

Advances in brain imaging: a new ethical challenge

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Summary. - Technical advances in the past 25 years permitted substantial advances in the neuroimaging field, expanding the diagnostic and research potentials and significantly reducing the use of old invasive imaging techniques for research purposes. The safer procedures now available allow acquisition of reference data, morphological assessment and functional characterisation from healthy volunteers. However, enrollment of volunteers is still a sensitive ethical issue. Ethical problems related to informed consent, for both research and diagnostic procedures, in patients with neuropsychiatric disorders represent an additional crucial issue. Furthermore, with both functional and structural neuroimaging studies, there is a theoretical risk of violation of individual privacy. Research in the neuroimaging field should tend to increase the amount of information obtained through appropriate post-processing procedures, including multimodality image fusion, and to limit stress and discomfort.

Key words: clinical ethics, brain imaging, brain research.

Riassunto (*L'evoluzione dell'imaging cerebrale: una nuova sfida della bioetica*). - I progressi tecnici degli ultimi 25 anni hanno permesso un sostanziale progresso anche nel campo delle neuro immagini, aumentando la potenzialità diagnostica e di ricerca, e riducendo significativamente l'uso delle tecniche invasive. Le procedure più sicure che sono ora disponibili permettono l'acquisizione di dati di tipo sia morfologico sia funzionale anche nel volontario sano. Tuttavia l'arruolamento di volontari è ancora un significativo problema etico. I problemi etici correlati al consenso informato, sia nelle procedure diagnostiche sia in quelle a fini di ricerca, in pazienti neuropsichiatrici costituiscono un'importante questione etica addizionale. Inoltre, con studi di neuro immagini a livello sia funzionale sia strutturale, esiste un rischio di violazione dei diritti alla privacy individuale. La ricerca nel campo delle neuro immagini dovrebbe tendere ad aumentare le informazioni usando appropriate procedure di "post-processazione", tra cui la fusione multimodale di immagini, e tendere a limitare lo stress e il disagio.

Parole chiave: etica clinica, imaging cerebrale, ricerca sul cervello.

Introduction

In the past three decades the development of a series of computer assisted imaging techniques determined major improvements in the non-invasive assessment of brain structures and functions.

Advances in the characterisation of brain structure have been permitted by computed tomography (CT) and magnetic resonance imaging (MRI) [1-3].

Non-invasive vascular imaging is now permitted by Doppler ultrasound (US) and magnetic resonance angiography (MRA), with progressively decreasing utilisation of conventional, invasive angiographic procedures [4]. Nuclear medicine techniques such as positron emission tomography (PET) and single photon emission tomography (SPET) have permitted *in vivo* evaluation of cerebral perfusion and metabolism as well as neuroreceptor imaging [5, 6]. Further advances in metabolic and functional brain characterisation can be foreseen with the development of magnetic resonance spectroscopy (MRS) and "functional MRI" (fMRI) [7-9].

Therefore, a wide range of non-invasive approaches is now available for *in vivo* assessment of brain functions and anatomy, compared to the initial decades of the century where *in vivo* imaging studies on the brain, prior to the availability of computer assisted imaging techniques, were based on invasive procedures such as pneumoencephalography, ventriculography, angiography [3].

Yet, in the past decades, several research studies, that would be nowadays considered totally unethical, were carried out, both on uninformed healthy "volunteers" as well as unhealthy subjects [10, 11]. In several instances, volunteers including prison inmates, have been "utilised", with different forms of compensation, for research purposes.

In the present context, the principal ethical issues to be addressed in neuroimaging research concern, respectively, basic research (development of new techniques and methodologies), selection of healthy volunteers and patients with neuropsychiatric disorders, and clinical utilisation of neuroimaging techniques. In both instances, ethical assessment should be associated with a correct evaluation of cost-benefit ratios, for single individuals as well as for the general population.

