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Frackowiak R S J, Lenzi G-L, Jones T & Heather J D. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure, and normal values. *J. Comput. Assist. Tomogr.* 4:727-36, 1980.
[MRC Cyclotron Unit and Dept. Medicine, Hammersmith Hosp., London, England and III Neurological Clinic, Univ. Rome, Italy]

Positron emission tomography (PET) theoretically permits the measurement of the distribution of radioactivity in sections of the human brain using noninvasive technology. The paper described the first practical implementation of a quantitative method for measuring cerebral blood flow and oxygen metabolism concurrently in the brain of man. Its merit lay in the solution of practical problems and the realization of the consequent emergence of PET as a scientific tool for clinical investigation. [The *SCI*®] indicates that this paper has been cited in over 285 publications, making it the most-cited paper from this journal.]

Measuring Focal Physiological Changes in the Human Brain Noninvasively

Richard S.J. Frackowiak
MRC Cyclotron Unit
Hammersmith Hospital
London W12 0HS
England

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The principles of tomographic reconstruction of data were introduced in the early 1970s and rapidly applied to X-ray tomography of the human brain with immediate diagnostic implications. It became clear to a small number of scientists that similar techniques could be applied to the detection of radiation emitted from the brain.

Positron emission tomography (PET) rapidly evolved into a working technology. The intrinsic attraction of PET was its ability to measure radioactivity in absolute physical units both locally and noninvasively in the human brain. The sensitivity of detection was extremely high, of the order of 10^{-12} molar, so that the application of classical tracer techniques to the study of living human tissue *in situ* could be envisaged using this technology.

Concurrently, my chief collaborator and mentor, Terry Jones, had been thinking about the use of positron emitting isotopes of oxygen-15 for the assessment of the relationship between cerebral perfusion and energy consumption. Our paper essentially represents the crossroads between these two developing strands of thought.

My own entry into the field of positron tomography coincided with the installation of the first positron camera by the Medical Research Council in the UK. The immediate task seemed to be to crack the problem of quantitation. Without the ability to express physiological variables in real units, we would not be able to communicate data or to carry out studies of the natural history of disease or to make comparisons between or within groups of patients or subjects.

We had many advantages on our side—an accurate PET camera, a tradition of working with positron emitting isotopes, and a genius of a nocturnal computer programmer in the form of Jon Heather. The crux of the problem lay in the correction of emitted radiation for the effects of attenuation by body tissues that led to distortions in the recorded distributions of radioactivity and hence deviation from true values. We demonstrated that this correction could be accurately and efficiently performed by measuring the attenuation characteristics for each tissue scanned subsequently in the emission mode after introduction of the positron tracer. A further development was the numerical treatment of the data from sequential scans with $C^{15}O_2$ and $^{15}O_2$, which were required to build up pictures of cerebral blood flow, cerebral metabolic rate for oxygen, and the arteriovenous oxygen difference (or fractional oxygen extraction).

A number of studies in normal subjects were presented and the consistency of the results with respect to previous invasive and global techniques was described. The solution of the problem of quantitation immediately led to the explosion of clinical scientific studies in various diseases in which the relationship between perfusion and energy consumption was of paramount interest. This was particularly so for the dementias in which the evidence for various pathogenic mechanisms was explored and in cerebral vascular disease. The coupling of flow and metabolic information has led to a reinterpretation of many of the classical data obtained in man previously and a reappraisal of the human pathophysiology of preischemic and ischemic states.[1-5]

Our own view of the importance of this paper lies in the fact that we turned a radiological technique into a true scientific tool by achieving solutions of scan data in reproducible physiological terms. This has now imposed new imperatives. The decade since publication has seen refinements and validations of the method, which has proven robust, accurate, and reproducible and has been used by many centres. The emphasis is now in increasing the temporal resolution of the method to permit rapid reproducible measures at the same session. Others have also taken on this challenge and new solutions are proliferating.[6]

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