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Functional Neuroimaging: A Historical Perspective

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1. Introduction

Modern in *vivo* functional neuroimaging techniques produce colorful computer images of the pattern of metabolic neuronal activity in living humans while engaged in performing cognitive and/or emotional tasks, and provide an unprecedented opportunity to examine how brain function supports activities in normal and abnormal conditions. The idea of the relation between blood flow and brain activity dates back to the second half of the 19th century, a time when some scientists made important contributions to this subject. In this period, functional brain activity began to be studied in the intact human brain by thermal recording from the scalp or by using techniques providing indirect graphical measurements of changes in cerebral flow when different mental tasks were performed. This relationship began to be quantified by measuring whole brain blood in animals and humans. The development of technologies that could measure these changes safely in normal human subjects would take another 60 years. Detailed mapping of regional flow changes during various mental and motor activities was achieved in 1970s and 1980s using new techniques (CT, PET and MRI) with further new valuable information about brain function in normal and in pathological conditions. This chapter will focus on a review of the historical background of functional brain imaging techniques.

2. The first evidence: Changes in scalp and cortex temperatures

Today, we know that brain temperature is a physiological parameter determined primarily by neural metabolism, regulated by cerebral blood flow, and affected by various environmental factors and drugs (Kiyatin, 2007). This aspect was already conjectured by some scientist in the mid-19th century. For example, the French physiologist Claude Bernard (1813-1878) in 1872 observed: '*If we now try to understand the relationship that one*

can obtain between the intensification of the circulatory function and the functional state of the organs, it is easy to see that the increase in blood supply is related to the increased intensity of the chemical metamorphoses that take place in tissues, and to the increment in thermogenetic phenomena which are the immediate and necessary consequence of those. . . . Each time the spinal or a nerve exhibit sensitivity or movement, each time the brain performs intellectual work, a corresponding amount of heat is produced' (Bernard, 1872; Conti, 2002). The famous psychologist William James (1842-1910), in 1892, concluded that : *'. . . brain-activity seems accompanied by a local disengagement of heat'* and speculated that cerebral thermometry may be valuable for experimental psychology to correlate cognitive and emotional states focally to brain regions (James, 1892).

Starting from this interesting hypothesis, researchers placed thermometers or more sensitive thermoelectric piles on the scalp to measure regional changes in temperature. Several measurements of brain temperature, in normal and abnormal subjects, engaged in performing cognitive, motorial or emotional tasks or after administration of drugs were conducted from the second half of the 19th century (see Albers, 1861; Lombard, 1867, 1879; Gray, 1878; Maragliano and Seppili, 1879; Bert, 1879; Amidon, 1880; Maragliano, 1880; François-Franck, 1880; Sciamanna and Mingazzini, 1882; Bianchi, Montefusco e Bifulco, 1884; Tanzi, 1888; Mosso, 1894; Berger, 1901). In at least two studies, thermometers were placed also in direct contact with the cerebral cortex via skull cracks in patients responding to sensory stimuli, doing mental tasks, and undergoing emotional experiences (Mosso, 1894; Berger, 1901).

Among the most famous researchers using the cerebral thermometry approach were Josiah Stickney Lombard in the United States (Lombard, 1867, 1879; Marshall and Fink, 2003), Pierre Paul Broca in France (Broca, 1879), Angelo Mosso in Italy (Mosso, 1894) and Hans Berger in Germany (Berger, 1901).

In 1866, Lombard, first commenced a series of experiments, with thermoelectric apparatus, to determine the amount of blood circulating in the brain and the exterior temperature of the human head, in the quiescent mental condition, and in states of intellectual and emotional activity. He demonstrated that the exercise of the higher intellectual faculties, as well as the different emotions, caused a rise of temperature in the head perceptible through the medium of delicate apparatus. Lombard reviewed the results on cerebral temperature in his 1879 monograph on *Experimental Researches on the Regional Temperature of the Head under Conditions of Rest, Intellectual Activity and Emotion*'. He observed: *'. . . there is good reason to suppose that a slight change of temperature at the surface of the brain can show itself in a degree readily perceptible by means of delicate apparatus, at the exterior surface of the head; and we shall see, in the experiments now to be given, that the changes of temperature observed in the integument during increased mental activity are usually of a degree which may be fairly accounted for by the direct propagation outward, through the intervening tissues, of slight thermal changes at the cerebral surface'* (Lombard, 1879).

Mosso, in his book *La temperatura del cervello. Studi termometrici* [The temperature of the brain. Thermometric studies] set out a very large number of sophisticated experiments on cerebral thermometry. The temperature was ascertained by means of a delicate thermometer which gave to the naked eye a reading of 0.01 degrees. Mosso made observations directly on the cerebral human cortex. For example, he examined Delfina Parodi, a girl of twelve years who had a wound on the right side of the skull (see Fig. 1).

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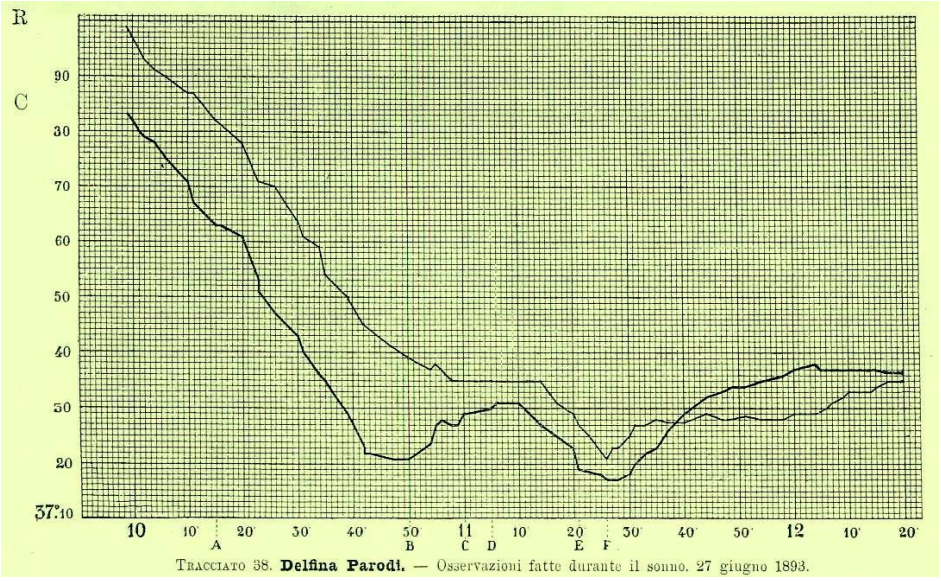

Tracciato 38. **Delfina Parodi.** — Osservazioni fatte durante il sonno. 27 giugno 1893.

Fig. 1. (A) Delfina Parodi (B) Tracing obtained during sleep showed an increase in brain temperature when a dog began to bark in the next garden (A and D) and when the girl was called by name, Delfina (F), R=rectum, C=brain. Source: Mosso (1894).

Neither mental nor motor exertions had any influence upon the brain temperature, but emotions such as fear of the administration of chloroform caused a rise of temperature of 0.01 degrees. Berger (1901) stated that his principal aim was to find: *'. . . and equivalence between the chemical and thermic energy of the brain and psychic 'energy'*. Broca tried to demonstrate the effect of different mental tasks, especially language, on the localized temperature of the scalp of normal subjects, and also studied the diagnostic value of the thermogenic exploration of the scalp to discover focal lesion of the brain (Broca, 1877). Studies of brain localisation were also carried out by other researchers (Gray, 1878; Maragliano, 1880; Putnamm Iacobi, 1880; Bianchi, Montefusco and Bifulco, 1884).

3. Brain volume produced through mental activity: The Mosso methods

Though cerebral thermometry was abandoned owing to methodological difficulties and contradictory results, it provided the basic rationale for later studies on the relationship between function and blood circulation in overlying brain tissue.

