From methods to meaning in functional neuroimaging

Reinders, Antje Annechien Talea Simone

1

Introduction

The human brain

A major challenge in the field of neuroscience is to understand the biological basis of emotion, cognition, and, ultimately, consciousness. Exploring the science of the mind involves studying the brain. The brain is part of the nervous system, which is a communication network that allows an organism to interact with its environment. The environment includes both the external environment (the world outside the body) and the internal environment (the contents of the body) (Willes, 1993).

The human nervous system can be subdivided into a peripheral and a central part. The peripheral nervous system controls voluntary muscle movement (somatic part) and involuntary muscle movement (autonomic part). The central nervous system (CNS) contains the spinal cord and the brain. The CNS is a mechanism that ensures the coordination of the actions in a part of the body with the actions in all other parts of the body. The CNS integrates internal and external environmental information to enable human behavior (Kalat, 1999a; Willes, 1993).

The brain consists of billions of neurons. Neurons transmit information from one location, e.g. brain area, to another location in the shape of electrochemical impulses. These impulses, the so-called action potentials, are transmitted by the neuron via dendrites (taking care of the information input) and axons (taking care of the information output). Axons are usually covered with a myelin sheath to quicken the information transmission (Kalat, 1999b). An action potential may involve one single neuron; however, more often clusters of neurons fire. Information from firing clusters is propagated through neuronal networks to establish a brain

function. Neurons in the brain need to function both locally (interactions between neighboring neurons) and globally (interactions among distant brain areas) to make human behavior possible.

Neuronal activity can be investigated using direct measurement, indirect measurement or a combination of both (Horwitz and Poeppel, 2002; Momjian et al., 2003). Direct measurement involves single cell recordings that are performed only chiefly in animal experiments. In humans, this is only possible during neurosurgery. Therefore, non-invasive procedures, i.e. indirect methods, are employed in man. These indirect methods comprise electromagnetic source imaging and measurements of metabolic changes. Electroencephalography (EEG) and magnetoencephalography (MEG) measure the electromagnetic signal caused by neuronal firing, whereas positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) measure physiologic or metabolic changes that are due to neuronal activity in the brain. To summarize, a broad spectrum of techniques is available to measure human brain activity (Horwitz et al., 2000).

Measuring brain activity

Many branches of scientific expertise are involved in monitoring the living human brain, such as medicine, pharmacology, mathematics and physics. The integration of these branches enables the study of the human brain in both normal and pathological conditions. The effects on behavior and mental functioning after external modification of the brain, such as brain lesions, transcranial magnetic stimulation (TMS), intracortical stimulation with electrodes, or administration of medication or drugs, can be studied. In addition, brain activation can be evoked in experimental settings by systematically manipulating the stimulus environment. The localized effects of such interventions on human activity can be examined. In other words, the brain and its dynamic interaction with the environment can be explored.

Direct single cell recording measurements are usually performed in primates. However, during human neurosurgery, single cell recording can also offer information on human single neuronal activity (Kreiman et al., 2000a,b; Fried et al., 2002). Single cell data provide detailed information on the moment of neuronal firing, that is temporal resolution, and on the location of the neuron, that is spatial resolution. The indirect measurement methods EEG and MEG are brain monitoring techniques which measure the electrical activity of the brain (Wheless et al., 2004; Kiebel and Friston, 2004). The stimulus dependent electromagnetic fields induced by neuronal firing are measured by electrodes attached to the scalp (EEG) or by magnetic detection coils (MEG). Applying techniques like EEG and MEG results in high temporal resolution, i.e. on a 10-100 ms scale, but poor spatial resolution, i.e. larger than 1 cm.

