

Review Article

Rooting "Ko-ko-ro" into the Brain: Toward the Neuroanatomy of Mind

Nozomu MORI

Department of Anatomy and Neurobiology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

"*Ko-ko-ro*", meaning 'mind', is a complex higher order function of the human brain. The two distinct activities of mind that are best understood are the ability to recognize oneself, i.e., self-awareness, and the ability to read another mind. These two functions form the fundamental basis of humanity, thereby allowing us to conform and live in harmony within a given family, community, or society. The mind is formed under certain conditions within neural systems in the human brain, and potentially in some other primate brains. This activity is built upon the harmonic orchestration of various sub-components of mind formation, e.g., perception, sensing, cognition, learning and memory, emotion, consciousness, thoughts, desire, beliefs, and willingness. The current understanding of the mechanism of mind is limited, but growing evidence suggests that molecular, cellular, genetic, psychological, cognitive, and system neurobiological methods could help to further our knowledge of the mind. In this review, I will overview current understanding of the components of mind, particularly from a molecular neurobiological perspective, with anticipation that mapping the mind anatomically in molecular terms may ultimately be possible in the human brain.

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"What is mind?"

"No matter."

"What is matter?"

"Never mind."

"Wouldn't you mind it?"

"No, it really matters!"

Introduction

It was another very hot morning, as I had read was the case before the atomic bomb attack on this city,¹ when I arrived at Nagasaki to settle into my new office in the basic biomedical research building on the campus of Nagasaki University School of Medicine. Surprisingly and unexpectedly, sad news had broken that afternoon. A 12-year-old girl was murdered by a box-cutter attack of her classmate in Okubo Elementary School in the northern city of Sasebo: the so-called "Sasebo Slashing".² This painful news was enough to make every adult think seriously about what problem in their minds could cause this happen at such an important developmental stage of their lives. In my case, this was the first moment that I became serious

about applying my mind to the mind.

How do we think of others? How do we think of ourselves? Currently '*ko-ko-ro*', meaning the mind in Japanese, attracts much attention in various scenarios from all aspects of life, including a social, educational, medical and scientific viewpoint. Understanding mind is indeed important to help solve the problems that arose between the two schoolgirls; however, it is also very important to understand more generally how mind is created and maintained within the brain. Certainly, mind is a matter of the brain, and not of the heart. As a molecular neurobiologist, I became very interested in how mind is created in the human brain during the evolution of hominids and also during the development of a human child. Mind develops, matures, ages, and occasionally falls into fatigue or illness. All of these matters occur in our brain, and therefore it is of both interest and importance to understand how mind resides in the brain. This matters indeed.

In this article I would like to overview our current understanding of the molecular and anatomical bases for how mind is formed in the brain. This is a first step toward exploring the neuroanatomy of mind.

Address correspondence: Nozomu Mori, Ph.D., Department of Anatomy and Neurobiology, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523 JAPAN

TEL: +81-(0)95-849-7017; FAX: +81-(0)95-849-7017; E-mail: morinosm@net.nagasaki-u.ac.jp

Mind from matter?

To begin the discussion on the thing that we call '*ko-ko-ro*' or 'mind', let me first ask what is mind? Mind is not merely feelings, mood, intelligence, or consciousness, but rather it is the brain's ability to recognize self, i.e. self-awareness, and to perceive another person's mind, i.e., mind reading.³ Self-awareness is a part of consciousness, but it is a higher order of consciousness to recognize one's own unique existence in the context of the world. Recognition of the self and the world is performed in certain neuronal processes within the brain. Without normal functioning of the brain, we recognize nothing, and the world would not be represented in the brain. In this sense, we exist only as the brain exists. This notion is clearly described in the concepts of "neuronal man" and "brainism", which were proposed by Jean-Pierre Changeux⁴ and Takeshi Yoro,⁵ respectively. Mind is indeed the matter of the brain.

