Functional Neuroscience: Evoked Potentials and Related Techniques
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Chapter 11

Cross-modal plasticity in the blind revealed by functional neuroimaging

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1. Introduction

In recent years, non-invasive cerebral functional-imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have becoming indispensable in our quest to understand higher brain functions. Local neural activity, especially synaptic activity, increases in parallel with the glucose metabolism in a particular region of the brain. In turn, the regional cerebral blood flow (rCBF) parallels the glucose metabolism, which is mediated by the oxygen supply to the region (Raichle, 1987). Thus, changes in local neural activity can be inferred by measuring changes in rCBF. These methods measure the cerebral blood flow while a subject executes a particular task, which is compared to the blood flow while the subject is in a resting state. The distribution of differences in activity between the active and resting states is then visualized, indicating the regions of the brain that are involved in a particular task.

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2. Historical background

2.1. Neural activity and cerebral blood flow

The Italian physiologist Mosso (1881) made the first reference to the relationship between cerebral blood flow and neural activity. Mosso measured the pulsation of the cerebral cortex in a patient whose cranial bone was partially missing after neurosurgery. Because this pulsation showed local increases that occurred simultaneously with mental activity, he concluded that the regional cerebral circulation (rCBF) changed following psycho-neuronal activity. Roy and Sherrington (1890) used animal studies to deduce that the increased metabolism associated with local activity in the brain causes an increase in blood flow to the location. Fulton (1928) found that a patient with arteriovenous malformation in the occipital lobe complained that he heard a murmur inside his head. This murmur, which was caused by the difference in arteriovenous blood pressure, was proportional to the blood flow. Fulton noted that this sound was stronger when the patient was reading than when he was just looking, and concluded that the rCBF correlated with the intensity of mental activity. Thus, it has been known for some time that cerebral activity can be measured by the changes in the rCBF. However, limitations in measurement techniques meant that this knowledge could only be put into practice at a much

later date. Kety (1951) developed a method of quantifying the rCBF in experimental animals. Rapid progress in medical imaging methods since the 1970s has enabled researchers to develop a non-invasive way to measure cerebral blood flow in humans.

2.2. Medical imaging

Medical imaging techniques use electromagnetic waves to visualize the human body. Information about the inside of the body is obtained using electromagnetic waves with a wavelength that is longer (radio waves) or shorter (X-rays or gamma rays emitted by an isotopic tracer) than that of visible light. Such information includes morphological and functional data: the former is found primarily through X-ray imaging and the latter by means of nuclear medicine. Measurements of cerebral blood flow in humans were first made possible by nuclear medicine techniques. These techniques are based on labeling a substance with a radioisotope. The substance is injected into the body and accumulates in regions of the brain in proportion to the regional blood flow; its levels are then measured from outside the body. Measurements of cerebral blood flow in humans were first conducted in the 1960s using ^{85}Kr gas (Lassen et al., 1963). In 1973, Hounsfield invented X-ray computerized tomography (CT) (Hounsfield, 1973). The tomographical reconstruction techniques of CT were used to construct positron emission tomography (PET) (Ter-Pogossian et al., 1975). PET is a tomographical technique based on the measurement of gamma rays (emitted when a positron is annihilated) and the calculation of the distribution of the positron-emitting tracer in the body. Using the appropriate tracer, various physiological and biochemical measurements can be conducted in addition to the measurement of cerebral blood flow.

2.3. MRI

Compared with the medical application of short electromagnetic waves, MRI is a relatively recent development. Information about the inside of the body is visualized using radio waves with long wavelengths. MRI is an imaging technique that utilizes the nuclear magnetic resonance (NMR) of the hydrogen atom. The phenomenon of NMR was discovered independently by Bloch (1946) and Purcell et al. (1946), and was developed principally in the field of chemistry. A report in the early 1970s revealed that this technique was useful in differentiating between malignant and benign tumors, which is of great importance to medical diagnosis (Damadian, 1971). This yielded a prime opportunity to create medical imaging systems based on the NMR phenomenon; subsequently, Lauterbur (1973) invented the MRI.

