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Review

The coupling controversy

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ABSTRACT

Functional magnetic resonance imaging (fMRI) relies on the well-known phenomenon of coupling between neuronal activity and brain blood flow. For nearly a century, the presumption was that hemodynamics were coupled to neuronal activity via energy demand and oxidative metabolism. Early ^{15}O positron-emission tomographic (PET) studies challenged this theory, demonstrating a physiological "uncoupling" between brain blood flow and oxygen metabolism. These PET observations played a pivotal role in guiding the development of fMRI, by demonstrating which physiological parameters were most closely coupled to neuronal activity and by presaging the BOLD-contrast effect. Subsequent PET studies were crucial for constraining theories concerning the physiological mechanisms underlying hemodynamic/neuronal coupling and, thereby, guiding the development of models for quantification of oxygen metabolic rate %Δ from fMRI. A first-person account of the PET "coupling" studies and their influence on the development of fMRI is provided.

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Introduction

The need for a rigorous reassessment of the ninety-year old, nearly universally accepted hypothesis of Roy and Sherrington (Roy and Sherrington, 1890) – that focal, stimulus-induced increases in brain blood flow are driven by local metabolic demand – was apparent to me by the Spring of 1982. Doing background reading in preparation for what was to be my first series of functional activation experiments, I was struck by the paucity of evidence establishing a chain of causality linking focal, physiological increases in neuronal activity with increases in regional cerebral blood flow (CBF.) Nevertheless, in the pre-PET functional brain mapping literature, the standard practice was to assert that increased neuronal activity was energetically expensive and caused increased metabolic demand that, in turn, up-regulated blood flow (e.g. Roland and Larsen, 1976; Roland et al., 1980). While this was certainly a plausible scenario, it was far from rigorously demonstrated. When I broached this striking lack of evidence for such a widely held belief with Marcus Raichle, my mentor, he agreed, and strongly encouraged me to pursue the issue experimentally.

The prospect of using ^{15}O tracers and PET for functional brain mapping had brought me to Washington University for a neurology residency in 1980. I majored in liberal arts and philosophy at St. Johns College in Annapolis, focusing my studies on the evolution of epistemology (i.e., the nature of scientific knowledge) from Aristotle to

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Descartes to Kant. When I applied to medical school, my vision was an academic career studying the neural bases of cognition. As a medical student at Georgetown University, I was fascinated by studies using ^{133}Xe, single-photon imaging to map language, reasoning, memory and other high-order brain functions (e.g. Larsen et al., 1978; Risberg and Ingvar, 1973; Roland and Larsen, 1976). Guided by my medical school mentor, neurologist Stanley Cohen, I was aware that Michel Ter-Pogossian, Chief of the Radiation Sciences Division at the Mallinckrodt Institute in Saint Louis, was well along in the process of implementing ^{15}O-based methods for PET measurements of brain hemodynamics and metabolism. Ter-Pogossian had sited the first cyclotron in a medical institution, designed and built the first PET scanners, and selected ^{15}O as the molecular centerpiece of his laboratory. Marcus Raichle had been recruited into this team because of his experience in cerebral oxygen metabolism, gained both through studies of cerebral autoregulation as a resident at Cornel University and studies of high-altitude physiology, as a neurologist at Brooks Air Force base. In my residency interview, Raichle confirmed that Cohen's information was correct and that, if I wished, I could have access to this laboratory for human brain mapping studies. The Chair of Neurology, William Landau, endorsed this plan, indicating that I could use my elective rotations for research and could have additional post-graduate years funded under his NINDS T32 grant until I obtained my own funding. This convinced me. I arrived in Saint Louis in July, 1980 to start neurology residency.

The CBF stimulus-rate experiments

Putting my long-term goal of mapping cognitive operations on temporary hold, I focused on the issue of neural-vascular coupling. An ideal experiment to explore the causal link between neuronal activity, metabolic rate and blood would simultaneously measure oxygen metabolism, glucose metabolism, and blood flow over a range of neural response intensities. In 1982, however, this wasn't a possibility. Glucose measurements using ^{18}FDG were being carried out at a handful of institutions, but this synthesis hadn't been implemented at Washington University. Oxygen metabolic rate ($CMRO_2$) measurements had been implemented several years earlier, using carotid injection of ^{15}OO-labeled blood (Raichle et al., 1976), but were deemed too invasive to continue. $H_2^{15}O$ CBF measurements were, however, in advanced stages of development and validation (Herscovitch and Raichle, 1983; Herscovitch et al., 1983). So, $H_2^{15}O$ CBF measurements were the place to start.