A researcher who championed the idea of studying changes in brain blood flow was the Italian physiologist Angelo Mosso (1848-1910) who, at about the same time when he conducted his research on regional temperatures in the head and brain, began to investigate brain blood flow during certain emotional and cognitive tasks (Zago, Ferrucci, Marceglia and Priori, 2009). In his textbook on blood circulation in the human brain, printed in Germany in 1881, Mosso observed: '*Of all the body's organs, the brain is that in which the most frequent and most radical changes in the state of the blood vessels occur. Physiology has not yet determined which of these changes are produced reflexively by the action of a central motion vessel and which arise from purely local actions as an effect of the chemical transformations which occur in a given brain region. That there are, however, local changes due to local chemical action is undeniable*' (Mosso, 1881). The concepts expressed by Mosso engender the idea that when brain areas are active, changes in the amount of blood flowing in circumscribed brain regions, and specific biochemical processes, in the same areas, increase to ensure adequate energetic support to the active neurons. This mechanism, is actually termed *functional hyperaemia* (Iadecola, 2004).

In his investigations on human cerebral circulation Mosso proposed some new and valuable non-invasive procedures for detecting the functional correlates of various physiological and psychological states. The first method involves the development of a bed scales in which the body was placed in perfect balance and where it was possible to measure small tilts of a few millimeters of its longitudinal axis determined by the passage of blood from the legs to the head and vice versa (see Fig. 2).

With this apparatus Mosso verifies that the breath and sleep rhythms, the effect of pharmacological substance, and the response to particular mental states, determined minimal oscillations of the balance corresponding to changes in the distribution of blood (Mosso, 1882,1883). He observed that: *'. . . the spontaneous movements of the blood vessels and the undulations corresponding to psychic acts are equally visible by means of the balance*' (Mosso, 1882). Further research on bodily changes during mental activity appears to have been attempted with the Mosso apparatus, although with conflicting results (e.g. Weber, 1910; Lowe, 1935).

The second method used by Mosso consisted of recording the pulsations of the human cortex in individuals through the open skull, during mental tasks, by means of a system of pistons. For some time, the study of cerebral circulation within the cranial cavity presented

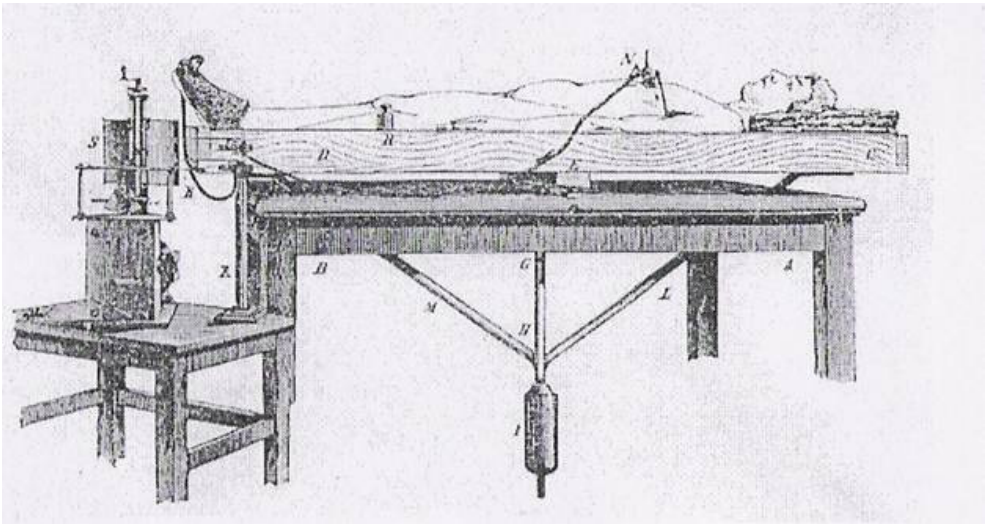

Fig. 2. Mosso's balance apparatus. Source: Mosso (1882).

difficulties due to relative inaccessibility of the brain *in vivo*. Mosso was inspired in his studies by some animals works carried out during the late 18th and early 19th centuries, which were designed to record pulsations of the brain during respiratory changes and modifications in cerebral blood circulation. In particular, he mentioned the work of the Italian physiologist Antonio Ravina, who invented a direct observation through a glass window for recording the change in volume of the cranial content of animal resulting from variations in the amount of blood present within the intracranial vessel (Ravina, 1811). Another researcher to deal with this type of investigation was the Dutch physiologist, Franciscus Cornelius Donders (1818-1889) who conceived the cranial window to observe in animals the ability of *pia mater* vessels to change their caliber in response to various kinds of stimulation (Donders, 1850).

The *Mosso method* consisting of recording simultaneous intracranial pressure changes in humans through a traumatic bone injury in the skull, compared to the pressure to the forearm or foot, to graphically demonstrate, the peculiar cerebral hemodynamic patterns during emotional and cognitive experiences. Hence, his work brought a modern perspective to the study of the central nervous system. Fig. 3 reports Mosso's instruments to analyse pressure changes in man.

The most famous case studied by Mosso was published in 1880. The report, titled, *Sulla circolazione del sangue nel cervello dell'uomo* [On the blood circulation in the human brain] presented the case of Michele Bertino, a 37-year-old farmer who had a large fracture to the skull (Mosso, 1880). The fractured bone pieces were removed and the cerebral mass was exposed through a bone breach measuring about 2 centimeters in diameter in the right frontal region. Intelligence, memory, language, motility and sensitivity all remained almost unchanged. Changes in brain volume related to cerebral blood flow were recorded through a button fixed to the wooden cupola with a sheet of gutta-percha resting on Bertino's exposed dura mater and connected to a screw on the recording drum (see Figure 4).

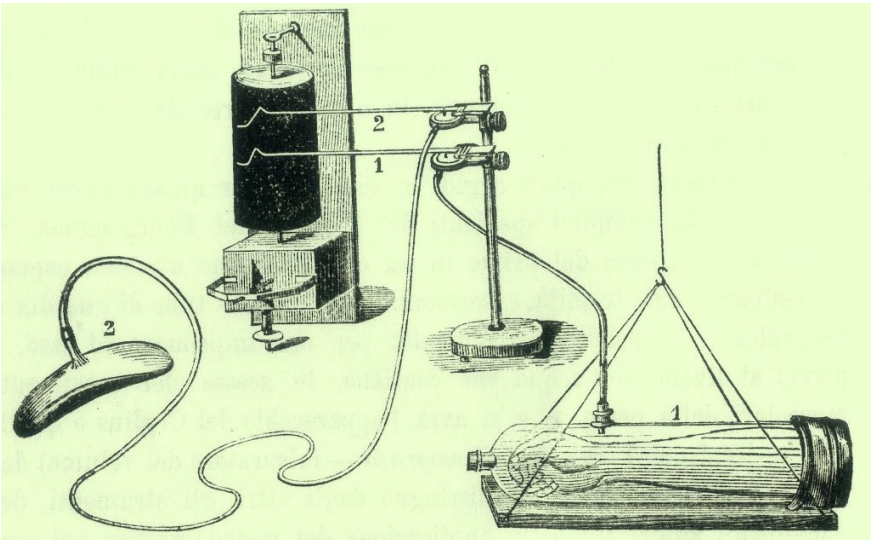

Fig. 3. Mosso's devices for recording the blood volumes in arm and brain.
Source: Patrizi (1896).

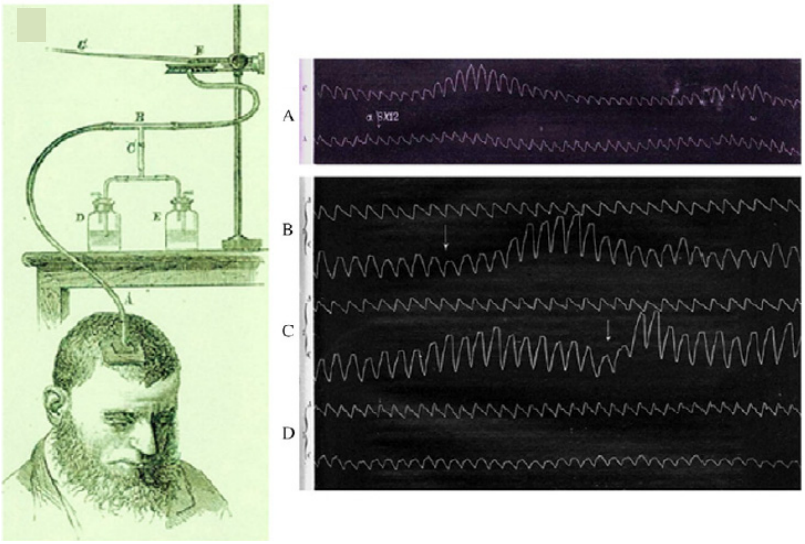

Fig. 4. Brain pulsation recordings when (A) Bertino was requested to multiply 8×12. Top trace is brain pulsation and bottom trace is the forearm pulsation. α: when the question was made, (B) a room clock strikes 12 (arrows). Top trace is forearm pulsation and bottom trace the brain pulsation; (C) Mosso asked (arrows) Bertino if Ave Maria should have been said. Top trace is forearm pulsation and bottom trace the brain pulsation (D) resting state condition. Top trace is the forearm pulsation and bottom trace the brain pulsation. Source: Mosso (1880).