Neuroimaging techniques

Two different categories of neuroimaging are available: morphologic imaging techniques (CT, MRI) and functional imaging techniques (SPET, PET, MRS, Doppler US). Introduced by Hounsfield in 1973 [1], computed tomography (CT) was the first imaging technique permitting direct visualisation of brain structures *in vivo* using a tomographic approach based on measurement of local tissue densities through a computer-assisted assessment of the attenuation of X-ray beams. Initially named "zeugmatography" by Lauterbur [2], magnetic resonance imaging (MRI) entered the clinical field in the early eighties. With MRI, a high intensity static magnetic field and oscillating magnetic fields are used to create tomographic images of the brain, where signal intensity reflects magnetic tissue properties. Utilisation of non-ionizing radiation, direct multiplanar imaging acquisition and high intrinsic tissue contrast are considered the main advantages of MRI over CT. Functional brain imaging encompasses a wide series of technical modalities and examinations. A large part of functional neuroimaging is represented by nuclear medicine studies using either conventional gamma emitting or positron emitting radioisotopes. The *in vivo* evaluation of brain functions was prompted by the development of the Kety-Schmidt technique for measurement of cerebral blood flow [12]. These studies were performed with an invasive approach requiring arterial and venous catheterization and administration of nitrous oxide, a non radioactive gas. Radioactive krypton was subsequently used for *in vivo* evaluation of cerebral blood flow in humans by Lassen and Ingvar in the fifties and sixties [13, 14]. Then, radioactive Xenon was used for *in vivo* measurement of cerebral blood flow [15]. From there on, advances in equipment (development of gamma cameras, and of tomographic systems: SPET, PET) and development of new radiotracers for the study of blood flow, blood volume, capillary permeability, glucose metabolism, receptor interactions, permitted to address a wide series of pathophysiological and clinical issue in different vascular, degenerative, neoplastic and psychiatric CNS disorders [5, 6]. Progresses in nuclear medicine have been followed by improvements in other imaging techniques, including US, with the development of Doppler US permitting the assessment of blood flow and velocity in the extracranial arteries and in the major intracranial arteries. Quite recently MRI has entered the functional imaging field with the development of fast acquisition sequences that can be sensitised to transient signal modifications associated with changes in deoxyhemoglobin-oxyhemoglobin ratios as well as with bolus administration of contrast media, permitting the evaluation of cerebral perfusion and blood volume [4, 9].

Additional contributions to the *in vivo* assessment of brain functions are provided by MR spectroscopy (MRS) a technique based on the ability to discriminate signals coming from different molecules [7] and therefore permitting quantitative measurement of selected metabolites in the brain.

An additional promising non-invasive technique for *in vivo* assessment of brain functional activation is magneto-encephalography [16].

Regarding invasiveness, diagnostic imaging techniques can be grouped in three categories:

- a) those with no documented risks, such as ultrasound or MRI and MRS;
- b) those with negligible risks of side effects, such as X-ray (CT) or radioisotope studies (SPET, PET);
- c) invasive tests requiring catheterization of blood vessels such as angiography.

Concerning the application of these techniques in research studies, with the first category, the participation of both healthy volunteers and patients would be prevented only by subjective non compliance. With the other two categories investigators are ethically obliged to quantify the risk involved in each experiment.

Ethical issues and new technologies

Ethical issues in the neuroscience field, including brain imaging, can be discussed as a part of the more general ethical problem of biomedical research, even if philosophical and moral implications of "brain research", particularly investigation concerning cognitive and affective functions, are quite peculiar.

The improved safety and decreased morbidity associated with modern diagnostic procedures have, to some extent, decreased the emphasis on ethical issues for neuroimaging studies. However, does decreased invasiveness of modern neuroimaging techniques always imply diminished impact of ethical problems in carrying out research protocols and clinical studies? The perception by the physicians of a decreased risk associated with new technologies may indeed facilitate an uncontrolled use of these procedures. And, after all, do techniques with really negligible risk exist? Even with MRI, considered a safe and non-invasive imaging technique, we still do not have long-term studies on the potential delayed effects and we really do not know what biological effects could be associated with the more recent technical developments based on high magnetic field gradients [17].

Indeed all imaging procedures bear some intrinsic discomfort that should be taken into account when including the procedure in a diagnostic flow-chart or a research protocol. Also, risks associated with the use of ionising radiation, should not be minimised, even if radiation dose associated with CT, SPET, PET are now very limited.

Informed consent

Medical procedures should always be directed to the well being of patients and, in our opinion, medical research should be always aimed at the acquisition of information that could be eventually useful in a clinical setting.

Four general principles were defined in medical ethics by Beauchamp and Childless [18]: autonomy, non maleficence, beneficence and justice.

However, autonomy in a medical research action, must itself be defined by rules taking into account the patient's rights as well as general ethical considerations.