How was it possible such thing as mind to come into being during the evolution on earth? If natural selection applies, how did the evolutionary process give rise to minds capable of profound insight into the nature of life and universe? How could the capacity for knowing and understanding have grown out of inert matter? I believe that it was Max Delbrück, who first systematically asked these fundamental questions in a lecture series on what he called "evolutionary epistemology" at Caltech. These ideas can be traced back to his unfinished book entitled "Mind from Matter?"⁶ On the cover photograph of this book, we see young Max Delbrück, interestingly alongside Francis Crick, who later also seriously considered the nature of consciousness until his death last summer.⁷

How is the mind created in a mixture of matter? The brain, i.e. the organ of mind, is the most complex organ in our body, but is merely a mixture of neurons and glia, which are made up of molecules. So the brain is build up of matter, and thus mind is merely made from these matters. How can such a simple mixture of matter generate a complex activity, such as mind? One plausible answer would be provided by the key issue of the emergence of 'information' in a matter. Biological systems do acquire information, particularly in the genetic and neural systems. Our genome has information that flows from generation to generation. Our neural networks hold information that recreates its own world inside the brain. This 'information flow' is crucial to the emergence of mind within the brain. Mind may be a game of neural information flow, which is founded in signal transduction occurring at synapses (see below). However, compared with our current understanding of the biological rules of genetic information encoded by the linear sequence of a four-base language, it is currently unclear how this neural information is formulated into the mind.

Historical background of mind mining in the human brain

The medieval view of our mind or soul placed elements of mind, e.g. the common sense, fantasy, imagination, the power of shaping,

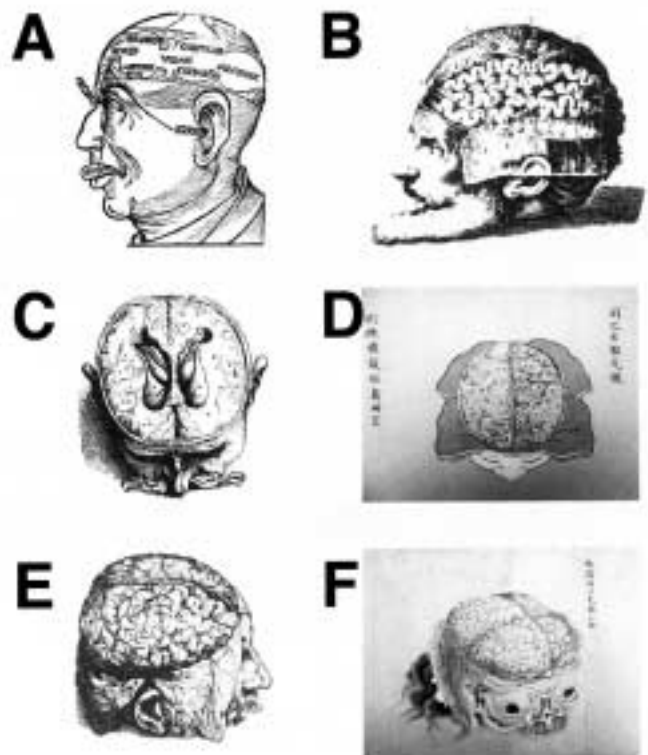


Figure 1. Medieval and pre-modern views of the brain anatomy: a comparison of western and eastern drawings. **A.** Brunschwig' engraving shows a representative medieval view that soul was localized in the brain and subdivided into three basic facilities (ventricles) (1525/1497). **B.** Casserio's illustration of the brain showing the cerebral convolutions and the arachnoid membrane (1627). **C.** Vesalius' illustration of a view of the brain showing the ventricles (1543). **D.** A Japanese painting illustrating the brain anatomy of a female, dissected by Tomon Yamawaki (1771), the second son of Toyo Yamawaki, who is known to be the first to have observed a postmortem dissection in Kyoto from the medical point of view. **E.** Vesalius's illustration of the form of the brain with the cerebral convolutions and their blood vessels (1543). **F.** Ranshu Yoshimura's Japanese painting showing "Heijiro's brain", contained in the book "Heijiro Organs" by Mototoshi Koishi (1783). Note the detail represented in this painting by the superb technique of the Maruyama school. Ranshu was a talented painter at the West Main (Nishi-Honganji) Temple in Kyoto.