When the brain volume changed, the pulsation of the brain increased, the pressure on the button also increased as did pressure on the screw, thus compressing the air inside the drum. Changes in air compression were trasmitted to a second recording drum, and then written on a rotating cylinder. When Mosso asked Bertino to multiply 8×12, the pulsations increased within a few seconds after the request. Similarly, when Mosso asked him if the chiming of the local church bell reminded him that he had forgotten his midday prayers, Bertino said yes, and his brain pulsated again. Mosso also demonstrated in this patient that the fluctuations in the blood supply to the brain were independent of respiratory changes. In another passage he also tackled the modern issue of the 'resting state' (Gusnard and Raichle, 2001; Morcom and Fletcher, 2007). He wrote: '*Because the brain is an organ that escapes our will why can we not arbitrarily bring it to absolute rest? The variations that the movement of blood in the brain can undergo during wakefulness refer far more often to variations in the energy needed for intellectual work, rather than to a real change in this organ's functions from a state of absolute rest to one of full activity*' (Mosso, 1880).

The work of De Sarlo and Bernardini (1891), who studied the variations of cerebral circulation during mental activity in a 50-year-old farmer, admitted for traumatic epilepsy, is also illustrative of the application of the Mosso's method (De Sarlo and Bernardini, 1891). At the age by 24, F. Carlo, while working in a petrol well was hit by falling rocks causing cranial fracture in the left parietal region. The injury resulted in a more or less triangular shaped opening, measuring between 1.5 cm and 2.5 cm approx. on each side. The posterior side was aligned with the Rolandic fissure. The inner side, parallel to the sagittal line, measured 1.5 cm. The opening was about one centimeter deep. After positioning a specially designed copper helmet of 5 cm in diameter over the cranial breach, using glazier's putty, a funnel-shaped part of the helmet was connected above to a Marey's drum. The cerebral pulse was not evident when the head was held straight, and the patient was asked to rest the bowed head on a special support (see Fig. 5A). Figure 5B shows the outline in different emotional situations.

Mosso's cerebral pulse method was used by numerous experimenters to study changes in the brain blood flow during mental effort, as well as after the administration of drugs (e.g. Fleming, 1877; François-Franck, 1877; Burckhardt, 1881; Mays, 1882; Sciamanna, 1882; Sciamanna and Mingazzini, 1882; Bergesio and Musso, 1884; Morselli and Bordoni-Uffreduzzi, 1884; Musso and Bergesio, 1885; Petrazzani, 1888; Binet and Sollier, 1895; Patrizi, 1896, 1897; Berger, 1901).

Mosso's method was hindered by the technical limitations of his time that precluded him from correlating specific regional changes in brain activity to cognitive and emotional processes. Although present imaging techniques do not use the same principle as Mosso's, his idea of monitoring the cerebral blood flow nonetheless anticipated the main concepts of modern brain imaging tools such as SPECT, PET and fMRI, and could in this sense be considered a precursor to modern functional neuroimaging (Raichle, 2008; Zago, Ferrucci, Marceglia and Priori, 2009).

After only 50 years, a new work on a human being was performed by the American neurosurgeon John Farquhar Fulton (1899-1960), a resident of Cushing in Boston and attendant at the Oxford University with Sherrington, who reported the clinical study of the patient Walter K.. The patient had a gradually decreasing visual disorder caused by a vascular malformation of the occipital lobe. Surgery removal was unsuccessful leaving a bony defect above the primary visual cortex. Walter K. complained that he perceived a noise (i.e. bruit) at the back of his head during visual activity. See Fig. 6.

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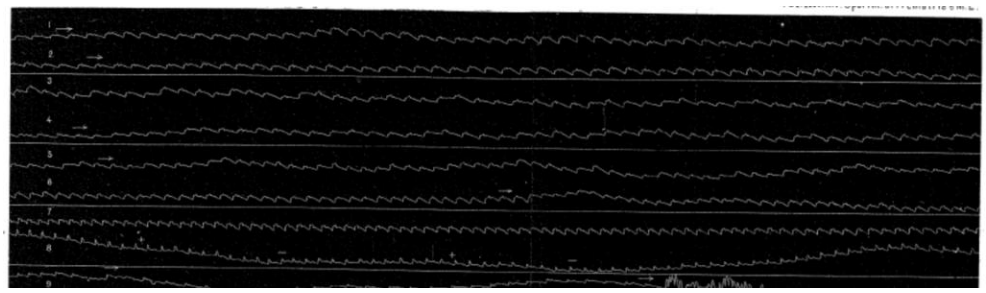

Fig. 5. (A) F. Carlo, the patient studied by De Sarlo and Bernardini (1891). The cranial fracture in the left parietal region is visible. (B). Brain pulsation recordings when: (1) F. Carlo was threatened with a penalty (2) He was promised a prize (3) At the beginning of the trace the subject looked for a focal point on the floor. At half way he found it (attention effort) (4) He was given different images of the Holy Virgin and kissed one of them (5) A nurse entered the room talking excitedly about something terrible that had happened (6) At the beginning of the trace he finds himself in pleasant spirits (he spoke about his return home) (7) He was shown images of scantily dressed women. He became irritate (8) Continued from trace six. Source: De Sarlo and Bernardini (1891).

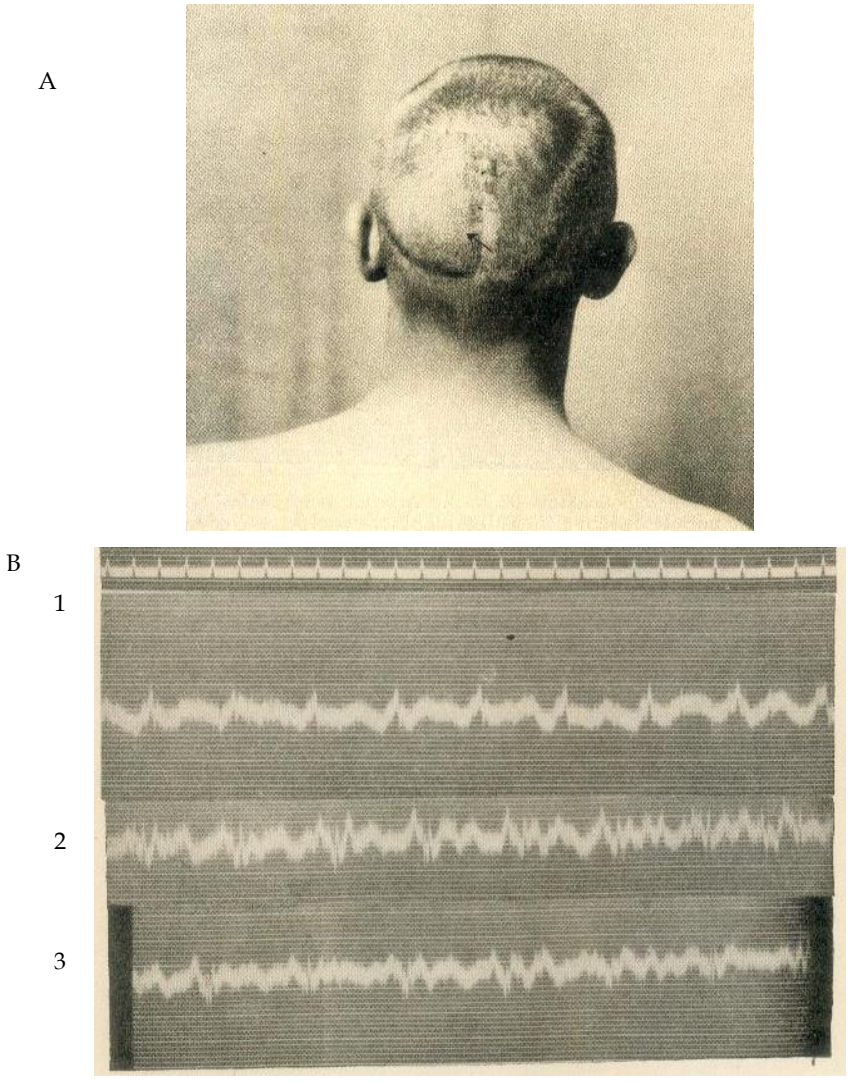

Fig. 6. (A) Walter K, the patient studied by Fulton in 1928. The arrow indicates the point of maximum intensity of the bruit. This overlies the region of greatest vascularity of the angioma. (B) Typical electrophonograms. (1) after ten minutes rest in a darkened room; (2) after two minutes reading small print illuminated by a single 40-watt tungsten bulb at 5 feet; (3) three minutes later, after two and half minutes rest in darkened room. It is evident an increased size of main deflections in b and the greater number of secondary deflections. Source: Fulton (1928).