In addition to the four principles, a crucial issue is represented by the patient's right to take "informed" decisions about clinical procedures and participation to research protocols. In fact, both clinical and experimental studies on humans should be performed according to principles of information as well as non-maleficence on both patients and volunteers.

The basic principle of information was introduced by the Code of Nuremberg, following the discovery of atrocities performed by the Nazis.

However the application of the informed consent in medical research has been quite slow, particularly in countries with large fractions of uneducated, low income population.

The introduction of the informed consent has been paralleled by the establishment of institutional "ethical committees" in charge of the assessment of research projects. Many research projects around the world are still performed without peer review of the ethical aspects. In Italy, ethical committees have been established by major medical schools and research institutions in recent years; however, many important hospitals and research centres still do not have an ethical committee.

Therefore, while the international health organisations such as WHO should actively promote the diffusion of such committees, a more active role could be attributed to the editors and to the editorial boards of the scientific journals where the results of research studies are published. Scientific journals do usually require official statements concerning the approval of described research protocols by local institutional committees. Yet, we believe the review process should also include an ethical evaluation in addition to the standard scientific assessment. Attempts to obtain breakthroughs by unethical means could be markedly cut down if researchers knew their study would go through a pre-publishing ethical assessment.

With neuroimaging, a particularly sensitive issue is the informed consent to be obtained by patients with neuropsychiatric diseases and severe cognitive and affective impairment. With neuropsychiatric patients, the physician ought not to be prevented from giving full and complete information to the relatives or legal guardians, because the risk of patient exploitation is much higher. Indeed with such patients there may be a

voluntary or involuntary underestimation of patient's rights, with improper assessment of the risk/benefit ratio.

In neuropsychiatric patients, diagnostic procedures of immediate potential benefit to the patient are ethically correct, if based on proper information and agreed upon by the physician and the legal guardian. However, research procedures shall be discussed and approved by both the patients and his/her guardian. And if the patient does not or is not able to provide his/her consent, the procedure, in our opinion, shall not be performed.

An additional risk is represented by the possibility of obtaining an apparently voluntary consent from a neuropsychiatric patient, through plagiarism of his/her weakened personality, with a factitious presentation as full informed consent by a person unable to take such decisions.

Part of the ethical issue involved with informed consent, are the extent and quality of information to be provided. In addition to information concerning the technical details of the procedure, including any possible direct or indirect discomfort, as well as immediate or delayed health risks, the patient should be clearly informed of the potential benefits of the procedure for his/her health, or, in the case of a normal volunteer, of the potential advantages that the research protocol could involve in terms of basic knowledge and/or clinical impact on future patients.

The physician who has the responsibility to assess individual risk/benefit ratios, may be even tempted to apply different judgement criteria to different patient categories. In fact, severely ill and terminal patients could be improperly considered as subjects that can undergo any sort of diagnostic or therapeutic procedures. In these patients while the risks of secondary effects of ionising radiation associated with the use of some diagnostic procedures can be neglected, one should always consider the psychological and physical discomfort and stress associated with diagnostic procedures, particularly in the terminal phase of the disease, when even minimal stress could be abnormally amplified and perceived as a very negative event.

Even in patients who do not have neuropsychiatric diseases the informed consent may be not fully voluntary, since the patient can provide his/her consent, if convinced that he/she will receive better treatment, by the use of the diagnostic test results or simply by complying with the physician's instructions. This psychological type of "blackmail" could be sometimes willingly created by the physician, in order to obtain a consent to a study that has a purely academic value. Improper conduct of the physician can happen more frequently in a context of limited health insurance coverage, both in the case of public and private health services (due to limited availability and ineffective utilisation of resources, in the first case, and to limited income of the patients in the latter case).

Healthy volunteers

In several countries such as the US, a large amount of research projects in the neuroscience field has been carried out utilising paid volunteers. Different forms of compensation have been used for particular categories of "volunteers" like prisoners and conscientious objectors utilized in the US during World War II.

Compensation for volunteers is a difficult issue to deal with. A general set of criteria for assessment of appropriate monetary compensation of different risks is very difficult to establish. With marked socio-economic differences within a country, but principally between developed and undeveloped countries, researcher and even more the research companies could be tempted to use low cost volunteers in third world countries. In Italy, the participation of volunteers in experimental protocols cannot be financially supported by official institutions because the current laws do not allow any reward for this type of service.