imaging, the power of cogitating, estimation, and memory, into the vacant structure of ventricles in brain immaterially^{8,9} (Figure 1 A). In the pre-modern era, it was gradually believed that mind materially resides in the cerebral cortex⁸ (Figure 1 B). Historically, Japanese believed that mind resided in the heart rather than the brain, as Japanese writing for the organ of '*ko-ko-ro*' is heart in Chinese characters; however, it is interesting to see that pre-modern Japanese painters already seemed to have been influenced by western ideas, as well-known drawings of brain anatomy closely resemble those found in the western medical textbooks^{4,5,8,10} (Figure 1 C-F). This was of course made possible through Nagasaki, the only port accessible to the western (and Chinese) cultures during the '*sa-ko-ku*' (seclusionism)-period (1633-1853) of the Edo era.

In Europe, the concept of mind remained elusive until Rene Descartes proposed the notion of primacy of consciousness, in which

the mind knows itself; "*cogito ergo sum*" ("I think, therefore I am").^{8,9} Certainly, the concept of consciousness is crucial for understanding the mechanism of mind, but another important feature of mind is the ability to read another person's mind. Later in the 19th century, classical functional brain mapping was developed by Franz Gall, Pierre Broca, Korbinian Brodmann, Carl Wernicke and many others, whose works revealed that various components of mind, such as visual perception, cognition, emotion, and language, could be broadly located into various portions of the cerebral hemispheres.⁸ A realistic view today locates mind in the neural networks and circuits within the brain cortexes. Neither a single neuron, nor a single synapse can retain any mind, but rather mind is formed through the harmonic orchestration of neural networks.

From an evolutionary point of view, mind (and/or intelligence) would probably have been under the pressures of natural selection for a vast span of time on earth. This notion was developed of course by Charles Darwin¹⁰:

Everyone who believes, as I do, that all corporeal structures and mental organs.....of all beings have been developed by natural selection.....will admit that the organs have been formed so that their possessors may compete successfully with other beings, and thus increase in number.

He believed that natural selection was the force of evolution not only for the biological structure (or shape) but also for the biological function (or intimate activity) of organisms. Darwin thus assumed mind to be a material corporeal (brain) structure. The human mind would therefore have evolved from the mind of other lower organisms or our more direct ancestors. It is quite reasonable to assume that the mind function co-evolved with the brain structure during primate and hominid evolution.¹¹

During the last 3.5 million years of human evolution, brain size increased as body size, but the increase of brain mass versus body size was tremendous in the case of hominid evolution to compare with those of primate (great apes) or Australopithecines (Figure 2 A). However, it may not necessarily need to be big in order to acquire an intelligent and/or smart brain. It is worth considering the recent discovery of *Homo floresiensis* in the islands of Indonesia. This is a pygmy-sized (1 m-tall in adult), small-brained (estimated ca. 380 cm³) hominid (Figure 2 B), which lived as recently as 18,000 years ago.¹² Although the *Homo floresiensis* brain size is as small as that of chimpanzee (see Figure 2 A), the predicted structure suggests that this Flores hominid shows signs of advanced cognition, as it possesses highly convoluted frontal lobes.^{13,14} Even if we believe that the Flores hominid had higher cognitive function, it is uncertain to what degree they might developed causal understanding of, for example, tool-making and use, syntactical-grammatical language, consciousness, self-awareness, or theory of mind (see below). However, this hominid would probably have possessed the abilities for imitation and syntactical language, which are the foundation of a primitive intelligence.