This disturbance persisted for several years but he had: '. . . *never thought much of it*'. Fulton underlined: '*It was not difficult to convince ourselves that when the patient suddenly began to use his eyes after a prolonged period of rest in a dark room, there was a prompt and noticeable increase in*

the intensity of his bruit. Activity of his other sense organs, moreover, had no effect upon his bruit'. This single case showed that blood flow to the occipital lobe was sensitive to the attention paid to objects in the environment. Fulton elicited a history of a cranial bruit audible to the patient whenever he engaged in a visual task. Remarkably consistent changes in the character of the bruit could be appreciated depending upon the visual activities of the patient (Fulton, 1928).

4. Functional activity, metabolism and blow flow in animal brain

In their seminal animal experimental observation on the cerebral circulation, Charles Smart Roy (1854-1897) and Charles Scott Sherrington (1857-1952), both working in the Cambridge Pathological Laboratory in England, mentioned the 'Mosso method' as one of the main techniques for investigating brain blood flow, however nothing the limitations (Roy and Sherrington, 1890).They remarked that studies with the Mosso apparatus had not '. . . *sufficiently recognized the necessity of taking, simultaneously with the curve from the cranial cavity, graphic records both of the arterial and venous pressures. The influence of changes in these latter where this method is employed, is so great that results obtained without due control of them must, we think, be looked upon as likely to mislead*' (Roy and Sherrington, 1890).

In their work, Roy and Sherrington suggested two distinct mechanisms for the control of the cerebral circulation, one of them acting through the vasomotor nervous system, and another intrinsic one by which the blood supply of various parts of the brain can be varied locally in accordance with regional requirements.

Roy and Sherrington's experiments were applied chiefly on exposed dogs' brains but controlled by repeating them on cats and rabbits using a trepanation near the middle line of the vertex of the cranium. They then registered pressure and blood variation after stimulations by inducing currents through parts of the body. Their experimental conclusion was that: '. . . *the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the caliber of the cerebral vessels: that in this re-action the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity'*. This statement, implying that cerebral functional activity, energy metabolism, and blood flow are closely related, and presumably most responsible for the concept of '*tight coupling*' that has played an important role in recent years.

It was observed that experimental data obtained by Roy and Sherrington were inadequate to support the interrelation between functional activity, metabolism and blood flow, because they hadn't examined any of the relevant processes, energy metabolism and functional activity, but only an indicator of cerebral cortical blood volume rather than cerebral blood flow (Sokoloff, 2001). They believed that cerebral blood flow was regulated mainly by arterial blood pressure and fine-tuned chemical substances in that they affirmed that '*the blood supply of the brain varies directly with blood pressure in the systemic arteries*' (Roy and Sherrington, 1890).

Later in 1914, Joseph Barcroft (1872-1947), at the University of Cambridge, contended that an enhanced functional level in a tissue can be sustained only by increasing the rate at which oxygen is consumed. Blood flow was measured without use of extensive surgery or profound anaesthetic procedures, and its mechanism was based on the autoregulation of the cerebral circulation and the influence of chemical factors. Barcroft supported the association between functional activity and energy metabolism and he wrote: '*There is not instance in*

which it can be proved that an organ increase its activity, under physiological condition without also increasing its demand for oxygen' (Barcroft, 1914).
In the case of the brain interrelation between functional activity, metabolism and blood flow experimental studies on animals by the physiologist Edward Horne Craigie was also of note. He demonstrated that the vascular demand in different parts of the brain parts related to functional activity, and that increases found in localized areas parts due to a major metabolic demand of these regions associated with functional activity (Craigie, 1924).

5. Subsequent investigations: The diffusible indicators for the determination of brain circulation and metabolism in animals and humans

As pointed out by Raichle (2008), despite this promising study interest in brain circulation and metabolism decreased during the first quarter of the 20th century for two main reasons: (1) a lack of sufficiently sophisticated tools to pursue this line of research, and (2) criticism by some influential researchers who concluded that no relationship existed between brain function and brain circulation.
In particular, the work of Leonard Erskine Hill (1866-1952), physiologist and professor of the *Royal College of Surgeons in England*, was very influential on the research that followed. His eminence as physiologist covered the inadequacy of his results and led him to affirm that there was no relationship between brain function and cerebral circulation and resolutely denied the existence of local metabolic regulation. He proclaimed that: '*We have been entirely unable to confirm the result of Roy and Sherrington obtained with acids and have not found the slightest evidence of active dilation of the cerebral vessels . . . In every experimental condition the cerebral circulation passively follows the changes in the general arterial and venous pressures . . . The brain has no vasomotor mechanism . . .*' (Hill, 1896).
Progress in the field of cerebral circulation and metabolism was correlated with technological development. In the early 20th century, measurement methods were confined to indices of brain tissue volume or blood volume and the diameter of retinal or superficial cerebral vessels. Following, thermoelectric instruments such as thermostromuhrs, heated or cooled thermocouples with other devices were inserted into cerebral vessels or tissue.
Subsequent investigators determined that cerebral metabolism and blood flow increased during the normal activation of the specific region when engaged in brain activity. In 1937, Carl Frederik Schmidt (1893-1988) and James P. Hendrix of the *University of Pennsylvania School of Medicine* recorded a localized increase in the blood flow through the visual cortex of a cat when a small spot on the animal's retina was illuminated (Schmidt and Hendrix, 1937). It is now clear that there is local change in nerve-cell activity and metabolic rate that gives a rise in the increasing blood flow in the active region. This discovery gave a suggestion to study brain regional variation in blood flow related to its function. Dumke and Schimdt in 1943 studied, for the first time, the circulation of blood to the brain of an anesthetized rhesus monkey, by means of a flow meter inserted directly into the cerebral arteries (Dumke and Schmidt, 1943).
On this basis, studies followed to apply quantitative in measuring cerebral blood flow associated with cerebral metabolic rates. The turning point was the mid 1940s, in which the American Seymour Kety (1915-2000) and colleagues at the *University of Pennsylvania and National Institutes of Health*, introduced the first technique for measuring whole brain blood flow in unanesthetized humans (Raichle, 2010). In 1944, Kety took part in a meeting of the *Federation of American Societies for Experimental Biology* (FASEB), where there was a symposium on the cerebral circulation. The main theme of the symposium was

measurement methods for cerebral blood flow in unanesthetized men. At that time, there were two non quantitative methods of detection of cerebral blood flow in humans: the thermoelectric probe placed into the internal jugular to detect changes in flow within the vein, and the measurement of cerebral arteriovenous oxygen differences, which varies inversely with changes in cerebral blood flow and consumption of oxygen if it remains constant. Both techniques were unable to distinguish between blood flow and the constant oxygen consumption. The only practicable method for detecting the two parameters: the *bubble-flow technique of Dumke and Schmidt*, required anesthesia in addition to extensive surgery and only ever been tried on monkeys (Dumke and Schmidt, 1943). Kety attended this symposium and explained his idea on the observation rate at which the brain was satured or desatured using an inert gas. The method was based on the venerable '*Fick Principle*' on the conservation of matter (Fick, 1870). According to the principle, cerebral blood flow (volume per unit of mass per unit of time) is related to the time course of the arterovenous difference and to the final tissue concentration of a diffusible trace. Following this, Kety with Schmidt applied the central idea that the amount of an inhaled, highly diffusible, inert gas (*nitrous oxide*) taken up by the brain per unit of time is equal to the amount of that gas brought to the brain by the arterial blood minus the amount carried away in the cerebral venous blood. The subject inhaled 15 percent *nitrous oxide* for ten minutes, during which time the concentration of the gas was followed by drawing samples of arterial and venous blood from the brain. The area between the arterial and the venous saturation curves yielded a measure of the average blood flow, which is normally about 50 milliliters of blood per 100 grams of brain tissue per minute. As pointed out by Kety: *'A method is described applicable to unanesthetized man for the quantitative determination of cerebral blood flow by means of arterial and internal jugular blood concentration of an inert gas . . . human subjects by this method have thus far been made and suggest the feasibility of applying this method to clinical investigations'* .