Enrollment of large number of normal subjects, without some form of compensation, may be limited and even impossible in cases involving invasive procedures. In our opinion, however, payment of volunteers creates ethical risks.

In order to overcome this limitation, investigators and their colleagues could themselves agree to participate as volunteers in their own experimental studies.

Since they are aware of the content, the aims and the technical procedures of the research project, they can evaluate exactly the risk and the benefits associated with the experiments.

Even in this case, ethical risks could not be completely avoided, if one considers that students and residents may feel obligated to participate in such studies without having complete knowledge of the involved risks. This psychological type of "blackmail" could be sometimes willingly created by the physician, in order to obtain a consent to a study that has a purely academic value.

Research developments and ethics

Research can itself provide valuable contribution to the ethical issues associated with investigation of the central nervous system by developing new non-invasive or less invasive procedures, and by improving the quality and the amount of data that can be obtained with a neuroimaging study. In fact, reduction of risks and discomforts associated with diagnostic procedures has been the principal goal of several research studies. Two examples of simplified non invasive or less invasive approaches using PET are provided hereinafter. With PET, radioactive concentration can be accurately measured *in vivo*. Nevertheless, in order to measure brain functions such as glucose metabolism or capillary permeability, the tracer input function (i.e. the arterial concentration of the tracer during the experimental time

period) must be measured. The input function can be determined by sampling the arterial blood during the PET study. While a PET study *per se* is non-invasive (except for administration of minimal amounts of radioactivity), sampling arterial blood requires catheterization of either the radial or the femoral arteries. Arterial catheterization turns the PET study into an invasive procedure with increased, even though still limited, risks for the patient. With PET studies for measurement of brain glucose utilisation using 48F-fluorodeoxyglucose, Phelps *et al.* [19] demonstrated that arterialized venous sampling (i.e. venous blood obtained from heated arms) provides comparable information to arterial blood. Therefore, brain glucose metabolism can be calculated with PET using arterIALIZED venous samples for measurement of the tracer input function, obviating the need for arterial catheterization. In the study of blood-brain barrier permeability, with a dynamic PET examination using 68Ga-EDTA, transfer constants and plasma volume can be obtained by measuring the arterial tracer input function. Since the blood-brain barrier has very low tracer permeability, no measurable extraction occurs in a single passage through the brain vascular bed. Therefore, brain arterial and venous concentration curves essentially overlap. With the radioactive tracer mainly concentrated in the brain vasculature and with very low amounts in the parenchyma, the venous concentration curve of the tracer can be accurately determined directly from the PET study, measuring tracer activity from the images obtained at the level of the superior sagittal venous sinus. After normalisation of the curve with a single venous sample at the end of the study an accurate estimate of the input function can be obtained. With this procedure for measurement of capillary permeability and blood volume, a single venous blood sample is required instead of a series of arterial samples [20].

In general, research protocols as the above described studies, aimed at decreasing invasiveness of diagnostic procedures, as well as at reducing examination time are particularly useful for *in vivo* functional brain studies. Efforts to simplify the diagnostic procedures with appropriate validation protocols should be encouraged since this type of research usually does not involve significant additional distress to patients/volunteers involved in the study. On the other end, less invasive protocols can also help decreasing the costs of the examinations and increasing the diffusion of examinations in clinical settings or, at least, in wider research settings. Optimisation of the amount of information obtained in any diagnostic/research neuroimaging study should always be aimed at. A stimulating area of imaging research involves enhancing the information obtained by improving image quality, by producing new types of images and by obtaining quantitative information. Image post-processing is a fundamental tool to obtain such results. Post-processing is presently becoming a very popular topic in the neuroimaging field. It essentially

