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Review article

The future of real-world neuroscience: Imaging techniques to assess active brains in social environments

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ABSTRACT

The human brain is characterized by an evolutionarily new, highly developed neocortex, which has characteristic connections with phylogenically older structures to enable adaptation to complex social environments. Adaptive social behavior requires successful mental representations of the self and others' emotions and intentions. Measurement of brain activity under laboratory-based settings has been the gold standard in previous cognitive neuroscience studies. However, these measurement settings may be sub-optimal if we want to visualize brain function in active individuals in real-world environments. Neuroscience has historically developed through generations of the "sensing brain," "emotional brain," "social brain," and "ego brain." The next generation is the "action brain" combined with "real-world neuroscience" perspective. To enable in situ measurement of the action brain, real-world or two-person neuroimaging techniques are necessary to visualize brain dynamics during natural social situations, such as the presence of others. This review discusses recent literature describing non-human primate (NHP) and human brain functions during active behaviors in social environments. Uncovering the neurobiological mechanisms of the active brain in the presence of others by using real-world neuroimaging will be an important step toward fully understanding the human brain and its mental functions.

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1. Introduction: investigations into the active brain using next-generation real-world neuroimaging

The human brain is characterized by phylogenetically newer prefrontal and other neocortices that have evolved to realize adaptive social life (Teffer and Semendeferi, 2012). Real-world social situations require adaptive behaviors that are realized by conscious and unconscious representations, as well as future expectations of self and others' emotions and intentions. To investigate the neural mechanisms underlying such active behaviors, "real-world neuroimaging" or "two-person neuroimaging" should be developed as a novel technology to enable the visualization of brain dynamics associated with socially adaptive actions in relatively more natural settings than the laboratory. To understand how the era of the active brain using real-world neuroimaging has emerged as the next generation of neuroscience research, it is important to understand the historical perspective of brain research development.

1.1. Historical perspective of the four stages of brain research development

Human brain research that has investigated brain function from a systems neuroscience viewpoint can be categorized into four stages: the "sensing brain" era starting in late 1950s, the "emotional brain" era beginning in the late 1970s, the "social brain" era in the late 1990s, and the "ego brain" era starting in the late 2000s (Fukuda, 2008).

1.1.1. Sensing brain

The sensing brain era was mainly driven by animal studies. The neuronal mechanisms underlying vision were excellently described based on the results of cat studies that were started in 1958 by the pioneering neuroscientists D.H. Hubel and T.N. Wiesel, who were awarded the 1981 Nobel prize in physiology or medicine. Their work was followed by studies of more complicated information processing and memory by L.R. Squire and E.R. Kandel. Their sophisticated analyses resulted in major findings around 1990, and they were awarded a Nobel prize in 2000. These studies focused on intellectual aspects of input information processing; that is, objective processing of the outside world.

1.1.2. Emotional brain

The emotional brain era was also primarily driven by findings from animal studies. The important roles of the limbic system in emotion were impressively demonstrated in lengthy studies starting in late 1970s by J.E. LeDoux. His summarizing monograph "Emotional Brain" was published in 1996. Based on these studies, emotion came to be regarded as a rapid evaluation system of the biological significance of information. This role of emotion indicates subjective processing of outside world, which is in contrast to objective processing by the sensing brain. In humans, such subjective and objective processes roughly correspond to unconscious and conscious processing. This may explain why LeDoux was also interested in psychoanalysis, a subdivision of psychiatry that deals with the unconscious aspect of human mind.

1.1.3. Social brain

By necessity, the social brain era was driven by NHP and human studies because social abilities have only fully evolved in primate species. It is noteworthy that these advances were supported by technological advances in brain imaging, including functional magnetic resonance imaging (fMRI) starting in 1990. fMRI enabled in vivo brain activity measurement in humans; previous techniques such as unit neuron recording or direct brain recording methodologies were not considered appropriate for human use. Starting in the late 1990s, the neural substrates of representation of other individual minds were identified as the mirror neuron system, theory of mind system, and empathy system for motion, thoughts, and emotion, respectively. These developments have opened a new social brain era that moves past the traditional isolated brain studies to assess interpersonal relationships.

1.1.4. Ego brain

The fourth and most recent ego brain era is an extension of the social brain era that started in the late 2000s and has focused on the brain substrates of self functions in humans (ego). Topics in ego brain studies include the metacognitive aspects of one's own personality as self-referential judgment and one's own emotion as alexithymia and the motor aspect of the self as sense of agency. Because conscious and overt self functions are considered specific to humans, study of the ego brain is limited to fMRI analyses of human subjects.

1.2. The action brain as the fifth generation of neuroscience

Traditionally, studies conducted in real-world settings have multiple variables and can be affected by unexpected events; thus, they have been grouped into the category of applied sciences. Conversely, basic science studies are conducted in laboratory settings. However, when considering the most fundamental functions of the brain, surviving in the real world is more critical than providing correct responses to tests in a laboratory setting. That is, real-world life requires the brain to adapt to, alter, and survive social environments. The *action brain* deals with this essential function (Fig. 1).

Thus, the action brain is assumed to be the fifth stage of human brain research, and it can be desirably studied using real-world neuroscience methods. To date, human brain function has been examined while subjects remain motionless with minimum behavioral responses during MRI. Although they may perform social or metacognitive tasks while undergoing fMRI examinations, the obtained data should be interpreted as constrained by the unnatural, behaviorally covert, and solitary nature of examination settings. Actual brain functions can also be monitored in more natural situations during overt behaviors and communications.

The study of brain function during overt actions, especially in such real-world situations, will be the fifth stage of neuroscience research: the action brain in real-world settings. This neuroscience concept of the *action brain combined with real-world perspective* could also be termed "in situ neuroscience" and is supposed to include real social interactions ("*two-person neuroscience*"). Recently, the issue of "symbol grounding" in the fields of