The first measurements were obtained in a group of young male volunteers, yelding a mean value for blood flow of 54 ml/100 g/min or 750 ml/100 g/min for the whole brain (Kety and Schmidt, 1945, 1948). This indirect, minimally invasive technique, applicable to normally conscious animals and humans, made a great contribution to estimate the overall brain blood flow and metabolic activity of the brain.

With numerous collaborators, Kety's methods was applied in neurology, psychiatry, and medicine leading to greater knowledge of normal physiology, pathophysiology, and pharmacology of the circulation and metabolism of the human brain in healthy and diseased conditions, especially regarding the role of glucose in brain metabolism (Kety, 1950).

In the cat, Kety's team used a soluble gaseous radioactive tracer, fluorinated methane labelled with ^{131}I, and a quantitative application to obtain values for perfusion connected with functional activity in 28 cerebral structures (Landau, Freygang, Rowland, Sokoloff and Kety, 1955). This method used a unique quantitative autoradiographic technique in which the optical densities in autoradiographs of brain sections were quantitatively related to the local tissue concentrations of the radioactive tracer. These concentrations were in turn determined by the rate of blood flow to the tissue. In summary, the method provided pictorial maps of the local rates of blood flow throughout the brain exactly within each of its anatomic structures. This technique was called autoradiography because images were acquired by laying radioactive brain sections directly onto X-ray film (Kety, 1960; Taber, Black and Hurley, 2005). The study included CBF images showing clear changes between a baseline (sedated) and stimulated (awake, restrained) state (see Figure 7).

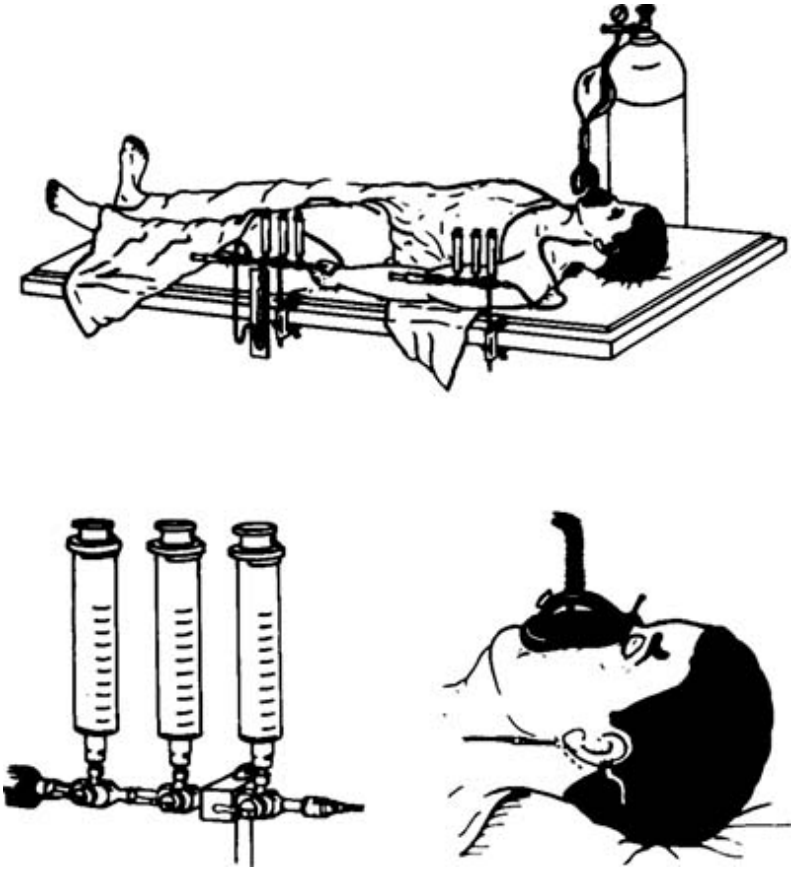

Fig. 7. Whole-brain, inert-gas (nitrous oxide) technique for the measurement of blood flow and metabolism in humans. Source: Kety and Schmidt (1948).

Kety and Sokoloff emphasized that the metabolic homeostasis hypothesis of Roy and Sherrington does not fully explain the increase in cerebral blood flow accompanying increased metabolic activity. Moreover, the association of two events (metabolism and flow) does not prove one (metabolism) to be determinant of the other (flow). Other factors on the coupling between cerebral metabolism and perfusion can describe the concept of perfusion governed by the effects of change in the metabolic rate. Metabolic demands of the cerebral tissue is accompanied by focal neural activation and modification of vessels, which may be mediated by neurotransmitters or the action of drugs on the cerebral circulation (Freygang 1958; Sokoloff, 1959, 1961; Lou, 1987).

These studies were a catalyst for the development of new cerebral blood flow modifications to the original Kety-Schmidt nitrous oxide method. Kety's group continued to refine the measurement of CBF introducing new radiotracers; in particular ^{131}I-antipyrine, ^{14}C-antipyrine, and C-antipyrine, an inert and freely diffusible tracer that had many

advantages over previous diffusible indicators (Kety, 1965; Reivich, Jehle, Sokoloff et al., 1969).

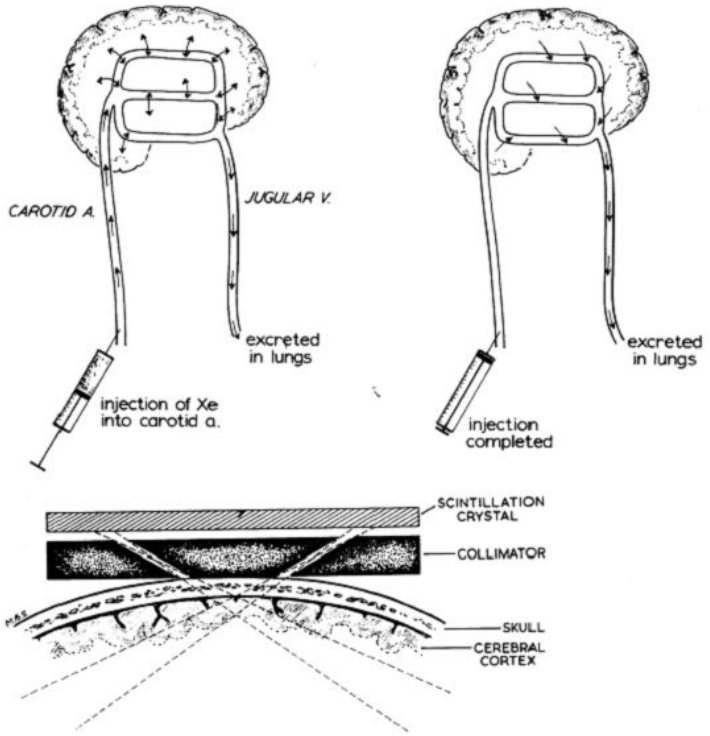

Fig. 8. The rationale of inert gas clearance method with a diagram of simple collimator. Following its injection into the carotid artery, xenon diffuses in a known ratio between the blood and brain tissue. After a sufficiently long injection period the brain tissue and venous blood will be in equilibrium. On cessation of the injection the carotid arterial blood, now containing virtually no radioactive xenon, will wash out the xenon in the brain tissue and the rate at which this takes place will depend on the quantity of blood perfusing the brain. Source: Harper, Glass, Steven and Granat (1964).

