Functional Neuroimaging:

Where does it come from,

Where is it going

A review of Marcus Raichle's "*Functional Neuroimaging: A Historical and Physiological Perspective*"[1]

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Functional Neuroimaging

- 4 Main Imaging Techniques:
  - PET (positron emission tomography)
  - MRI (magnetic resonance imaging)
  - EEG (electroencephalography)
  - MEG (magnetoencephalography)

- 3 Main Neurophysiological Variables:
  - Blood Flow
  - Glucose Utilization
  - Oxygen Consumption

- Objective: to further our understanding of brain function

Key Issues

- What is the relationship between neural activity in the brain and the underlying physiology?
- How does neural activity affect blood flow, glucose utilization, and oxygen consumption?
- How are neuroimaging techniques used to observe cognitive processes?

Early Observations of Brain Circulation

- Paul Broca[2], 1861 – studied the effects of various mental activities, especially language, on the localized temperature of the scalp.

- Angelo Mosso[3], 1881 – recording the pulsation of the human cortex in patients with skull defects, showed that these pulsations increased regionally. Mosso concluded that brain circulation changes selectively with neuronal activity.

- Roy and Sherrington[4], 1890 – conducted animal experiments that suggest a link between brain circulation and metabolism.

- Leonard Hill[5], 1896 – an eminent physiologist, concluded that no relationship exists between brain function and brain circulation.

Neurophysiology Revived

- John Fulton[6], 1928 – reported that cortical blood flow changes according to the complexity of the visual task and the attention of the subject to that task.
- Kety et al[7,8], 1955 – Kety and colleagues developed the first quantitative methods for measuring whole brain blood flow and metabolism in humans.
- Ingvar & Risberg[9], 1965 – demonstrated directly in normal human subjects that blood flow changes regionally during changes in brain activity.

The Emergence of Neuroimaging Technology

- In 1936, Pauling and Coryell[10] observed that changing the amount of oxygen carried by hemoglobin changes the degree to which hemoglobin disturbs a magnetic field.
- In 1946, the physical principles of nuclear magnetic resonance (NMR) were discovered independently by Felix Block[11] and Edward Purcell and his colleagues[12]. These principles governing the behavior of protons in a magnetic field would lead to MR technologies.
- In 1973, Paul Lauterbur[13] expanded NMR principles to be utilized for imaging, thus introducing magnetic resonance imaging (MRI). Initially, MRI provided valuable anatomical information, and would not be for functional brain imaging until 1990.
- Also in 1973, Godfrey Hounsfield[14] introduced X-ray computed tomography (CT).
- By 1975, Positron Emission Tomography (PET) was derived from CT[15]. It was realized that highly accurate measurements of human brain function could be made with measurements of either blood flow or metabolism. Blood flow became the favored technique because it could be measured quickly (< 1 min) using $H_2{}^{15}O$, allowing for many repeat measurements in the same subject.
- In 1986, it was discovered that there are local changes in the amount of oxygen in the tissue during changes in neuronal activity[16,17]. This discovery, combined with Pauling and Coryell's discovery about oxygenated hemoglobin in 1936, allowed for the development of functional MRI (fMRI) by Ogawa and colleagues in 1990.
- In 1990, Ogawa et al.[18] demonstrated that in vivo, localized changes in blood oxygenation could be detected by MRI. This MRI signal, known as T2*, became known as the blood oxygen level dependent (BOLD) signal.

What's the point

- How can these imaging technologies be used to examine the functional organization and processing of the human brain?
- What can be learn about brain activity by measuring localized changes in physiology?
- How can these methods be used to further our understanding of brain physiology?
- What assumptions must we make?

The BOLD Signal

- When blood flow changes more than oxygen consumption, in either direction, there is a reciprocal change in the amount of deoxyhemoglobin present locally in the tissue.
- Changing the amount of deoxyhemoglobin present, changes the magnetic field properties.
- Therefore, when blood flow to a region of brain has changed out of proportion to the change in oxygen consumption, a BOLD signal is detected.[19]
- There are multiple hypotheses attempting to explain the exact causal relationship among blood flow, glucose utilization, and oxygen consumption.

BOLD Signal Decreases

- One may assume that a decrease in the BOLD signal reflects a reduction in neuronal activity, caused by increased activity of inhibitory interneurons.
- However, activity of inhibitory interneurons may cause increased blood flow and increased BOLD signal just as much as excitatory activity.
- One hypothesis is that a large number of neurons reduce their activity together[20]. Such reductions would likely be mediated through the action of diffuse projecting systems like dopamine, norepinephrine, and serotonin, or through a reduction in thalamic inputs to the cortex.
- Also, a BOLD signal increase seen by subtracting a control state from a task state becomes a BOLD signal decrease if you reverse the two states.

Conclusions

- 1) Local increases and decreases in brain activity are reliably accompanied by changes in blood flow.
- 2) These changes in blood flow exceed any accompanying change in the oxygen consumption. This fact allows for fMRI based on the BOLD signal.
- 3) A limited amount of data suggests that blood flow changes are accompanied by changes in glucose metabolism of approximately equal magnitude and spatial extent.

Functional Neuroimaging of the Future

- "We have at hand tools with the potential to provide unparalleled insights into some of the most important scientific, medical, and social questions facing mankind. Understanding those tools is clearly a high priority."
- "Combining fMRI with ERPs, recorded with either EEG or MEG, will likely provide the spatial and temporal information necessary to understand information processing in the human brain."
- "PET remains our gold standard for the measurement of many critical variables of physiological interest in the brain, such as blood flow, oxygen consumption, and glucose utilization."
- "Also of importance will be *changes* in neurotransmitter and neuromodulator release. Such changes are probably involved in learning, reinforcement of behavior, attention, and sensorimotor integration. Here PET is at present in almost sole possession of the agenda."

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