In this thesis, the indirect measurement methods PET and fMRI are used to monitor brain function. These techniques involve recordings of metabolic changes that are caused by neuronal activity. Changes in brain activity give rise to changes in energy consumption. This increased energy consumption is supported by an increase in glucose metabolism, which requires an increase in glucose and oxygen uptake (Shulman, 2001). The brain facilitates this by vasodilatation, resulting in a higher perfusion. This higher cerebral blood flow correlates with synaptic activity (Attwell and Laughlin, 2001; Sheth et al., 2004). The adjustment of the cerebral blood flow (CBF) to changes in neuronal activity occurs within a few seconds. Interestingly, the change in CBF is larger than the change in metabolism. Both PET and fMRI measure these CBF changes (Jueptner and Weiller, 1995).

In PET, regional cerebral blood flow (rCBF) is assessed directly by measuring the regional uptake of the radioactive $H_2{}^{15}O$, which is defined by the regional perfusion. FMRI on the other hand is based on the deoxyhemoglobin signal. FMRI takes advantage of the different magnetic properties of oxygenated and deoxygenated hemoglobin. The signal changes in fMRI are due to the mismatch between oxygen extraction and CBF. In other words, the oxyhemoglobin concentration correlates with CBF (Turner and Jezzard, 1994; Turner, 1994; Jueptner and Weiller, 1995). FMRI measures changes in these blood oxygenation levels, the so-called blood oxygenation level dependent (BOLD) response (Howseman and Bowtell, 1999; Bandettini et al., 2000; Matthews and Jezzard, 2004). The most common fMRI data acquisition method is echo-planar imaging (EPI), which allows for the collection of whole brain data within seconds (Mansfield, 1977).

FMRI allows for multiple studies to be performed on the same subject, because the subject is not exposed to ionizing radiation. However, PET suffers less from motion artifacts, and is therefore useful for studies which include patients with anxiety related disorders (Boshuisen et al., 2002; Reinders et al., 2003) or brain stem studies (Holstege et al., 2003). BOLD fMRI and PET with newer scanners, the so-called 'brain PET' scanners, have a similar spatial resolution. However, temporal resolution differs from a few seconds (limited by the hemodynamic response) for fMRI to around one to two minutes for standard water activation ($H_2{}^{15}O$) PET measurements. Direct quantitative rCBF comparison between PET and fMRI of conjoint activations shows no differences in rCBF change (Ramsey et al., 1996; Feng et al., 2004). Other comparison studies show higher statistical values for fMRI (Kinahan and Noll, 1999; Joliot et al., 1999), a higher detection sensitivity at the deep nuclei level for PET (Joliot et al., 1999) and a negative influence of draining veins for fMRI (Kinahan and Noll, 1999).

Functional neuroimaging

Functional neuroimaging aims to define the relationship between brain function and brain anatomy, in other words, mapping function into anatomical space (Friston, 1997a). Analyzing functional neuroimaging data incorporates finding a signal embedded in noise (Petersson et al., 1999b). Therefore, imaging conditions must be optimized for separating signal from noise to ensure a high signal-to-noise-ratio (SNR). This entails a number of steps; the optimal design and execution of each of these steps is essential to obtain a highly sensitive method producing results which are very reliable. Generally, the steps comprise experimental design and execution, data analysis (including pre- and post-processing), and data interpretation which is followed by the presentation of the data.

Experimental design

The different conditions under consideration are expected to change the blood flow in the brain in different ways. *A priori* hypotheses, which pin-point a limited specific set of brain areas, or cognitive mechanisms of interest need to be specified. Specific experimental stimuli and design settings can be considered to optimize statistical inference possibilities. Normally, functional imaging experiments comprise a simple subtraction design, which approaches the difference between two tasks. Simple subtraction analysis assumes that two, e.g. cognitive, components are completely separated (Friston et al., 1997), and can therefore be addressed separately in two tasks. Simple subtraction analysis can be extended to cognitive conjunction analysis by combining a series of subtractions to test whether task pairs sustain joint activations (Price and Friston, 1997). Furthermore, a factorial design can be considered, which incorporates two or more factors in one experiment, to investigate regionally specific main effects, interaction effects, differences and conjunctions (Friston et al., 1996b; Price et al., 1997). A parametric design incorporates a systematic variation of regional physiology depending on the degree of task variation (Friston et al., 1997; Büchel et al., 1998).