Lassen and Munck (1955) modified the classical Kety-Schmidt technique by substituting the inhalation of a radioactive inert gas, the ^{85}Kr, in place of nitrous oxide (see also Lassen, Munck and Tottey, 1957). In the early 1960s, thanks to the studies with radioactive tracers by Niels Alexander Lassen (1926-1997), David Henschen Ingvar (1924-2000) and their Scandinavian colleagues, it was becoming possible to measure local blood flow in the cerebral cortex. Lassen and Ingvar, injected a radioactive isotopes into the internal carotid artery (^{85}Kr), measuring the rate of clearance from the underlying cortex of the beta emissions of the isotope (Lassen and Ingvar, 1961; Ingvar and Lassen, 1961, 1962).
(Lassen and Edt-Rasmussen, 1966). Another report described the measurement of regional blood flow evoked by brain activity in the cerebral cortex of man through intact skull monitoring the low incidence gamma emissions of ^{85}Kr using scintillation detectors arrayed

like a helmet over the head (Lassen, Høedt-Rasmussen, Sørensen, Skinhøj, Cronquist, Bodforss and Ingvar, 1963). The use of collimated scintillation detectors allowed blood flow measurement in small neural populations of the cortex. Sveinsdottir and Lassen (1973) calculated that a regional blood flow was simultaneously measured in about 256 regions of a hemisphere. This application signalled the dawn of the modern era in human brain imaging. The rationale of inert gas clearance methods with a diagram of simple collimator is illustrated in Figure 8 as reported by Harper, Glass, Steven and Granat (1964).

The method devised by Lassen and Ingvar was suitable for clinical use, following the injection of ^{133}Xe, a radioactive tracers originally introduced by the group of *University of Glasgow* headed by Glass and Harper (Glass and Harper, 1963; Harper, Glass, Steven and Granat, 1964).

Some years after, Lassen, Ingvar and Skinhøj, wrote about their application: '*The radioactive gas was dissolved in a sterile saline solution, and a small volume (two to three milliliters, containing from three to five millicuries of radioactivity) is injected as a bolus into one of the main arteries to the brain. The arrival and subsequent washout of the radioactivity from many brain regions is followed for one minute with a gamma-ray camera consisting of a battery of 254 externally placed scintillation detectors, each of which is collimated to scan approximately one square centimetre of brain surface. Information from the detectors is processed by a small digital computer and is displayed in graphical form on a colour-television monitor, with each flow level being assigned a different colour or hue. Owing to the attenuation of radiation from structure deeper in the brain, the gamma radiation detected comes from the superficial cortex. Thus the radioactive-xenon technique provides a fairly specific picture of the activity of the cerebral cortex directly below the detector array*' (Lassen, Ingvar and Skinhøj, 1978).

The ^{133}Xe tecnique has been extensively and very effectively used as a clinical and research tool for several decades (Glass and Harper, 1963; Lassen and Ingvar, 1963; Ingvar, Cronqvuist, Ekber, Risberg and Høedt-Rasmussen, 1965; Høedt-Rasmussen, Sveindottir and Ingvar, 1966; Ingvar and Risberg, 1967; Olesen, Paulson and Lassen, 1971; Ingvar and Lassen, 1973; Ingvar and Schwartz, 1974; Ingvar and Franzen, 1974; Soh, Larsen, Skinhøj and Lassen, 1978; Lassen, 1985). The Figure 10 adapted by Lassen and Ingvar (1972) illustrates their apparatus to detect rCBF changes and the results in a normal male adult using ^{133}Xe at rest and during a mental task.

Early techniques such as ^{133}Xe inhalation provided the first blood flow maps of the brain as they able to demonstrate directly in normal human change of blood flow within discrete parts of the cerebral cortex during mental activation. The first study on induced variation of brain blood circulation using this method was reported by Ingvar and Risberg in 1965 at the first *International Meeting on the Brain Blood Metabolism*, held in Lund. This research was received with caution because of its potential importance regarding human studies of regional change in blood flow using these techniques in normal humans and in conditions with neurological disorders.

6. The origin of new functional imaging techniques: PET, SPECT and fMRI

The introduction of an *in vivo* tissue autoradiographic measurement of blood flow in laboratory animals by Kety's group many years later became important for the measurement of blood flow in humans when positron emission tomography (PET) provided a means of quantifying the spatial distribution of radiotracers in tissue without the need for invasive autoradiography (Kety, 1999).

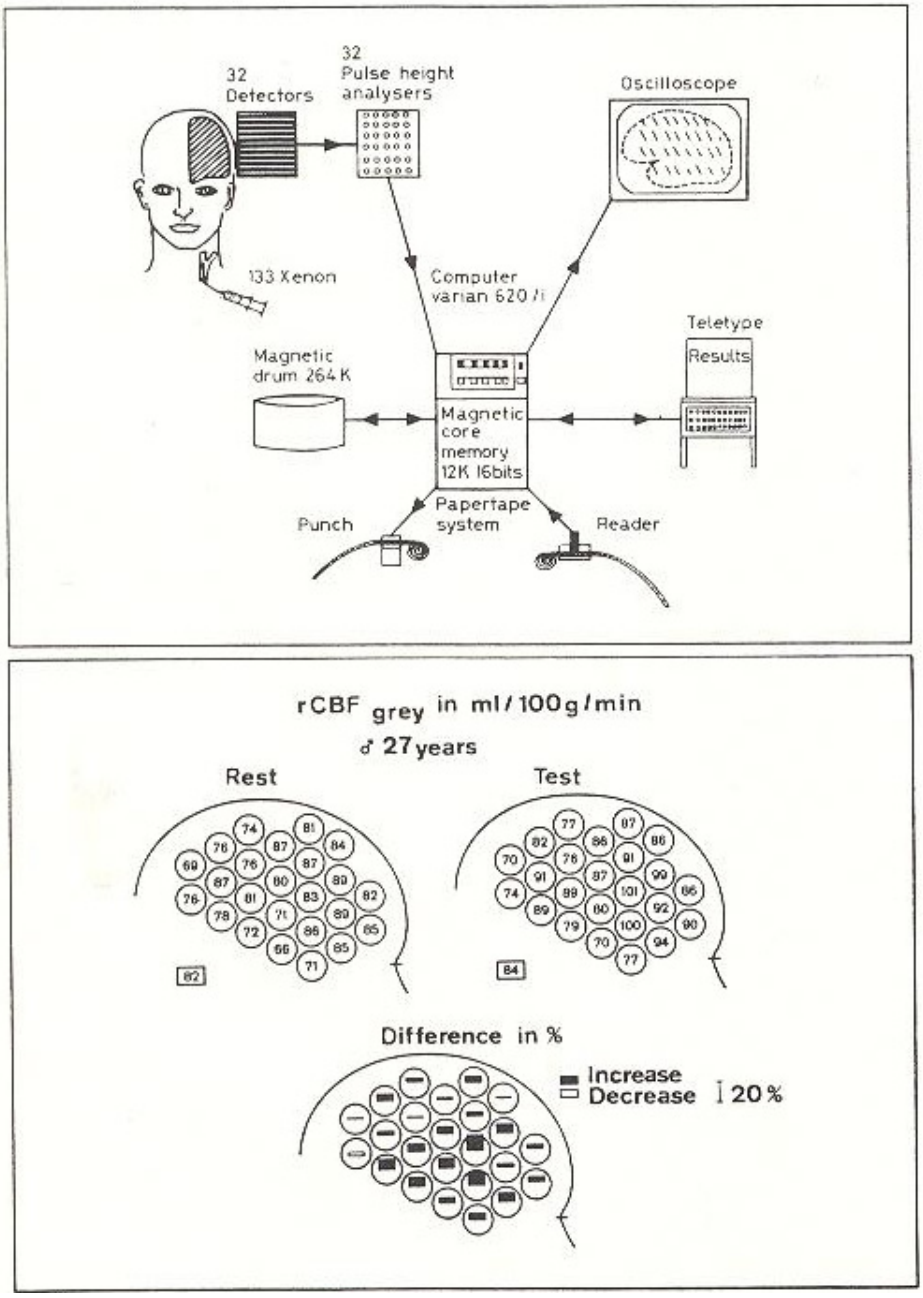

Fig. 9. Regional cerebral blood flow estimated from counts of arterially xenon-133 in a normal male adult at rest and during a mental task. Areas of large blood flow increase were found in temporal and precentral regions of gray matter. Source: Lassen and Ingvar, (1972).

