Image Acquisition and Processing Techniques in Neuroscience

F. Kruggel

Max-Planck-Institute of Cognitive Neuroscience
Stephanstraße 1, D-04103 Leipzig, Germany
email: kruggel@cns.mpg.de

Jagath C. Rajapakse

School of Computer Engineering
Nanyang Technological University
Singapore 639798 email: asjagath@ntu.edu.sg

Abstract

Imaging techniques are now commonplace in clinical and experimental neuroscience. Briefly reviewing the achievements of recent years, an increase in spatial resolution is identified as the major goal for the years ahead. At a resolution of 0.25 mm, the mesoscopic organization level of the brain becomes accessible for examination. Advances in examination techniques must be accompanied by the development of diligent signal and image analysis procedure in order to lift the treasures hidden in the recorded data.

1 Introduction

The purpose of this article is to briefly summarize recent advances in neuroimaging and their corresponding data analysis techniques. Last 25 years introduced a series of technical developments into the field of neuroscience. New non-invasive imaging techniques revolutionized the diagnostic and therapeutic procedures in the clinic and exposed new experimental perspectives of understanding brain function in-vivo.

It is almost impossible to give a comprehensive overview onto the broad range of methods to assess brain function in-vivo. In this short overview, we will focus on magnetic resonance (MR) imaging techniques and on methods used to analyze structure-function relationships in the brain. Emphasis will be on data processing techniques. Such methods are necessary whenever quantitative results are sought for ("getting numbers from images") or when results of different techniques (or different time points) need to be compared.

We will also attempt to estimate which developments might lead to "quantum leaps" in diagnostic procedures in the near future comparable to the introduction of cranial computer tomography (CCT) 25 years ago and functional imaging using magnetic resonance imaging (fMRI) 8 years ago. It is well understood that the view expressed here is limited - not only by space but also by personal experience.

2 Anatomical Imaging

MR brain imaging became widely available during the last 15 years. With the advent of the recent generation of MR scanners, economical (e.g., price per scan) or procedural (e.g., time per scan) advantages of CCT scanning became negligible. However, CCT is still superior whenever a precise delineation of boneous structures (i.e., for surgical planning) is required.

Today, it is possible to achieve a macroscopic description of the brain in different weightings or with respect to different MR properties of tissues (e.g., T_1, T_2, and proton density (PD)) at a spatial resolution of 1 mm in a single session of about 20 min. Curiously, these possibilities are largely untapped in a clinical setting since most diagnoses are still drawn by examining a sparse set of slices reproduced on film. Neuroradiologists have not yet adopted to work with consoles which allow browsing through volume datasets in orthographical slices or 3D projections or even analyzing images quantitatively.

In spite of the advances in image acquisition, analysis procedures matured only slowly and so far rarely found applications in clinical routine. Reasons for this fact are their computational complexity (i.e., a long computation time), a certain lack of robustness (i.e., stability against pathological findings) and insufficient experience in handling the often complex processing chains. Sometimes analytical procedures often have to be refined with the experience gained by various applications. However, whenever such procedures are sufficiently stable and mature, they quickly gain clinical acceptance.

Another area that made notable advances is recent years is image visualization. Rendering algorithms are now available on specialized hardware chips allowing to generate 2D projections of surfaces or volume datasets at speeds which are close to real time. This technique enables neurosurgeons to perform pre-surgical planning which is expected

to improve the outcome of interventions. Virtual surgery is another aspects that should be looked into with increased speed of visualization an processing [1].

Multimodality imaging techniques are useful because they combine advantages of many modalities to improve the image analysis and visualization. Registration procedures of multimodality images are necessary to map time series examinations of the same patient (or results of different imaging modalities) into the same coordinate space. These procedures are marked by their iterative nature and high computational time, which can also be improved by dedicated hardware.

The "holy grail" of neuroimage analysis is the invention of an electronic brain atlas. Eight years ago, the "Human Brain Project" was launched in the USA [2] with an aim to construct a probabilistic atlas to supercede the still widely adopted Talairach system [3]. In spite of some impressive results [4, 5], a coherent system has not been made available yet to the neuroscience community. Given the high individual variability of the human brain, it is evident that an atlas system must rather be symbolic (i.e., contain descriptions of object shapes and positions) than iconic (i.e., contain pictorial representations of objects). Only a symbolic approach offers sufficient stability and robustness against typical brain pathologies and retains the high spatial resolution offered by the imaging techniques available today [6].