Data analysis

During data acquisition, the different brain states are measured successively. After the data acquisition, the data need to be reconstructed, which is usually of little concern to the researcher. However, this step is of considerable importance for the quality and SNR of the reconstructed data (Howseman and Bowtell, 1999; Bandettini et al., 2000; Reinders et al., 2002a,b; Mesina et al., 2003a,b).

After data acquisition, the brain states of the various conditions can be compared to identify brain areas which have responded differently on each condition.

Analyzing functional imaging data usually depends on the comparison, or subtraction, of the effects that are caused by different experimental conditions. A commonly used data analysis program is 'statistical parametric mapping' (SPM) (Penny et al., 2001). After data acquisition and reconstruction, the scans have to be aligned. The realignment procedure corrects for head movement between scans of one subject (Friston et al., 1995a, 1996c). To be able to compare different subjects, all the scans are spatially normalized (Ashburner and Friston, 1995, 1999). The concept of spatial normalization is to map images of different subjects into the same standard coordinate space. This allows for comparing and averaging brain activations (or anatomy) of several subjects within or across studies. In this manner, the activation patterns (or structural anatomy) found in differently shaped brains can be compared. As a final step in pre-processing, data are spatially smoothed using an (an)isotropic Gaussian kernel (Ashburner and Friston, 1995; Petersson et al., 1999b). This procedure compensates for residual variability in anatomical localization between subjects after spatial normalization. Furthermore, spatial smoothing allows for the application of the Gaussian random field theory (Worsley et al., 1992; Worsley, 1994; Poline et al., 1995), which addresses the problem of multiple comparisons to obtain corrected statistical inferences.

In the process of statistical data analysis the data are fitted to a model. More specifically, the brain data need to be described by a mathematical model to be able to draw conclusions from the data. Within SPM, this mathematical model is always linear, that is the general linear model (GLM) (Friston et al., 1995b), and constructed from the variables, i.e. the conditions, and other measured parameters, i.e. the covariates. This way, SPM explains variance in the brain activation data (Friston et al., 1996a). Using this GLM, condition-specific effects can be assessed by assigning specific contrast weights to the parameter estimates. In addition, the data can be explored for contaminating effects, for example due to movement artifacts, medication effects, cardiovascular arousal or reported subjective feelings. The optimal model is the model which incorporates all experimental effects. Increasing the number of parameters in the statistical model decreases the error variance, which is variance in the data that cannot be explained by the GLM. However, it lowers the degrees of freedom for the statistical tests. To retain SPM's optimal statistical power, the covariates of interest can be condensed using a principal component analysis (PCA), which saves degrees of freedom for the statistical model. Obtaining the optimal balance between explained variance and degrees of freedom is known as model selection. Although hardly mentioned in scientific publications, the statistical model applied and its quality in assessing the experimental effects are of great importance (Razavi et al., 2003).

SPM constructs spatially extended statistical maps to test a hypothesis on regionally specific effects in imaging data against a null hypothesis. This null hypothesis states that there is no difference in blood flow patterns between the conditions tested (Friston et al., 1991; Worsley et al., 1992). More specifically,

measured differences in task-related cerebral blood flow changes can be tested by performing a student t test on the parameter, as estimated within the GLM, for each voxel of the brain. This way, SPM performs multiple statistical tests, namely for all voxels in the brain. Therefore, a correction for these multiple comparisons has to be applied. Possible procedures for multiple testing correction are Gaussian random field theory (Worsley et al., 1996), Bonferroni correction and controlling the false discovery rate (FDR) (Nichols and Hayasaka, 2003).