When a hydrogen atom is placed in a uniform static magnetic field, it absorbs (resonance) and emits (relaxation) a radio wave with a specific frequency (the phenomenon of NMR). By placing a coil in parallel to the static magnetic field, this phenomenon can be detected as a gradually decaying alternating current, which is the MR signal. The positional information embedded in this MR signal is captured based on the principles of CT. The image obtained primarily reflects differences in the distribution density and the speed of relaxation of the hydrogen atoms, which in turn reflects the different composition of tissues in the body.

By changing the data-acquisition parameters, images that emphasize various contrasts between tissues can be obtained. Compared with X-ray imaging, MRI has several advantages. First, because the radio waves have less energy than X-rays (approximately 10^{-12}), the probability of MRI causing tissue damage is lower. In addition, while X-rays are best suited to detecting heavy atoms, which are present only in small quantities in the body (for example, calcium contained in the bones), MRI is suitable for detecting hydrogen atoms, which are abundant throughout the body (primarily as water). For this reason, MRI is particularly useful for imaging neural tissue, which is tightly protected by the cranial bone and the spine.

2.4. Detection of rCBF by MRI: fMRI

Due to its high-contrast resolution, MRI was initially used clinically to image the anatomical details of the brain. At the beginning of the 1990s, however, the visualization of changes in rCBF was made possible through the use of blood oxygen as an endogenous

contrast medium, which paved the way for fMRI (Ogawa and Lee, 1990). fMRI is known as a "blood oxygen level-dependent" (BOLD) method, because it principally enhances small signals produced by local changes in the balance of intravascular blood oxygenation that appear during enhanced neural activity. It has long been known that oxyhemoglobin and deoxyhemoglobin have different magnetic properties (Pauling and Coryell, 1936), and that the presence of deoxyhemoglobin in the blood vessels produces a patchiness of the local perivascular magnetic field. The uneven local magnetic field causes the NMR signal to decrease compared to the signal in a homogeneous magnetic field. During enhanced neural activity, there is an increase in cerebral blood flow, supplying oxygen above and beyond the local demand of the neural tissue, which in turn lowers the local deoxyhemoglobin level. As a result, the NMR signal is augmented (Ogawa and Lee, 1990). The advantage of this method is that changes in the cerebral blood flow to the entire brain can be recorded at intervals of a few seconds, thereby providing much more data than PET. Presently, changes in the rCBF can be measured every second, with a spatial resolution of a few millimeters.

3. The study of brain plasticity following loss of vision

3.1. Braille reading

Braille is a tactile letter system, which consists of a series of raised dots that can be read with the fingers, and is a well-known sensory substitution for the blind. Braille symbols are formed within units of space known as Braille cells. A full Braille cell consists of six raised dots arranged in two parallel columns, each having three dots. Sixty-three combinations are possible using one or more of these six dots. A single cell can be used to represent a letter of the alphabet, number, punctuation mark, or even a whole word. Braille is not a language; rather, it is a code by which languages can be written and read. The Braille system has its roots in the military field. In the early nineteenth century, it was invented as the tactile "night writing" code for sending military messages that could be read on the battlefield without light. The system used 12 raised dots to represent sounds, and was too complicated to be of practical use. In 1821, Louis Braille, who was blind from the age of 4 years, realized how useful this system of raised dots could be and simplified it from the original 12 to 6 dots. Braille has now become a worldwide standard. It is not only an effective means of communication, but is also a proven avenue for achieving and enhancing literacy for the blind.

3.2. Activation studies with Braille tasks

Braille reading requires the conversion of simple tactile information into meaningful patterns that have lexical and semantic properties (Sadato et al., 1998). The perceptual processing of Braille might be mediated by the somatosensory system, whereas visual letter identity is routinely accomplished within the visual system. Adult subjects with early blindness of peripheral origin showed a higher glucose metabolic rate in striate and prestriate areas than sighted subjects at rest as well as during tactile or auditory stimulation (Wanet-Defalque et al., 1988). This finding raised the possibility that the visual cortices of the blind might participate in the processing of non-visual information, although they failed to reveal specific task-related activation. Tactile imagery or Braille reading in blind subjects caused task-related activation in occipital electroencephalography (EEG) leads (Uhl et al., 1991), suggesting that somatosensory input is redirected to the occipital area.