Two recent developments in MR imaging offer exciting perspectives for an advanced analysis of the human brain. *Diffusion tensor imaging* (DTI) [7] allows mapping of the principal directions of water diffusion in the brain, which is facilitated along the direction of the white matter fiber bundles. On the basis of DT images, a delineation of not only the big cross-hemispheric tracts but also the much smaller cortico-cortical connections [8] is possible. Thus, an in-vivo analysis of the individual connectivity in the brain is within reach.

A second development is a consequence of increasingly higher spatial resolution at a reasonable signal-to-noise ratio. It is well known that neocortical fields are bounded by different cytoarchitectotic patterns [9], and a higher fiber content of a layer is reflected in a higher optical density [10]. At a resolution of 0.25mm (corresponding to a matrix of 1024^2 pixels) it is not unreasonable to assume that the layered structure is detectable by MR imaging as well. Connected with suitable image analysis procedures, a parcellation of the individual neocortical surface into (functionally related) areas appears feasible. Combining both techniques, it may be possible to achieve an in-vivo description of individual neocortical fields and their short- and long-range interconnections. Imagine the consequences for understanding brain functioning!

3 Functional Imaging

Besides the anatomical imaging, the imaging modalities such as PET (positron emission tomography), SPECT (single positron emission tomography) and fMRI (functional MRI) provides techniques to view the working or functional brain in-vivo. The recent discovery of functional MR imaging using the blood-oxygen-level-dependent (BOLD) effect in 1992 [11] marked another breakthrough for neuroscience. Because fMRI is non-invasive and easily implemented on recent scanners, this technique quickly became a major tool in cognitive neuroscience and is now performed at hundreds of research sites throughout the world.

The most common protocol to measure the BOLD effect is echo-planar imaging (EPI), which allows per-second imaging rates of typically 12 slices at a resolution of 64^2 voxels, i.e., a temporal resolution of less than 100 ms at a spatial resolution of less than 4 mm.

It is now commonly accepted that the origin of the BOLD effect is a transient hypooxygenation in the venules related to a cortical activation site [12]. The temporal dynamics of the so-called hemodynamic response (HR) is approximately described by the "balloon model" [13]. This HR is typically lagged by 4-5 s and dispersed by 4 s with respect to the stimulation onset raising the question whether any correlate of the underlying neuronal activation may be read from this response. Recent advances in modeling of the signal time course have clearly demonstrated that statistically significant relations between stimulation context and parameters of the signal shape (gain, lag and dispersion) are detectable [14]. Behavioral reaction times and responses may be linked to the hemodynamic parameters gain and lag, thus allowing inferences about "a longer computation time" and/or "a more profound activation" of a certain brain region given a specific experimental task. In parametrically varied designs at an image repetition time of 1 s, a temporal resolution of less than 70 ms may be achieved [16]. Also it has been possible to infer functional connectivity of the brain using resting brain fMRI experiments [15].

Using increasingly refined pre-processing and modeling techniques, it has become possible to increase the statistical power enormously so that statistically valid inferences which initially required experimental blocks in group studies may now be drawn from a few trials, i.e., subsets of parametri-

cally varied experimental designs in single subjects [16]. It is not unreasonable to assume that a reliable measurement of single hemodynamic responses becomes possible within the near future. Moreover more clinical applications may come into light with the increasing power of fMRI.

Unlike the situation in anatomical imaging, analytical procedures for functional images matured rapidly. There is a wide consensus today about the necessary preprocessing steps [17], the statistical models [18] and the presentation of results [19]. Commercially and freely available software packages [20] ease the evaluation of fMRI experiments.

While the temporal resolution of fMRI is limited by the smoothness of the hemodynamic response, the lower spatial limit is still under discussion. Seminal experiments by Ugurbil et al. [21] have demonstrated a spatial resolution of 700 μm in mapping ocular dominance columns of the visual cortex. In animal experiments using intrinsic optical signals the "unit of activation" was found to be the area supplied by a single cortical arteriole which was in the order of 300-400 μm for sensory cortex [22]. Raising the spatial resolution by a factor of 10 is certainly a major task for fMR imaging in the next years. However it should be then possible to address functional activation to certain cortical layers. Combined with an advanced anatomical analysis as outlined above, brain functioning may be analyzed at the mesoscopic level: in its local vicinity (a neuroanatomical field) or in its remote connections (via fiber bundles), statically (by defining the connectivity) and dynamically (by combining parametrically varied functional designs).

Recently fMRI experiments have been combined with complimentary examination techniques to yield better diagnositc and treatment procedures. In what follows we discuss three such techniques which may be combined with fMRI scanning: In *repetitive transcranial magnetic stimulation* (rTMS) [23], a short sequence of magnetic pulses are applied to a specific brain region. This field perturbs local neuronal activation effectively leading to a temporary functional loss. Thus, a known cortical network involved in a specific task may be studied more closely by dynamically modulating the functionality of its components using rTMS. However since this is a more invasive procedure, ethical issues have to be respected. Moreover solving the neuro-navigational problem of influencing a rather small brain region at an individual location inside the confined space of a scanner tunnel is tough.