The next decision points were to select a stimulus modality and develop an experimental design. In the course of an electroencephalography rotation, I came across a pre-market advertising brochure from Grass instruments for a new visual-stimulation system (S10-VS), which consisted of a set of swimming goggles into which circuit boards holding an array of light-emitting diodes had been placed. The system delivered full-field flashes of fixed wavelength, luminance and duration over a range of frequencies from 1 Hz to 128 Hz. Knowing that the time for full recovery of the visual-evoked potential (VEP) was in the range of 125 ms and that $H_2^{15}O$ PET measures integrated over a period of 40 s, I reasoned that the CBF response should be linear at least up to a repetition rate of 8 Hz. While not providing insight into the physiological cascade producing the CBF response, at least this experiment would test whether there was a one-to-one relationship between a measure of neural response magnitude (i.e., the number of VEP's elicited during the scanning interval) and the hemodynamic response magnitude. I presented this experimental design to Marcus Raichle, who agreed that it was feasible and would be an important contribution.

Moving forward with this plan, the first obstacle we encountered was trying to obtain a set of the Grass goggles. The S10-VS, it turned out, was not yet available for purchase. The local company representative told me we would simply have to wait until they went into production. This posed a significant problem for me, as my research

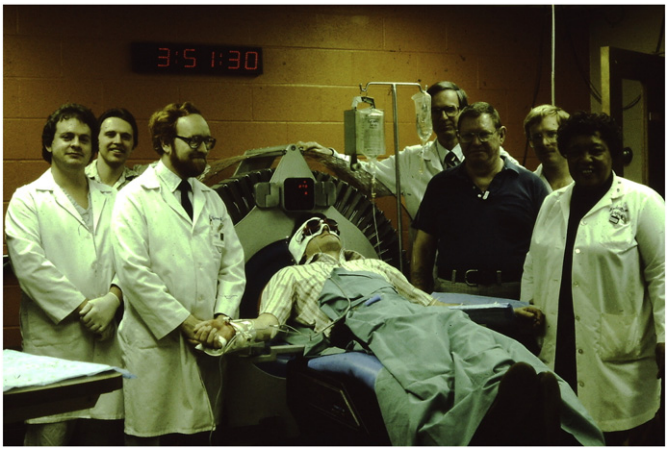

Fig. 1. The team performing the visual-stimulation, rate-response pilot study is shown. The author (PTF) is in the scanning chair, wearing the Grass S10-VS goggles mounted over the eye-holes of a thermoplastic mask, used for head restraint. A radial arterial catheter is placed in the right wrist and an intravenous catheter is placed in the left anti-cubital fossa. Peter Herscovitch is third from the left. Marcus Raichle is fourth from the right. The scanner is a PETT VI, manufactured by PETT Electronics, a spin-off company created by M. Ter-Pogossian.

elective time was already scheduled. Lacking other options, I wrote directly to Mary Grass, the Grass CEO at the time. I explained my circumstances and requested a pre-release version of the goggles. They came by return mail, with no invoice. A gift from Mrs. Grass. This gift, as it turned out, would be put to extraordinarily good use.

I started a 6-month elective block in my 3rd year of residency in January, 1983. Feeling an obligation to be thoroughly versed in all aspects of the PET procedures before recruiting volunteers, I performed my first experimental session on myself (Fig. 1). As the rate-response experiments were intended to test a hypothesis about hemodynamic physiology, we performed them in a fully quantitative manner. This implied having arterial access, to obtain a time-activity curve of blood tracer concentration. For my self-study, Marcus Raichle placed the arterial and venous catheters. The technicians put on the face mask, placed the Grass goggles over the eye-holes and adjusted the stimulus rates according to my instructions. Peter Herscovitch oversaw the data acquisition.

My self-experiment worked as well as I could have hoped. Robust, well-localized, rate-graded CBF responses were present in visual cortex (Fig. 2). Confident in the procedures, I performed the same

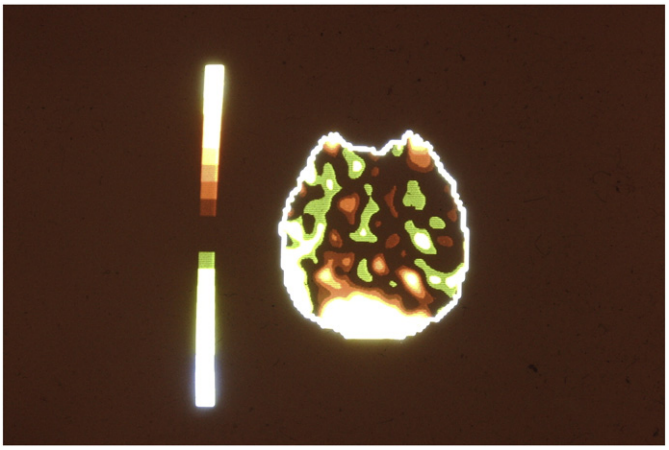

Fig. 2. The image is CBF %Δ (8 Hz stimulation minus rest) in an axial plane passing through the visual cortex of the author (PTF), obtained during the scanning session shown in Fig. 1. The response produced by the Grass goggles was readily apparent even in a single image frame (40 s) in a single subject.