PET, based on the decay of radioactive atoms that release positrons, derives its name and its fundamental properties from a group of radionuclides (^{15}O, ^{11}C, ^{18}F and ^{13}N). The properties of these radionuclides include short half-lives, a unique decay scheme involving the emission of positrons and chemical properties whose relevance to studies in biology and medicine arises from the fact that these chemical elements are building blocks of most biological molecules (Raichle, 2010).

The concept of emission and transmission tomography was introduced in the late 1950s by the American physic David Edmund Kuhl, who has been called the father of emission tomography. In the early 1960s, with the collaboration of Roy Edwards, Kuhl designed and made a detector which scanned in a series of tangential traverses, rotating about the patient on a circular path between scan passes. Their work later led to the design and construction of several tomographic instruments (Kuhl and Edwards, 1963). At the *University of Pennsylvania in Philadelphia*, Kuhl headed a group that developed a series of SPECT (single photon emission computed tomography) devices, the Mark II in 1964, the Mark III in 1970 and the Mark IV in 1976. The group also advanced the medical use of tomographic image reconstruction based on numerical computation, and made the transaxial section tomography of a living body possible. In the mid-1960s, Kuhl and collaborators, who improved tomographic image quality, proved their clinical efficacy for image separation pathological conditions of the brain and succeeded in the axial transverse tomographic imaging of humans. One such important milestone was the introduction of a new instrument: X-ray computed tomography (CT), that had enormous impact on the development and evolution of various methods of computed tomography, including PET (Kuhl, Hale and Eaton, 1966).

The CT method was invented by a British electronic engineer Godfrey Newbold Hounsfield (1919-2004), at the *Atkinson Morley Hospital* in London, who in 1971 built an instrument that combined an X-ray machine and a computer and used certain principles of algebraic reconstruction to scan the body (Hounsfield, 1973). Unknown to Hounsfield, the American nuclear physicist Allan MacLeod Cormack (1924-1998) had published essentially the same idea in 1963 (Cormack, 1963), using a reconstruction technique called the *Radon transform*. Although Cormack's work was not widely circulated, in 1979 he and Hounsfield shared the Nobel prize in Medicine and Physiology for the development of CT (www-Nobelprize.org). In creating CT, Hounsfield had arrived at a practical solution to the problem of the three-dimensional transaxial tomographic images of an intact object using data obtained from by passing highly focused X-ray beams through the object and recording their attenuation. Hounsfield's invention was fundamental in changing the approach for observing the human brain.

During the mid-1970s, at the *Washington University School of Medicine in St. Louis*, the Armenian-American physic Michel Ter-Pogossian (1925-1996) lead a research team of physicists scientist, chemists, and physicians to build the first PET scanner for medical application. Previously, Ter-Pogossian performed a quantitative measurement of regional brain blood flow and oxygen consumption in humans using a radiotracer technique developed by him (Ter-Pogossian et al. 1969, 1970). A fundamental role was played by Ed Hoffman and Michael E Phelps which led to the production of the first PET camera, PET III (Ter-Pogossian, Phelps and Hoffman, 1975; Phelps, Hoffman, Mullani and Ter-Pogossian, 1975; Phelps, Hoffman, Mullani, Higgins, Ter-Pogossian, 1976; Hoffman, Phelps, Mullani,

Higgins and Ter-Pogossian, 1976). As pointed by Raichle (2010): *'With PET, we had a tool that brought quantitative tissue autoradiography from the laboratory into the clinic. Such things as brain blood flow, blood volume, oxygen consumption, and glucose utilization, not to mention tissue pH and receptors pharmacology, could now be measured safely in humans'*.

At approximately the same time of the Kulh's and Ter-Pogossian's studies, at the *Laboratory of Cerebral Metabolism at the National Institutes of Health in Bethesda*, Sokoloff and colleagues, directly disclosed, in the brain of experimental animals (rats and monkeys), cerebral utilization of an energy-rich substrate, 2-deoxyglucose tagged with carbon-14 (Sokoloff, Reivich, Kennedy, Des Rosiers, Patlak, Pettigrew, Sakurada and Shinohara, 1977). Sokoloff and colleagues studied cerebral metabolism on a microscopic scale by injecting a radioactive analogue of glucose into the brain demonstrating that the rate at which the substance is taken up by nerve cells reflects their functional activity. The brain's oxygen consumption is almost entirely determined by the oxidative metabolism of glucose which in normal physiological conditions is the exclusive substrate for the brain's energy metabolism (Clarke and Sokoloff, 1999).

Aiming to employ the [^{14} C] deoxyglucose technique clinically, Kuhl's team conducted joint research with Alfred P Wolf of the *Brookhaven National Laboratory* and with Sokoloff's group, ultimately reaching the conclusion that ^{18}F-2-fluoro-2-deoxy-D-glucose or 'FDG' was the most appropriate positron emitting tracer for human use (Ido, Wan, Casella, Fowler, Wolf, Reivich and Kuhl, 1978; Reivich, Kuhl, Wolf, Greenberg, Phelps, Ido, Casella Fowler, Hoffman, Alavi and Sokoloff, 1979; Phelps, Huang, Hoffman, Selin, Sokoloff and Kuhl, 1979).

The development of the [^{14}C] deoxyglucose method made it possible to measure the local rate of glucose utilization throughout the brain. The method employed a quantitative autoradiographic technique like that of the [^{131}I] trifluoroiodomethane method but, subsequently, added computerized processing techniques which scanned the autoradiographs and redisplayed them in colour with the actual rate of glucose utilization encoded in a calibrated colour scale. This was the first use of the deoxyglucose technique for the regional measurement of glucose metabolism in laboratory animals and the basis for an application for clinical purpose (Sokoloff, Reivich, Kennedy, Des Rosiers, Patlak, Pettigrew, Sakurada and Shinohara, 1977). These [^{131}I] trifluoroiodomethane and [^{14} C] deoxyglucose methods were used to measure local cerebral blood flow and glucose utilization in studies in animals. Both methods were subsequently were adapted for use in humans by substituting positron-emitting tracers and PET in place of autoradiography: [^{18}F] fluorodeoxyglucose in place of [^{14} C] deoxyglucose to measure glucose utilization (Raichle, Phelps, Larson, Grubb, Welch and Ter-Pogossian, 1973; Reivich, Kuhl, Wolf, Greenberg, Phelps, Ido, Casella Fowler, Hoffman, Alavi and Sokoloff, 1979; Phelps, Huang, Hoffman, Selin, Sokoloff and Kuhl, 1979) and $^{15}H_20$ instead [^{131}I] trifluoroiodomethane to measure blood flow (Herscovitch, Markham and Raichle, 1983).

PET method has had some advantage, such as: the blood flow was measured quickly (<1 min) by using an easily produced radiopharmaceutical ($^{15}H_20$) with a short half life (123 sec) that allowed many repeat measurements in the same subject. However, PET present some disadvantages: few spatial resolution than the autoradiography methods, in the mm instead of µm range; they contributed very little to define mechanisms that relate blood flow and energy metabolism to functional activity in the brain, their application did initiate and establish the field of functional brain imaging in humans (Sokoloff, 2008).

Raichle and his colleagues, at the *Mallinckrodt Institute of Radiology of the Washington University of St Louis*, used PET technology to measure cerebral blood volume (CBV) in normal right-handed human volunteers following inhalation of trace quantities of cyclotron-produced, ^{11}C-labeled carbon monoxide. The CBV was significantlylarger in the temporal left cerebral hemisphere in the tomographic scans during speech, a region which is thought to be larger in individuals with left cerebral dominance for speech. As pointed out the authors: *'This observation is the first in vivo demonstration of a structural correlate of a known functional difference in the cerebral hemispheres of man'* (Grubb, Raichle, Higgins, Eichling, 1978).

In the 1980s, Raichle and colleagues systematically applied PET technique to the normal human brain, using oxygen-15 labelled water and to demonstrate regional metabolic activation induced by cognitive tasks. The labelled water, which emits positrons as it decays with a half-life of approximately two minutes, accumulates in the brain in less than a minute, forming an accurate image of blood flow. In a series of original works Raichle and colleagues firstly studied the manner in which the normal human brain processes single words, from perception to speech (Raichle, 1996) (see. Fig. 10).