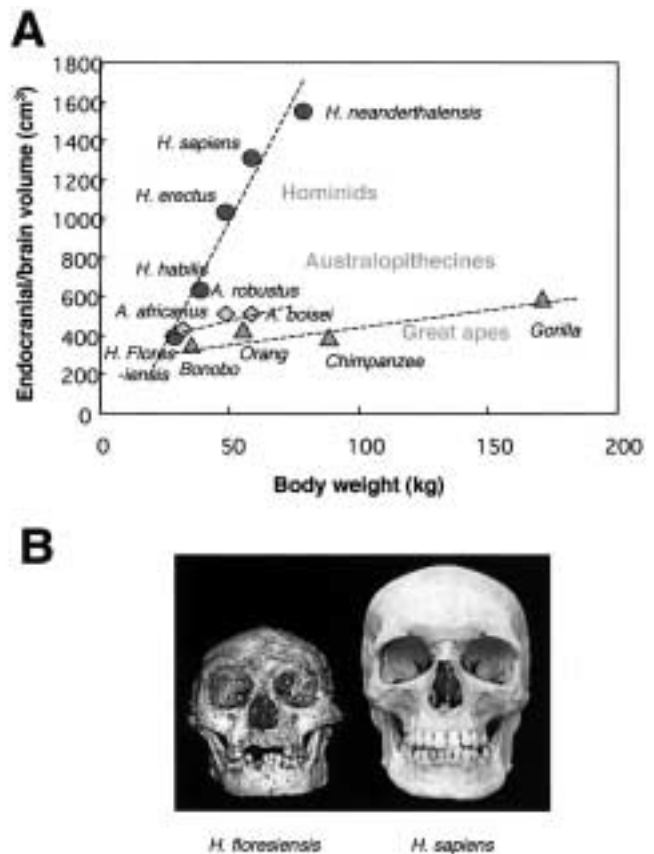


Figure 2. Little is not too bad: *Homo floresiensis* vs. *Homo sapiens*. **A.** The relationship between body size and brain size or endocranial volume (for extinct species) in hominids (circles), Australopithecines (diamonds), and great apes (triangles). Note that the *Homo floresiensis* brain size is as small as that of chimpanzee. Data adapted from Roth and Dicke,¹⁶ Brown et al.,¹² and Falk et al.¹³ **B.** Skulls of *Homo floresiensis* and *Homo sapiens*. Photographs are represented with the courtesy of Carl Zimmer.

Higher brain functions: from learning and memory to conscious mind

Evolutionary development of consciousness or intelligence is a sign of higher brain function,^{15,16} but consciousness and intelligence are merely a prerequisite of much higher brain function such as the 'mind'. It is often said that 'learning and memory' are a representative of higher brain function, but this is only the case amongst molecular biologists or neurobiologists who deal with mouse genetics and behavior studies. Certainly mice and rats provide useful models for many neurobiological studies, but even though rodents can be tested for cognitive behavior, they cannot be tested for mind or consciousness. Only humans and primates are suitable subjects for mind research. The study of mind is at the forefront of higher cognitive neuroscience. Currently, cognitive neuroscience has provided a new framework for the study of memory, perception, action, language, and conscious awareness.¹⁷ Amongst these various topics, recent progress in memory research is profound, especially in understanding its mechanisms at the molecular level. However, for other

topics in this field, understanding at the molecular and cellular level is still in its infancy. The efficient fusion of molecular biology with cognitive neuroscience flourished in the study of memory, for example, Eric Kandel described the molecular biology of memory storage as "a dialogue between genes and synapses" in his Nobel lecture at the end of 20th century.¹⁸

Whilst the study of learning and memory is the only higher brain function that can be currently described in molecular terms, the study of mind and consciousness will hopefully reach a similar stage during this century. Consciousness is complex, and even though it has to reside in the brain, we do not yet know the underlying neural mechanisms of consciousness. Consciousness would probably be attributable to some specific brain areas or group of neurons, but it may also reside in certain types of neural process.^{19,20}

To begin the discussion on mind, we need to dissect the conceptual components of mind. Before mind, or even consciousness, understanding of the mechanisms of 'thinking', 'consideration', or 'thoughts', would be the next logical step onwards from studies of learning and memory. Understanding the origin and development of 'concepts' is one of the most central themes in cognitive neuroscience, and deals with the 'language' with syntactic structure. This would give us the opportunity to explore the logical, rather than mental, foundation of mind. This is the logical portion of mind "*Chi*" (in Japanese), which is based primarily upon learning and memory, and thoughts (Figure 3).