While the hemodynamic response is only an indirect measure of the neuronal activity, a direct correlate is the electrical potential recorded as the electroencephalogram (EEG) on the scalp. Unlike conventional EEG recording, a combination with fMRI poses a lot of delicate technical problems: even very small movements of the electrodes and cables in the magnetic field introduce currents in the wires, which easily reach a few hundred μV and thus hide the EEG. Besides movements induced by acoustic scanner noise, the pulse-related inflow of blood into the head introduces small head movements, the so-called cardio-ballistic effect. Secondly, the presence of a set of cables across the scalp shields the high-frequency (HF) electromagnetic signal which is recorded for fMR image acquisition. With an increasing number of electrodes, shimming the MR field and obtaining a good signal quality become increasingly harder. In spite of these technical issues, continuos EEG [24] and event-related potentials [25] have been obtained while fMRI scanning, rendering this technique an interesting addition to the palette of in-vivo examination methods.

Brain activation interacts with light in two different ways: the electrical activation of a neuronal population changes the local scattering properties of the tissue. This effect is detectable as a phase shift in HF-modulated infrared light [26] and since it is correlated with the electrical activity, it features the same millisecond time scale as the EEG. However, the signal-to-noise ratio is low and multiple repetitions are required to obtain an interpretable signal. Secondly, the relative amount of deoxygenated vs. oxygenated hemoglobin is measurable from the infrared spectrum. In functional near infrared spectroscopy (fNIRS) [27], a correlate of the hemodynamic response is measured which resembles the BOLD effect in its time course and signal strength. This is why the first method is called a "fast optical method" while the second one is called "slow". Both techniques are compatible with fMRI scanning, and offer interesting perspectives. However, their full potential is still untapped.

4 Synthesis

During the last 25 years, neuroscience has seen a tremendous development in neuroimaging techniques: from the "first look onto the brain" by CCT to the widely available fast high-resolution MR imaging protocols today. Functional MRI added a dynamical view onto the brain, allowing to monitor brain activity non-invasively at a spatial resolution of less than a millimeter and a temporal resolution of less than 100 ms.

MR methodology is still far from reaching technological limits. One of the most exciting advances to be expected within the next five years is an increase in spatial resolution: while this is *per se* an

evolutionary process, it will make the mesoscopic functional level of the brain accessible for examination. The gap to microscopic anatomical techniques (staining, labeling) and functional techniques (single cell recording) becomes narrower and thereby will perhaps lead to a convergence of understanding brain functioning at different organizational levels.

Technical advances must be backed up by elaborate signal and image processing methods in order to ensure quantitative and statistically confirmed relationships between hypotheses and experimental measurements. As the spatial resolution is increased, the data collected in one experiments is increased proportionally. A task for data analysis is to explore the full information content of data recorded in neuro-functional experiments: What can we learn about co-operation of sequential and parallel processes in the brain? How is a specific task embedded among others? Is possible to derive a common model of brain activation? What are the components of the "operating system" of the brain? It is possible to observe correlates of learning (i.e., plasticity) in functional experiments? - These are just a few of the imaginable questions, which might turn into experimental projects within the next couple of years. Let's take up the challenge!

References

[1] *IEEE Spectrum*, July 2000.

[2] Mazziotta J.C., Toga A.W., Evans A., Fox P.T., Lancaster J.L. (1995) *A probabilistic atlas of the human brain: theory and rationale for its development.* NeuroImage 2, 89-101.

[3] Talairach J., Tournoux P. (1988) *Co-Planar Stereotactic Atlas of the Human Brain.* Thieme, Stuttgart.

[4] Thompson P., Toga A.W. (1996) *A surface-based technique for warping three-dimensional images of the brain.* IEEE Transactions on Medical Imaging 15, 402-471.

[5] Evans A.C., Collins D.L., Holmes C.J. (1996) *Computational approaches to quantifying human neuroanatomical variability.* In: Brain Mapping: The Methods. Academic Press, San Diego.

[6] Mangin J.F., Frouin V., Bloch I., Regis J., Lopez-Krahe J. (1995) *From 3D Magnetic Resonance Images to Structural Representations of the Cortex Topography using Topology Preserving Deformations.* Journal of Mathematical Imaging and Vision 5, 297-318.

[7] Basser P.J., Mattiello J., Le Bihan D. (1994) *MR Diffusion Tensor Spectroscopy and Imaging.* Biophysical Journal 66, 259-267.