Statistical parametric maps (SPMs) are usually inspected at a threshold of $p \leq 0.05$ corrected for multiple comparisons across the whole image. However, in the case of an *a priori* hypothesis, this correction is overly conservative, since it is known that the activation is restricted to a limited volume. In this case, SPMs can be explored at a liberal threshold of $p \leq 0.001$ uncorrected for multiple comparisons (Friston et al., 1991), from which the corrected significance level can be obtained subsequently using a small volume for multiple testing (Friston, 1997b), the so-called small volume correction (SVC). Furthermore, the data can be subjected to cluster analysis (Friston et al., 1994; Hayasaka et al., 2004). A cluster is defined as a set of voxels, e.g. voxels surviving an uncorrected threshold of $p < 0.001$, which are spatially connected with each other in terms of edge, face or vertex. The cluster level statistics include clusters reaching a statistical threshold of $p < 0.05$ (corrected for multiple comparisons). Besides reporting statistical values as p values, significant effects can furthermore be reported in t values or as Z scores, which is the conversion of t statistics to normal distribution.

After standard statistical analysis, additional post-processing steps can be taken for data analysis. For example, the latency of the BOLD response can be calculated in addition (Miezin et al., 2000; Calhoun et al., 2000; Henson et al., 2002; Liao et al., 2002) to explore early responses in for example the amygdala. To investigate the cooperation of several brain areas in action and the connections between these cooperating brain areas, the data can be analyzed in the context of 'functional integration'. Most of these so-called 'connectivity analyses' are post-processing steps (Petersson et al., 1999a; Sporns et al., 2000; Friston et al., 2003).

Data presentation and interpretation

Using the coordinates from the SPM output, the data can be localized anatomically by identifying the coordinates in the Talairach and Tournoux atlas (Talairach and Tournoux, 1988). In addition, the location of activation can be compared to and described with another brain atlas (e.g. see Mai et al., 1997). With all images in standard space (due to spatial normalization), the results of studies can easily be compared with reports in literature. The Talairach and Tournoux atlas is the classical accepted coordinate system in which coordinates are presented in the so-called 'Talairach space'. The SPM95 and SPM96 versions included a

Talairach template for spatial normalization. More recent SPM versions (SPM99 and SPM02) use the MNI (Montreal neurological institute) template (Evans et al., 1993) during spatial normalization. This current standard template is based on averaging 152 brain scans of normal subjects, i.e. the ICBM152. Statistical results can be converted from MNI space to approximate Talairach space (see: www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Talairach space coordinates reported in literature can also be converted to approach MNI space, and vice versa, creating the opportunity to make comparisons between studies.

The described methodological steps to analyze functional imaging data serve the effort of understanding normal and abnormal mental functioning. After the localization of focal activations in PET or fMRI data, the results are presented in tables or figures. On the basis of the *a priori* hypotheses, the raw functional imaging data are interpreted via methods into meaningful explanations.

References

Ashburner, J., Friston, K. J. (1995). Spatial transformation of images. *http://www.fil.ion.ucl.ac.uk/spm/course/notes97/Ch2.pdf* , 1–36.

Ashburner, J., Friston, K. J. (1999). Nonlinear spatial normalization using basis functions. *Hum. Brain Mapp.* 7, 254–266.

Attwell, D., Laughlin, S. B. (2001). An energy budget for signaling in the grey matter of the brain. *J. Cereb. Blood Flow Metab.* 21, 1133–1145, review.

Bandettini, P. A., Birn, R. M., Donahue, K. M. (2000). Functional MRI: background, methodology, limits, and implementation, in: Cacioppo, J. T., Tassinary, L. G., Berntson, G. G. (Eds.), Handbook of Psychophysiology. Cambridge University Press, New York, pp. 978–1014.

Boshuisen, M. L., Ter Horst, G. J., Paans, A. M. J., Reinders, A. A. T. S., den Boer, J. A. (2002). rCBF differences between panic disorder patients and control subjects during anticipatory anxiety and rest. *Biol. Psychiatry* 52, 126–135.

Büchel, C., Holmes, A. P., Rees, G., Friston, K. J. (1998). Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. *NeuroImage* 8, 140–148.

Calhoun, V., Adal, T., Kraut, M., Pearlson, G. (2000). A weighted least-squares algorithm for estimation and visualization of relative latencies in event-related functional MRI. *Magn. Reson. Med.* 44, 947–954.