It is widely accepted that 'language' plays a fundamental role in the development of human 'reasoning' and intelligence, that relates to the acquisition of 'thoughts'.²¹⁻²³ There is debate regarding whether propositional reasoning (involving 'theory of mind' understanding (see below)) in adult patients with aphasia reveals that reasoning can proceed in the absence of explicit grammatical knowledge.²¹ Conversely, the presence of such knowledge is not sufficient to account for reasoning in developing children. Children's reasoning

about objects and action is guided by inferences about others' communicative intention. Thus 'reasoning' can occur largely independently from grammatical language.²¹ However, grammar adds elegance to communication, and is critical for reducing mistakes in the transmission of knowledge. The 'reasoning' would possibly provide a bridge between the logical portion "*Chi*" and the intentional (or motive) portion of "*I*" (meaning consciousness or motivation in Japanese), which conforms 'willingness', 'desire', and 'motivation', including the core mechanisms of self-consciousness (Figure 3).

Another major sub-component of the mind is 'emotion', which is represented as "*Joh*" in Japanese. Emotion is an aspect of one's mental state of being, normally based on our internal (physical) and external (social) sensory feeling. Love, hate, courage, fear, joy, sadness, pleasure, and disgust can all be described in both physiological and psychological terms. Emotion represents a situation where logical thought and mental physiology are inextricably entwined, and where the self is inseparable from our individual perceptions of value and judgment toward ourselves and others. In many cases, troubles of the mind reside in, or arise from, emotional changes, as was possibly in the case for the two aforementioned schoolgirls at Sasebo. Emotion is sometimes hard to control, but the capacity to control emotion is important for human adaptation. Recent studies suggest that emotion may be controlled through several cognitive processes,²⁴ possibly through neural networks of the limbic-forebrain and limbic-midbrain systems.²⁵

'Emotion' is apparently affected by 'sensation', an internal process of sensing and interpreting sensory stimuli from environment. 'Sensation' is a process that connects sensory perception, i.e., "*Kan*" (in Japanese), and emotion, i.e., "*Joh*". Although knowledge of the mechanisms of sensory perception is growing, it is still hard to understand the neural basis of 'qualia', e.g., the redness of a red rose, the refreshingness of morning air, the brightness of blue sky, etc.^{26,27} However, if we ask about each particular aspect of conscious sensing, rather than all forms of consciousness, it may be possible to find neural correlate(s) of consciousness; and then the nature of qualia becomes clearer. Of course, the recognition of qualia relies upon the sensory portion "*Kan*", which deals with perception and cognition of various sensory stimuli from the environment and/or another person (Figure 3).

The concerted interaction of the so-called "*Chi-Joh-I*" (in Japanese), together with the stimulatory engagement of "*Kan*" would presumably merge into the formation of mind (see Figure 3 and Figure 4 A). Neural networks physically mediate these interactions. Thus the true higher brain function such as human mind would be approachable neurochemically and systemically through step-by-step understanding of each feature of the brain functions that forms the mind.

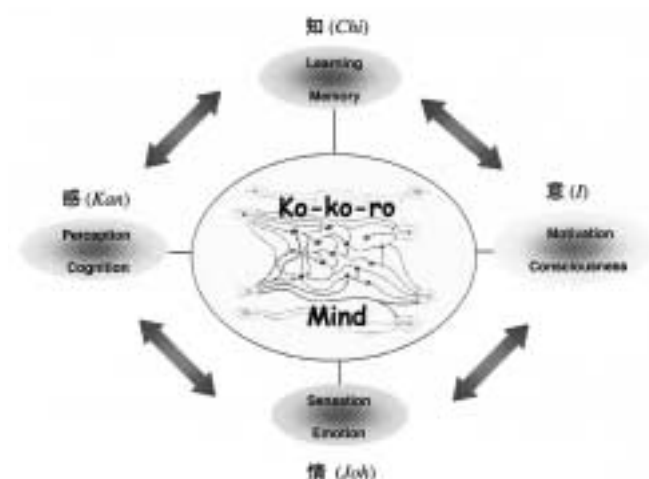


Figure 3. Separation and interaction of sub-components of mind. The mind components are arbitrarily sub-divided into four separable neural activities: Perception and cognition '*Kan*', learning and memory '*Chi*', sensation and emotion '*Joh*', and motivation and consciousness '*I*', each of which is processed in distinct brain areas, but interplay to orchestrate to form a higher order neural activity of mind, '*ko-ko-ro*'. See text for details.