indicates any sort of manipulation, transformation, filtering, reconstruction etc. carried out on images. Post-processing can add diagnostic information to morphologic imaging studies such as CT and MRI, and permits the creation of parametric maps, i.e. images where quantitative information is displayed in each element of the image with grey levels or colours corresponding to a specific value of the studied parameter. While maps of brain functional parameters are commonly obtained with nuclear medicine procedures, and particularly with SPET and PET, they are only infrequently used with the morphologic imaging modalities such as CT and MRI. Nevertheless, radiologists are now facing increasing requests for quantitative information from neurologists and psychiatrists. In addition requests for image standardisation in the morphologic imaging field could increase. In particular, MRI has a wide spectrum of parameters affecting to different extents signal intensity depending on the selected acquisition protocol. With MRI multiple series of images with varying contrasts between the various tissues are obtained in a single study [3]. In an effort to provide a standardised reproducible type of MR images a postprocessing technique, quantitative magnetic colour imaging (QMCI), has been developed by our group [21]. QMCI allows conversion of the magnetic resonance signal intensity data into a single colour image where the three fundamental MR parameters, T_1 and T_2 relaxation rate and proton density, codify the three fundamental colours (red, green, and blue). This technique provides a chromatic tissue characterisation simplifying the recognition of normal and pathological tissues through a standardised presentation.

Image post processing research does not require supplemental patient studies and can be very useful in increasing the accuracy of diagnostic examinations, without giving any additional- discomfort to the patient. Several attempts have been performed to obtain quantitative information from MRI studies, and several groups are now investigating the possibility of obtaining functional maps from MR studies at high magnetic fields and using special acquisition protocols to study cerebral blood volume and tissue perfusion changes during selective stimulation tasks [9].

Obtaining quantitative information

An accurate evaluation of risks and benefits for volunteers and patient must be performed in all cases where quantitative functional information is to be obtained by invasive procedure. In all instances where quantitative information can be obtained without using invasive procedures, the non-invasive alternative approach ought to be selected.

In MRI studies of the brain, volumetric information can be obtained with new segmentation procedures [22] and there is an ongoing effort to set up new accurate

segmentation technique to achieve quantitative morphologic data from MRI. Since this post-processing procedures do not imply additional stress for patient and look very promising, such research effort should be encouraged.

A very stimulating area of research in neuroimaging is presently represented by integration of information obtained with different technique.

Post-processing can be very helpful for correlation of morphologic and functional information, by matching images obtained with different devices, such as PET or SPECT and CT or MRI.

Functional information produced by PET and SPET with low spatial resolution need morphological information in order to clearly localise biological functions.

Therefore coregistration of PET or SPET studies with MRI or CT studies can generate additional information or improve the quality of obtained data.

Whenever possible, correlative functional and morphologic brain imaging must be based on image fusion approaches where morphological images can help in the spatial localisation and interpretation of functional abnormalities. On the other end, functional data can improve the characterisation of complex morphologic tissue abnormalities, by indicating areas with specific functional/metabolic changes for selection of biopsy sites, as well as for guiding surgery and radiation treatment.

Post-processing matching procedures, normally, do not need any extra examination time for the patient and their cost in terms of operator and computing time will become negligible in a few years.

Functional imaging studies can be performed to detect brain activation, such as local increases of blood flow and/or metabolism, during specific mental tasks: Such studies may suggest that it could be possible to quantify mental activities and performance, creating an *a priori* classification of intelligence levels of different individuals. Morphometric studies can be performed to detect and quantify brain atrophy and or focal lesions, that could be associated with decreased mental capabilities and/or age. Once again, these studies may suggest the possibility of quantitative correlations between mental performance and amount of brain parenchyma as assessed from imaging data. The investigation of functional and morphological abnormalities as a part of routine evaluations for assessment of personnel qualifications at different levels (hiring, career developments, job change) can indeed be considered an ethical risk of neuroimaging procedures. Yet, this is unlikely in terms of practical implementation and unjustifiable on strict scientific ground, given the still limited amount of knowledge about brain functions and intellectual abilities. In particular, recent studies concerning neuronal plasticity, i.e. redistribution of selective brain functions to different cortical areas following focal injuries, as well as the possible rearrangement of neuronal functions during

normal ageing, suggests that mere assessment of amount of brain parenchyma or even regional flow/metabolism cannot be used as a reference "measure" of brain capacities. On the other end, if the risk of *a priori* quantification of individual capabilities would become real, ethical guidelines should be defined to direct the use of knowledge.

Conclusions

Non-invasive or minimally invasive imaging technique permit the acquisition of impressive amounts of data about brain structures and functions in normal conditions and in several brain disorders.

Neuroimaging research, particularly with potential assessment of brain functions and correlations of functional and morphologic abnormalities create new ethical problems.

Research protocols in the neuroimaging field should undergo careful scrutiny by ethical committees and peer review process.