Evans, A. C., Collins, D. L., Mills, S. R., Brown, E. D., Kelly, R. L., Peters, T. M. (1993). 3d statistical neuroanatomical models from 305 mri volumes. in: Proc. IEEE-Nuclear Science Symposium and Medical Imaging Conference. pp. 1813 – 1817.

Feng, C. M., Narayana, S., Lancaster, J. L., Jerabek, P. A., Arnow, T. L., Zhu, F., Tan, L. H., Fox, P. T., Gao, J. H. (2004). CBF changes during brain activation: fMRI vs. PET. *NeuroImage* 22, 443–446.

Fried, I., Cameron, K. A., Yashar, S., Fong, R., Morrow, J. W. (2002). Inhibitory and excitatory responses of single neurons in the human medial temporal lobe during recognition of faces and objects. *Cereb. Cortex* 12, 575–584.

Friston, K. J. (1997a). Imaging cognitive anatomy. *Trends Neurosci.* 1, 21–27, review.

Friston, K. J. (1997b). Testing for anatomically specified regional effects. *Hum. Brain Mapp.* 5, 133–136.

Friston, K. J., Ashburner, J., Poline, J. B., Frith, C. D., Heather, J. D., Frackowiak, R. S. J. (1995a). Spatial registration and normalization of images. *Hum. Brain Mapp.* 2, 165–189.

Friston, K. J., Frith, C. D., Liddle, P. F., Frackowiak, R. S. (1991). Comparing functional (PET) images: the assessment of significant change. *J. Cereb. Blood Flow Metab.* 11, 690–699.

Friston, K. J., Harrison, L., Penny, W. (2003). Dynamic causal modelling. *NeuroImage* 19, 1273–1302.

Friston, K. J., Holmes, A., Poline, J. B., Price, C. J., Frith, C. D. (1996a). Detecting activations in PET and fMRI: levels of inference and power. *NeuroImage* 4, 223–235.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. P., Frith, C. D., Frackowiak, R. S. J. (1995b). Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp.* 2, 189–210.

Friston, K. J., Price, C. J., Buechel, C., Frackowiak, R. S. J. (1997). A taxonomy of study design. *http://www.fil.ion.ucl.ac.uk/spm/course/notes97/Ch7.pdf* , 1–22.

Friston, K. J., Price, C. J., Fletcher, P., Moore, C., Frackowiak, R. S. J., Dolan, R. J. (1996b). The trouble with cognitive subtraction. *NeuroImage* 4, 97–104.

Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S., Turner, R. (1996c). Movement-related effects in fMRI time-series. *Magn. Reson. Med.* 35, 346–355.

Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent. *Hum. Brain Mapp.* 1, 214–220.

Hayasaka, S., Phan, K. L., Liberzon, I., Worsley, K. J., Nichols, T. E. (2004). Nonstationary cluster-size inference with random field and permutation methods. *NeuroImage* 22, 676–687.

Henson, R. N., Price, C. J., Rugg, M. D., Turner, R., Friston, K. J. (2002). Detecting latency differences in event-related BOLD responses: application to words versus nonwords and initial versus repeated face presentations. *NeuroImage* 15, 83–97.

Holstege, G., Georgiadis, J. R., Paans, A. M. J., Meiners, L. C., van der Graaf, F. H. C. E., Reinders, A. A. T. S. (2003). Brain activation during human male ejaculation. *J. Neurosci.* 23, 9185–9193.

Horwitz, B., Friston, K. J., Taylor, J. G. (2000). Neural modeling and functional brain imaging: an overview. *Neural Netw.* 13, 829–846, review.

Horwitz, B., Poeppel, D. (2002). How can EEG/MEG and fMRI/PET data be combined? *Hum. Brain Mapp.* 17, 1–3, review.

Howseman, A. M., Bowtell, R. W. (1999). Functional magnetic resonance imaging: Imaging techniques and contrast mechanisms. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 354, 1179–1194.