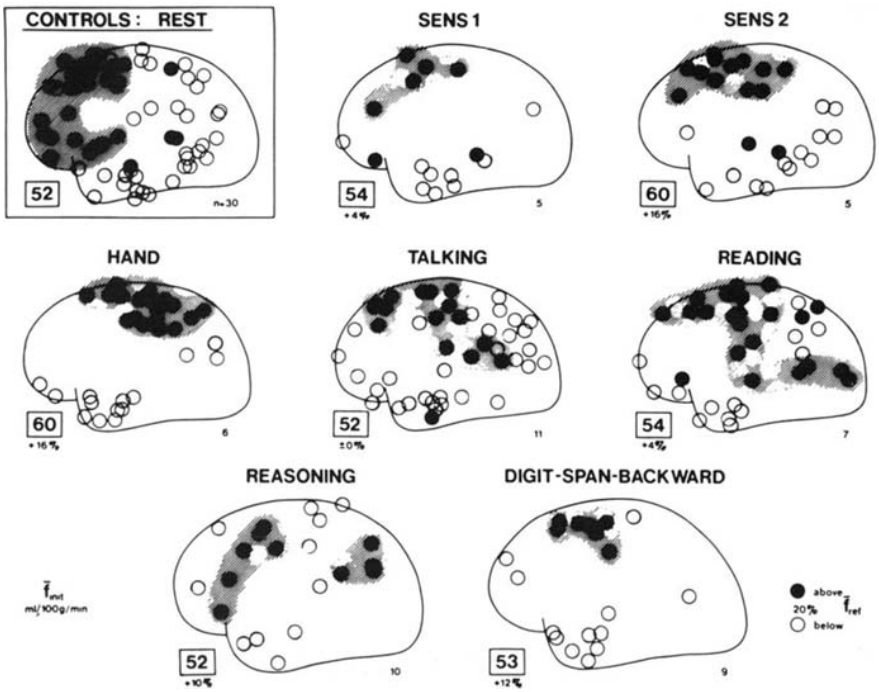

Fig. 10. Four different hierarchically organized conditions are represented in these mean blood flow difference images obtained with PET. All of the changes shown in these images represent increases over the control state for each task. Source: Raichle (1996).

This approach was not embraced by most neuroscientists or cognitive scientists until the 1980s after increase of technological, procedural and conceptual sophistication at the beginning of the 20th century (Raichle, 1987; 1998; 2008).

The advent of the nuclear magnetic resonance imaging (MRI) introduced a new and now the most convenient and widely used technique for functional brain imaging (fMRI) in both animals and humans. It is based on the physical property of atomic nuclei that, when first oriented in an magnetic field and then reoriented by radiofrequency pulses, emit during their return to their chemical species, concentrations, and environments. The strongest signals are those obtained from hydrogen nuclei because they are in water and thus prevalent.

The physical principles associated with MRI were discovered independently by the Swiss-American Felix Bloch (1905-1983), at *Stanford University*, and the American Edward Mills Purcell (1912-1997), at *Harvard University*. In December 1945, at the American Physical Society, they met and discussed their research. Both recognized that the theoretical basis of their respective projects was the same, although they had been using slightly different techniques to achieve experimental results. So they decided to split up the field: Bloch would use the effect in the study of liquids; Purcell would examine crystals. The Stanford group gathered its first positive results in January 1946 (Bloch, Hansen and Packard, 1946; Purcell, Torrey and Pound, 1946). In 1952, Bloch and Purcell were awarded the Nobel Prize for Physics for the 'development of new methods for nuclear magnetic precision measurements and discoveries in connection therewith' (Nobelprize.org). Many years of research followed, in which the technique was used for basic research in chemistry. During this time it was known as nuclear magnetic resonance (NMR).

In 1973, the American-chemist Paul C Lauterbur (1929-2007) came up with a strategy in which the NMR signals could be used to create cross-sectional images in much the same manner as a CT (Lauterbur, 1973). In 2003, he was awarded with the Nobel Prize in Medicine along with the British physicist Peter Mansfield for their research on NMR. Mansfield is credited with showing how the radio signals from MRI can be mathematically analyzed, making interpretation of the signals into a useful image a possibility. He is also credited with discovering how fast imaging was possible by developing the MRI protocol called echo-planar imaging. Echo-planar imaging allows T2* weighted images to be collected many times faster than previously possible. It has also made functional magnetic resonance imaging (fMRI) feasible (Mansfield and Baines 1976). This method had an immediate use because the technique was free of ionizing radiation, but also for the quality of images of the human body with detailed information, when compared to CT it proved more sensitive to soft tissue. An opening for MRI in the area of functional brain imaging emerged when it was discovered that during changes in neuronal activity there are local changes in the amount of oxygen in the tissue (Fox and Raichle, 1986). By combining the above observation with another much earlier one by Linus Pauling (1901-1994) and Charles D Coryell (1912-1971) it was shown that change in the amount of oxygen carried by the hemoglobin alters the degree to which hemoglobin disturbs a magnetic field (Pauling and Coryell 1936).

It was Michael Faraday (1791-1867) who first studied the magnetic properties of hemoglobin. In 1845, he noted (to his surprise that hemoglobin contains iron) that dried blood was not magnetic, noting '*Must try fluid blood*' (Faraday, 1933). Many years later Pauling and Coryell found that the magnetic susceptibility of oxygenated and deoxygenated hemoglobin differed significantly. In 1982, Keith Thulborn and collaborators found the difference in magnetic susceptibility of oxy and deoxyhemoglobin for the measurement of brain oxygen consumption with MRI (Thulborn, Waterton, Matthews and Radda, 1982).

They demonstrated clearly the feasibility of measuring the state of oxygenation of blood *in vivo* with MRI. This step was important for the further study of Sieji Ogawa and colleagues for the so-called Blood-Oxygen-Level Dependent (BOLD) effect. The physical effect is based on the difference between reduced hemoglobin in venous blood, paramagnetic, and oxyhemoglobin prevalent in the arterial blood is diamagnetic and has no such effect. During the oxygen consumption from the blood by the tissue, the venous system draining the tissue within the field of view, contains more oxyhemoglobin and less in deoxthemoglobin. This leads to a small increase in the MRI signal, i.e.: the BOLD effect. Owaga labeled his finding 'BOLD contrast' and noted that BOLD contrast adds an additional feature to MRI and complements other techniques that are attempt to provide PET-like measurements related to regional neural activity (Ogawa, Lee, Kay and Tank, 1990). The potential for BOLD fMRI was seen in three groups in 1992 (Ogawa, Tank, Menon et al 1992, Kwong, Belliveau, Chesler et al., 1992, Bandettini, Wong, Hinks et al, 1992), in especially from the group at the *Massachuttes General Hospital* led by Ken Kwong. Although MRI also offers additional approaches to the measurement of brain function, it is BOLD imaging that has dominated the research agenda to date.

fMRI is the new non-invasive imaging tool for its remarkable high quality and it is considered by Raichle a tool for the 'masses' (Raichle, 2010). fMRI could be viewed as a logical extension of PET although fMRI can acquire images every few seconds and secondly is the neuronal responses occurring in the brain are 'filtered' by a hemodynamic response, which is responsible for the fMRI signals that can give the most powerful strategies for neurocognitive studies. According to Raichle, the future in functional brain imaging research has two developmental routes. The first is the research on individual differences improving the functional imaging in the clinical area. The combination of anatomical and functional imaging with genetic information opens new areas of research on the human brain in healthy and pathological conditions (Raichle, 2010). The second is an attempt to integrate work from functional brain imaging with neurophysiology in relation to various kinds of intrinsic rhythmic activity of the brain (Buzsaki, 2006).

However, the success of human brain imaging was not only the involvement of physiologists, who provided information on basic mechanism of neuronal activity, but also of different figures such as neurologists, neuropsychologists, psychiatrists who had the strategies and influence to provide an important tool in the understanding of '*how the mind works*' in normal and pathological conditions.

The scope of brain function imaging in future is to study the brain without requiring the subject to remain in a scanner approaching the organization of intrinsic activity of the neuronal cells in normal functional activity not only to addresses a specific feature of its activity. Another important step is to achieve rapidly changing electrical events instead of changes in slow activity of the brain's intrinsic work after an '*environmental stimuli* '. A possible anticipatory signal that could prevent negative behavior neural activity of latent brain diseases.

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