human fMRI studies, several other issues must be considered for animal work. Restraint is stressful for animals but must be employed to prevent image degradation. Typically this is resolved by anesthetizing the animals, but some groups have successfully obtained fMRI from awake animals. In either case, the physiological condition of the animals must be monitored and reported, as deviations from the normal range can alter or eliminate the response to stimulation. For some anesthetics, animals must be intubated, which requires especially careful monitoring and correction of arterial blood gas levels. Care must be taken to maintain body temperature, particularly over long experiments. The use of anesthesia also limits fMRI to studies of response to sensory stimulation rather than cognitive paradigms, and the stimulus must be carefully chosen to elicit the optimal response. For example, the optimal forepaw stimulation frequency for rats under isoflurane is much higher than the optimal frequency under α -chloralose.

Strengths of animal studies: Animal studies provide a level of information and control not available in human subjects. Imaging data can be supplemented with invasive recording or histology; genetic manipulation can provide insight into alterations; disorders such as stroke can be modeled and examined. The use of anesthetized animals allows long studies (~6 hours) that are not tolerated by human subjects. Animal studies also allow the use of exogenous contrast agents not approved for use in human functional studies. Iron oxide particles given IV allow changes in blood volume rather than blood oxygenation to be examined, and manganese can provide functional maps based on neural activity rather than hemodynamics.

Limitations of animal studies: Most anesthetics have effects on the vasculature in addition to their effects on neural activity, which complicates the interpretation of the results. Unanesthetized animals usually exhibit some level of stress in the scanner, and a rise in blood pressure in response to a stimulus

can make it appear that the entire brain activates. The use of anesthesia can also interfere with administered drugs. Animals also have smaller brains requiring higher resolution, which is approximately compensated by the use of high field, small bore scanners. As with all animal studies, the question of correspondence with human work arises, particularly in disease models.

Examples: We will briefly touch on several papers that link neural activity to the BOLD response in rodents and primates, exhibit the spatial and temporal resolution of the BOLD response, use clever paradigms to probe the timing of circuit activity, look at alterations induced by surgical manipulations, and demonstrate the use of fMRI in identifying the actions of drugs.

Suggested background reading on functional imaging techniques in animals:

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