Joliot, M., Papathanassiou, D., Mellet, E., Quinton, O., Mazoyer, N., Courtheoux, P., Mazoyer, B. (1999). FMRI and PET of self-paced finger movement: comparison of intersubject stereotaxic averaged data. *NeuroImage* 10, 430–447.

Jueptner, M., Weiller, C. (1995). Review: does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. *NeuroImage* 2, 148–156, review.

Kalat, J. W. (1999a). Anatomy of the nervous system and the methods of investigation, in: Biological Psychology. Brooks/Cole publishing company, Pacific Grove, California, pp. 94–149.

Kalat, J. W. (1999b). Nerve cells and nerve impulses, in: Biological Psychology. Brooks/Cole publishing company, Pacific Grove, California, pp. 22–55.

Kiebel, S. J., Friston, K. J. (2004). Statistical parametric mapping for event-related potentials: I. Generic considerations. *NeuroImage* 22, 492–502.

Kinahan, P. E., Noll, D. C. (1999). A direct comparison between whole-brain PET and BOLD fMRI measurements of single-subject activation response. *NeuroImage* 9, 430–438.

Kreiman, G., Koch, C., Fried, I. (2000a). Category-specific visual responses of single neurons in the human medial temporal lobe. *Nat. Neurosci.* 3, 946–953.

Kreiman, G., Koch, C., Fried, I. (2000b). Imagery neurons in the human brain. *Nature* 408, 357–361.

Liao, C., Worsley, K., Poline, J.-B., Aston, J. A. D., Duncan, G. H., Evans, A. C. (2002). Estimating the delay of the response in fMRI data. *NeuroImage* 16, 593–606.

Mai, J. K., Assheuer, J., Paxinos, G. (1997). Atlas of The Human Brain. Academic Press, San Diego.

Mansfield, P. (1977). Multi-planar image formation using NMR spin echoes. *J. Phys. Chem.* 10, L55–L58.

Matthews, P. M., Jezzard, P. (2004). Functional magnetic resonance imaging. *J. Neurol. Neurosurg. Psychiatry* 75, 6–12, review.

Mesina, C., Boellaard, R., Jongbloed, G., van der Vaart, A. W., Lammertsma, A. A. (2003a). Experimental evaluation of iterative reconstruction versus filtered back projection for 3D [15O]water PET activation studies using statistical parametric mapping analysis. *NeuroImage* 19, 1170–1179.

Mesina, C. T., Boellaard, R., van den Heuvel, O. A. Veltman, D. J., Jongbloed, G., van der Vaart, A. W., Lammertsma, A. A. (2003b). Effects of attenuation correction and reconstruction method on PET activation studies. *NeuroImage* 20, 898–908.

Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., Buckner, R. L. (2000). Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage* 11, 735–759.

Momjian, S., Seghier, M., Seeck, M., Michel, C. M. (2003). Mapping of the neuronal networks of human cortical brain functions. *Adv. Tech. Stand. Neurosurg.* 28, 91–142, review.

Nichols, T., Hayasaka, S. (2003). Controlling the familywise error rate in functional neuroimaging: a comparative review. *Stat. Methods Med. Res.* 12, 419–446, review.

Penny, W., Ashburner, J., Kiebel, S., Henson, R., Glaser, D., C., P., Friston, K. J. (2001). Statistical parametric mapping: An annotated bibliography. *http://www.fil.ion.ucl.ac.uk/spm/bib.pdf* , 1–16.

Petersson, K. M., Nichols, T. E., Poline, J. B., Holmes, A. P. (1999a). Statistical limitations in functional neuroimaging. I. Non-inferential methods and statistical models. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 354, 1239–1260, review.

Petersson, K. M., Nichols, T. E., Poline, J. B., Holmes, A. P. (1999b). Statistical limitations in functional neuroimaging. II. Signal detection and statistical inference. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 354, 1261–81, review.

Poline, J. B., Worsley, K. J., Holmes, A. P., Frackowiak, R. S., Friston, K. J. (1995). Estimating smoothness in statistical parametric maps: variability of p values. *J. Comput. Assist. Tomogr.* 19, 788–796.