Normal volunteers should be enrolled on a voluntary, non compensated basis.

Consent for research studies and routine diagnostic procedures should be based on a wide and correct information particularly to limit the risk of plagiarism of patients and/or their guardians in the case of neuropsychiatric disorders. Research can itself play an important role in connection with ethical problems by increasing the amount of information achievable from clinical studies and decreasing invasiveness of imaging procedures.

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REFERENCES

- HOUNSFIELD, G.N. 1973. Computerised transverse axial scanning tomography. Part I. Description of the system. *Br. J. Radiol.* **46**: 1016-1022.
- LAUTERBUR, P.C. 1973. Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature* **242**: 190-191.
- ATIAS, S.W. 1991. *Magnetic resonance imaging of the brain and the spine*. Raven Press, New York.
- KELLEY, R.E. 1994. *Functional neuroimaging*. Futura Publishing Co, Armonk (NY).
- PHELPS, M.E., MAZZIOTTA, J.C. & SCHELBERT, H.R. 1985. *Positron emission tomography and autoradiography: principles and applications for the brain and the heart*. Raven Press, New York.
- Clinical SPECT imaging*. 1995. E.L. Kramer & J.J. Sanger (Eds). Raven Press, New York.
- ROSS, B. & MICHAELIS, T. 1994. Clinical applications of magnetic resonance spectroscopy. *Magn. Reson. Quart.* **10**: 191-247.
- ROSEN, B.R., ARONEN, H.J., KWONG, K.K. *et al.* 1993. Advances in clinical neuroimaging: functional MR imaging techniques. *Radiographics* **13**: 889-896.
- BELLIVEAU, J.W., KENNEDY, D.N., MCKINSTRY, R.C. *et al.* 1991. Functional mapping of the human visual cortex using magnetic resonance imaging. *Science* **254**: 716-719.
- GORDON, R. 1983. *Great medical disasters*. Hutchinson, London.
- Medical ethics: a clinical textbook and reference for the health care professions*. 1993. N. Abrams & M.D. Brucker (Eds). MA MIT Press, Cambridge.
- KETY, S.S. & SCHMIDT, C.F. 1948. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J. Clin. Invest.* **27**: 476-483.
- INGVAR, D.H. & LASSEN, N.A. 1962. Regional blood flow of the cerebral cortex determined by krypton-85. *Acta Physiol. Scand.* **54**: 325-338.
- LASSEN, N.A. & MUNCK, O. 1955. The cerebral blood flow in man determined by the use of radioactive krypton. *Acta Physiol. Scand.* **33**: 30-49.
- OLESEN, J. PAULSON, O.B. & LASSEN, N.A. 1971. Regional cerebral blood flow in man determined by the initial slope of clearance of intraarterially injected 133 Xenon. *Stroke* **2**: 515-539.
- GALLEN, C.C., SOBEL, D.F., LEWIN, J.D. *et al.* 1993. Neuromagnetic mapping of brain function. *Radiology* **187**: 863-868.
- SHELLOCK, F.G. & KANAL, E. 1994. *Magnetic resonance: bioeffects, safety and patient management*. Raven Press, New York.
- BEAUCHAMP, T.L. & CHILDESS, J.F. 1983. *Principles of biomedical ethics*. Oxford University Press Inc., New York.
- PHELPS, M.E., HUANG, S.C., HOFFMAN, E.J. *et al.* 1979. Tomographic measurements of local cerebral glucose metabolic rate in humans with (F-18) 2-fluoro-2-deoxyglucose: validation of a method. *Ann. Neurol.* **6**: 371-388.
- LANNOTTI, F., FIESCHI, C., ALFANO, B. *et al.* 1987. Simplified, non-invasive PET measurement of blood-brain-barrier permeability. *J. Comput. Assist. Tomogr.* **11**: 390-397.
- ALFANO, B., BRUNETTI, A., ARPAIA, M. *et al.* 1995. Multiparametric display of spin echo data from MR brain studies. *J. Magn. Reson. Imag.* **5**: 217-225.
- JACKSON, E.F., NARAYANA, P.A. & FALCONE, J.C. 1994. Reproducibility of nonparametric feature map segmentation for determination of normal human intracranial volumes with MR imaging data. *J. Magn. Reson. Imag.* **4**: 692-700.