Synaptic plasticity and signal transduction in mind formation and control

'Information flow' is crucial, as discussed above, for mind formation, and this neural information flow is fundamentally based on

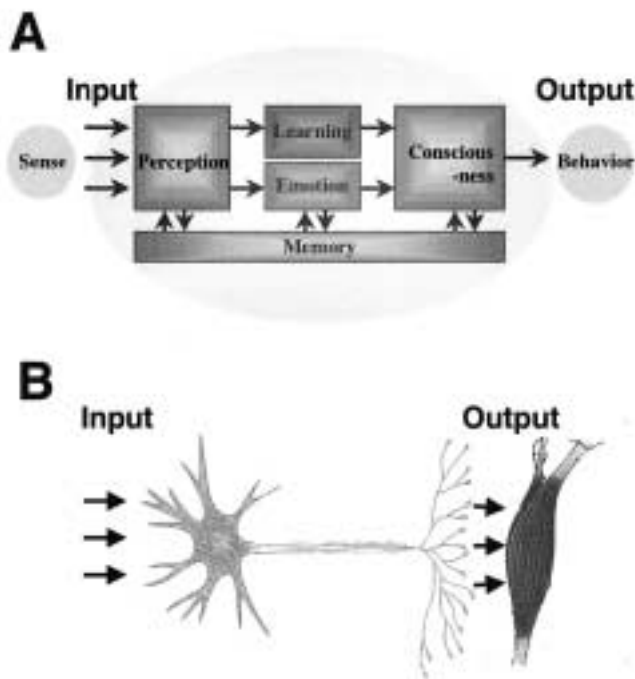


Figure 4. Neuronal processing of mind and muscle. **A.** Conceptual diagram of mind processing in the brain. Mind is a whole brain activity that determines a new behavior through the neuronal computations of perception, learning, emotion, and consciousness, balanced by comparison with stored memories. **B.** Neurons act as a processor of sensory stimuli to modulate muscle movement for digestion, locomotion, facial expression, eye movement, etc. This system could be the evolutionary basis of mind control.

signal transduction in the neural system.²⁸ The so-called neural dynamism or synaptic plasticity is a very important concept in considering mind formation. The ability of neurons to modulate or adjust neural networks in the adult brain, depending upon various stimuli is an essential component of neural plasticity or dynamism. Mind can be modulated by various chemicals that affect signal transduction at synapses. For example, inhibition of monoamine reuptake into nerve endings by antidepressants is one of the cornerstones of the monoamine hypothesis of depression. Cumulative evidence suggests that alterations in the levels of monoamines and their receptors affects mood disorders, i.e., depression or bipolar disorders, and thus the control of signal transduction at monoaminergic nerve terminals is very important to modulate mood, which itself is crucial for mind formation.²⁹ However, the importance of signal transduction is not limited to mood disorders. Mutations in genes of the signal transduction machinery at synapses can cause a wide range of psychological disorders.^{30,31} Therefore, understanding the components and mechanisms of signal transduction for synaptic plasticity in the developing and the adult brain is crucial for molecular exploration of mind formation and mind control.²⁷

Most cellular activities, including synaptic transmission at nerve terminals, are mediated by protein phosphorylation, and this phosphorylation is conducted by various protein kinases, including serine-threonine kinases and tyrosine kinases. Interestingly, tyrosine phosphorylation is only observed in the animal kingdom, and

thus seems to have emerged during the evolution of animals.³² A most obvious adaptation in the animal is the control of muscle movement, and the nervous system seems to have originally evolved to control muscle contraction (Figure 4 B). Interestingly, the essential mechanisms of mind processing by the cerebrum (Figure 4 A) and that of neuro-muscular control (Figure 4 B) are the same: regulating and fine-tuning certain muscles (output) depending upon sensory or pre-synaptic stimuli (input). The nerve-muscle connection is thus crucial for mind, as cranial nerves control facial expression, eye movement, vocal control and speech, all of which, particularly facial expression,³³ are important for the expression of one's mind (Figure 5). In this context, it is of interest to consider the roles of tyrosine phosphorylation and/or phospho-tyrosine mediated neuronal signaling in mechanisms of the mind.