[8] Poupon C., Clark C.A., Frouin V., Regis J., Bloch I., Le Bihan D., Mangin J.F. (2000) *Regularization of diffusion-based direction maps for the tracking of brain white matter fascicles.* Neuroimage 12, 184-195.

[9] Geyer S., Schleicher A., Zilles K. (1999) *Areas 3a, 3b, and 1 of human primary somatosensory cortex. 1. Microstructural organization and interindividual variability.* NeuroImage 10, 63-83.

[10] Rajkowska G., Goldman-Rakic P.S. (1995) *Cytoarchitectonic definition of prefrontal areas in the normal human cortex. 1. Remapping of areas 9 and 46 using quantitative criteria.* Cerebral Cortex 5, 307-322.

[11] Ogawa S., Tank D.W., Menon R., Ellermann J.M., Kim S.G., Merkle H., Ugurbil K. (1992) *Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging.* Proceedings of the National Academy of Sciences USA 89, 5951-5955.

[12] Gjedde A. (1997) *The relation between brain function and cerebral blood flow and metabolism.* In: Cerebrovascular Disease, pp. 23-40. Lippincott-Raven, Philadelphia.

[13] Buxton R. B., Wong E.C., Frank L. R. (1996) *A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation.* Journal of Cerebral Blood Flow and Metabolism 17, 64-72.

[14] Kruggel F., von Cramon D.Y. (1999) *Modeling the hemodynamic response in single trial fMRI experiments.* Magnetic Resonance in Medicine 42, 787-797.

[15] Piyaratna J., Rajapkse, J. C. (2000) *Spatiotemporal Analysis of fMR Images Incorporating Functional Connectivity.* In: International Conference on Neural Information Processing (ICONIP2000), Korea (This Issue).

[16] Kruggel F., Zysset S., von Cramon D.Y. (2000) *Nonlinear Regression of Functional MRI Data: An Item Recognition Task Study.* Neuroimage 12, 173-183.

[17] Kruggel F., von Cramon D.Y., Descombes X. (1999) *Comparison of filtering methods for fMRI datasets.* NeuroImage 10, 530-543.

[18] Worsley K.J., Marrett S., Neelin P., Vandal A.C., Friston K.J., Evans,A.C. (1996) *A Unified Statistical Approach for Determining Significant Signals in Images of Cerebral Activation.* Human Brain Mapping 4, 58-73.

[19] Cox R.W., Hyde J.S. (1997) *Software tools for analysis and visualization of fMRI data.* NMR in Biomedicine 4-5, 171-178.

[20] Gold S., Christian B., Arndt S., Gene Z., Cizadlo T., Johnson D.L., Flaum M., Andreasen N.C. (1998) *Functional MRI Statistical Software Packages: A Comparative Analysis.* Human Brain Mapping 6, 73-84.

[21] Duong T.Q., Kim D.S. Ugurbil K., Kim S.G. (2000) *Spatio-temporal dynamics of the BOLD fMRI signals: toward mapping submillimeter cortical columns using the early negative response.* Magnetic Resonance in Medicine 42, 231-242.

[22] Masino S.A., Kwon M.C., Dory Y., Frostic R.D. (1993) *Characterization of functional organization within rat barrel cortex using intrinsic signal optical imaging through a thinned skull.* Proceedings of the National Academy of Sciences USA 90, 9998-10002.

[23] Bohning D.E., Shastri A., Nahas Z., Lorberbaum J.P., Andersen S.W., Dannels W.R., Haxthausen E.U., Vincent D.J., George M.S. (1998) *Echoplanar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation.* Investigative Radiology 6, 336-340.

[24] Ives R.J., Warach S., Schmitt F., Edelmann R.R., Schmoer D.L. (1993) *Monitoring the patient's EEG during echo planar MRI.* Electroencephalography and Clinical Neurophysiology 87, 417-420.

[25] Kruggel F., Wiggins C.J., Herrmann C.S., von Cramon D.Y. (2000) *Recording the event-related potentials during functional MRI at 3.0 tesla field strength.* Magnetic Resonance in Medicine, 44, 277-282.

[26] Gratton G., Fabiani M., Corballis P.M., Hood D.C., Goodman-Wood M.R., Hirsch J., Kim K., Friedman D., Gratton E. (1997) *Fast and localized event-related optical signals (EROS) in the human occipital cortex: Comparisons with the visual evoked potential and fMRI.* NeuroImage 6, 168-180.

[27] Kleinschmidt A., Obrig H., Requardt M., Merboldt K.D., Dirnagl U., Villringer A., Frahm J. (1996) *Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy.* Journal of Cerebral Blood Flow and Metabolism 16, 817-826.