Price, C. J., Friston, K. J. (1997). Cognitive conjunction: a new approach to brain activation experiments. *NeuroImage* 5, 261–270.

Price, C. J., Moore, C. J., Friston, K. J. (1997). Subtractions, conjunctions, and interactions in experimental design of activation studies. *Hum. Brain Mapp.* 5, 264–272.

Ramsey, N. F., Kirkby, B. S., Van Gelderen, P., Berman, K. F., Duyn, J. H., Frank, J. A., Mattay, V. S., Van Horn, J. D., Esposito, G., Moonen, C. T., Weinberger, D. R. (1996). Functional mapping of human sensorimotor cortex with 3D BOLD fMRI correlates highly with H2(15)O PET rCBF. *J. Cereb. Blood Flow Metab.* 16, 755–764.

Razavi, M., Grabowski, T. J., Vispoel, W. P., Monahan, P., Mehta, S., Eaton, B., Bolinger, L. (2003). Model assessment and model building in fMRI. *Hum. Brain Mapp.* 20, 227–238.

Reinders, A. A. T. S., Nijenhuis, E. R. S., Paans, A. M. J., Korf, J., Willemsen, A. T. M., den Boer, J. A. (2003). One brain, two selves. *NeuroImage* 20, 2119–2125.

Reinders, A. A. T. S., Paans, A. M. J., de Jong, B. M., den Boer, J. A., Willemsen, A. T. M. (2002a). Iterative versus filtered backprojection reconstruction for statistical parametric mapping of PET activation measurements: a comparative case study. *NeuroImage* 15, 175–181.

Reinders, A. A. T. S., Willemsen, A. T. M., Georgiadis, J. R., Hovius, M., Paans, A. M. J., den Boer, J. A. (2002b). Interscan displacement-induced variance in PET activation data is excluded by a scan-specific attenuation correction. *NeuroImage* 17, 1844–1853.

Sheth, S. A., Nemoto, M., Guiou, M., Walker, M., Pouratian, N., Toga, A. W. (2004). Linear and nonlinear relationships between neuronal activity, oxygen metabolism, and hemodynamic responses. *Neuron* 42, 347–355.

Shulman, R. G. (2001). Functional imaging studies: linking mind and basic neuroscience. *Am. J. Psychiatry* 158, 11–20, review.

Sporns, O., Tononi, G., Edelman, G. M. (2000). Connectivity and complexity: the relationship between neuroanatomy and brain dynamics. *Neural Netw.* 13, 909–22, review.

Talairach, J., Tournoux, P. (1988). Co-Planar Stereotaxic Atlas of The Human Brain. Thieme Verlag, Stuttgart.

Turner, R. (1994). Magnetic resonance imaging of brain function. *Arch. Neurol.* 35, 637–638, review.

Turner, R., Jezzard, P. (1994). Magnetic resonance studies of brain functional activation using echo-planar imaging, in: Thatcher, R. W., Hallett, M., Zeffiro, T., John, E., Huerta, M. (Eds.), Functional Neuroimaging–Technical Foundations. Academic Press, San Diego, pp. 69–78.

Wheless, J. W., Castillo, E., Maggio, V., Kim, H. L., Breier, J. I., Simos, P. G., Papanicolaou, A. C. (2004). Magnetoencephalography (meg) and magnetic source imaging (msi). *Neurologist* 10, 138–153, review.

Willes, W. D. (1993). The nervous system, in: Berne, R. M., Levy, M. N. (Eds.), Physiology. Mosby Year Book, Missouri, pp. 93–108.

Worsley, K. J. (1994). Local maxima and the expected euler characteristic of excursion set of χ^2, F, and t fields. *Adv. Appl. Probab.* 26, 13–42.

Worsley, K. J., Evans, A. C., Marrett, S., Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *J. Cereb. Blood Flow Metab.* 12, 900–918.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C. Friston, K. J., Evans, A. C. (1996). A unified statistical approach for determining significant voxels in images of cerebral activation. *Hum. Brain Mapp.* 4, 58–73.