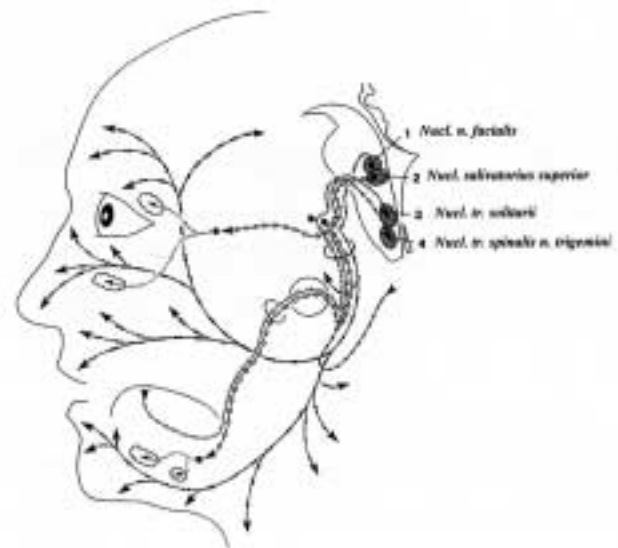


Figure 5. Diagram showing the pathways of the facial nerve fibers that control facial expressions. Lines with efferent arrows indicate the projections of facial nerves from the facial nerve nucleus (1). Note that the efferent fibers cover most of the face to control the facial muscles, thereby facilitating fine-tuning of facial expressions. Projections of the salivary nerves (2) control the secretion of tears, saliva and mucous. The solitary and trigeminal fibers, which have their endings in the ganglia (3, 4), are also indicated. Modified from Iwahori.⁵⁵

In the mechanisms of learning and memory in our brain, the NMDA receptor is of fundamental importance and the NMDA receptor complex in glutamatergic neurons consists of more than one hundred other synaptic signaling proteins.³⁴ The calcium ion channel activity of this receptor is controlled by Src and Fyn, cytosolic protein tyrosine kinases whose expression is enriched in the nervous system. In addition, phosphotyrosine-specific signal adaptors, such as Grb2 and Shc, are also critical for controlling the activity of NMDA receptor function.³⁵ Genetic manipulation of the NMDA receptor components, Fyn, and neuronal Shc (N-Shc/ShcC) in mice results in neural dysfunction, and some developed abnormal cognitive behavior. We recently reported that N-Shc deficient mice revealed elevated cognition as evidenced by Morris' water maze test

and the novel object recognition tests, which was associated with higher long-term potentiation (LTP) in the hippocampus.³⁶ Since N-Shc is a neural-specific Shc-related phosphotyrosine adaptor that affects signal transduction of both NMDA receptor and TrkB receptor for brain-derived neurotrophic factor, BDNF,^{36,37} N-Shc seems to be an interesting synaptic modulator that may contribute to modulate and adjust various steps of mind formation in the neural networks.

The importance of signal transduction for neuronal modulation is now well established, at least in the case of learning and memory, or mood and psychological phenomena.²⁹⁻³¹ A recent experiment by Ernst Fehr and his colleagues adds another very interesting example, as they demonstrated that oxytocin, a type of neuropeptide, could apparently affect 'trust' or reliability among humans.³⁸ Trust is essential for the normal operation of human societies, and without trust nothing would be possible including love, friendship, trade or leadership. Thus, trust is an essential concept to form partnership, family, community, and societies. It is of interest that 'trust' as seen in financial transactions could be affected by a simple neuropeptide such as oxytocin. Interestingly, oxytocin is also known as a key component in biological attachment, e.g., mother-infant attachment and adult-adult pair bond formation.³⁹ The human bonding and trust, in other words, physical and psychological attachments also involve neuronal signaling, and thus synaptic modulation would probably be an essential mechanism in the formation and control of mind.