PET with O-15 water revealed that the primary visual cortex is activated when congenital and early-onset (<5 years of age) blind subjects read Braille and performed other tactile discrimination tasks (Sadato et al., 1996, 1998). Different neural networks representing different modalities were activated during the performance of tactile discrimination tasks by blind and normal subjects: the tactile processing pathways that are usually located in the secondary somatosensory area (SII) are rerouted in blind subjects to the ventral occipital cortical regions originally reserved for visual shape discrimination (Sadato et al., 1998). This finding was confirmed using fMRI (Sadato et al., 2002).

This finding is not specific to Braille, as non-Braille tactile discrimination activates the visual cortex of blind

subjects (Sadato et al., 1998). As passive tactile discrimination showed similar activation patterns to those during active tactile discrimination (Sadato et al., 2002), exploratory finger movements might not contribute to the change in cortical activity. Furthermore, the effects of Braille learning itself might not be critical to the relocation of somatosensory processing to visual areas, as subjects who became blind later in life and who did not have Braille training showed similar activation in the visual association cortex (Sadato et al., 2004).

To investigate whether this dramatic functional restructuring is age-dependent, 15 blind people who lost their eyesight at various ages and were all proficient Braille readers were used as subjects in a brain activation study using fMRI (Sadato et al., 2002). The subjects performed a passive discrimination task using Braille stimuli. The results showed that in the subjects who lost their eyesight before the age of 16, the primary visual cortex was activated by the tactile discrimination task, while no such activation was seen in subjects who had lost their eyesight at a later age. No age-dependent activity was seen in the visual association cortex. The reason for this might be that the tactile stimuli activated the visual association cortex where competitive balance between the tactile and visual modalities is weighted towards the tactile modalities in an age-independent way (Sadato et al., 2002). It has thus been shown that, as a result of the deprivation of visual input over a long period of time, the tactile discrimination information might be processed in a different area to that receiving the original input (visual cortex).

3.3. Electrophysiological technique: transcranial magnetic stimulation (TMS)

A disadvantage of the activation study is that a task-related increase of the rCBF in certain brain regions does not prove their functional relevance. Hence, their functionality should be confirmed by other methods. Hamilton et al. (2000) reported on a woman who was blind from birth and who sustained bilateral occipital damage following an ischemic stroke. Prior to the stroke, the patient was a proficient Braille reader. Following the stroke, she was no longer able to read Braille, yet her somatosensory perception appeared to be otherwise unchanged. This case supports the emerging evidence for the recruitment of the striate and prestriate cortex for Braille reading in subjects who are blind from an early age. Experimentally, the functionality of the visual cortex of the blind was shown using TMS. TMS of the visual cortex induced a transient functional disruption of the identification of Braille letters in early blind subjects, but not in sighted subjects reading embossed Roman letters (Cohen et al., 1997) or in subjects with late-onset blindness (Cohen et al., 1999). As the neuroimaging study (Sadato et al., 2002) showed that the only difference in the task-related activation between the early- and late-blind groups was in the primary visual cortex, it was concluded that stimulation of the primary visual cortex with TMS caused errors in Braille reading only in the early-blind; hence, the primary visual cortex of the early-blind is functionally relevant when performing tactile discrimination tasks. These findings suggest a remarkable plasticity of the brain, potentially permitting the additional processing of tactile information in the visual cortical areas.

4. Conclusion

The advantages of fMRI are that it can measure changes in the rCBF simply, repeatedly and non-invasively over the entire human brain. The use of fMRI in combination with other complementary methods, such as electrophysiological techniques, is essential to the exploration of human cortical plasticity. By making good use of these advantages, it is expected that functional neuroimaging in humans will come to the forefront of the field of brain research.

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