"Look others!": Mirror neurons and roles of imitation in mind development

It is generally accepted that children develop their mind through 'imitating' the behavior of their parents and neighbors.^{40,41} A prevalent view is that 'imitation' is found only in humans, and that non-human primates exhibit 'stimulus enhancement' and/or 'emulation' rather than true imitation.¹⁶ 'True' imitation is defined as the acquisition of skills by observation, resulting in novel behavior. Studies of the macaque brain show that posterior parietal and frontal areas, including 'mirror neurons' in frontal area F5, are dedicated to the execution and recognition of meaningful hand-reaching and grasping as well as facial movements.^{42,43} The neural circuits that include these 'mirror neurons' in area F5 probably form the neuronal basis of imitation.

Growing evidence suggests that the existence and activity of 'mirror neurons' are central to the mechanisms of mind development through imitation. The first evidence for the existence of mirror neurons came from primate studies by Gallese and Rizzolatti in 1996.^{42,43} Populations of mirror neurons have been recorded from the frontal regions in macaques. A group of specific neurons fired when the macaque was shown a specific hand movement, and these same neurons also fired when the macaque was performing that movement, suggesting that the premotor cortex is active both when monkeys observe simple movements and when they perform them. Mirror neurons in the premotor cortex appear to form a cortical system matching observation and execution of goal-related motor

actions. Experimental evidence suggests that a similar matching system also exists in humans.⁴¹ In human, brain-imaging studies revealed that regions of the brain linked to movement were activated when people were asked to imagine or actually grasp an object. These regions included Brodmann area 6 in the inferior part of the frontal gyms of both cortical hemispheres, the anterior cingulate regions and the ventral parietal lobe. Interestingly, both the caudate nucleus of the basal ganglia and regions of the cerebellum were also activated. Moreover, a neural system that matches or imitates movement has also been shown to include neurons within the left inferior frontal cortex and the caudal region of the right superior parietal lobe; these areas are active when human subjects are asked to observe and imitate finger movements.

What might the functional significance of this matching system be? One possible function is to enable someone (a given organism) to detect specific mental states of others (observed conspecifics). This function could be a part of, or a precursor to, a more general 'mind-reading' ability.⁴²⁻⁴⁴

Reading another mind: Beyond the theory of mind

'Mind-reading' is the activity of representing specific mental states of others, e.g. their 'perceptions', 'goals', 'beliefs', 'expectations'. It is now well accepted that all normal humans develop this capacity to represent (or understand) mental states in others, in general, by the age of four.^{16,44,45} As outlined above mirror neurons are probably major components, at least in part, of the mind-reading in humans. While mirror neurons are present in primates, it is uncertain whether non-human primates also develop this activity.^{16,42-44}

The fundamental basis of 'mind-reading' is the so-called 'theory of mind', that is, the ability to understand another individual's mental state and take it into account in one's own 'behavior'.⁴²⁻⁴⁵ This theory, which was developed by Premack and Woodruff in 1978, refers to the attribution of mental states to both oneself and others. A well-known example for the test of 'theory of mind' is seen in the paradigm of Sally and Anne.⁴⁵ A related question concerns the concept of knowledge and the distinction between 'right and false beliefs'. In humans, theory of mind and the understanding that a person could hold a false belief develops between the ages of 3 and 4 years, and is fully developed only at the age of 5. It is currently believed that chimpanzees exhibit at least some aspects of this theory of mind, but that a full theory of mind is unique to humans.¹⁶

Recent functional magnetic resonance imaging (fMRI) studies in humans identified cortical areas related to 'theory of mind', imitation, and the distinction between self and others.⁴⁶ The brain regions activated when subjects were asked to focus either on themselves or on others includes the right inferior parietal and posterior temporal cortex plus the right dorsal lateral, orbital, anterior cingulate, and insular cortex. In this context, 'mirror neurons' in the monkey frontal area F5 are viewed as forerunners of the human cortical areas underlying 'theory of mind' and the distinction between self and others.^{42-44,47}

Interestingly, the human cortical area relevant to the 'theory of mind' is Broca's area, a center for speech control. Therefore, the representation of hand signals within Broca's area is in line with findings in stutterers and bilingual children, both indicating tight links between speech-related hand gestures and speech production. These findings agree with the suggested cytoarchitectonic correspondence between the monkey F5 and the human area 44 in Broca's region. The precursor of Broca's area has been suggested to play a crucial role in the evolution of the gestural basis for language and speech, being essential for the inter-individual communication by orofacial and hand gestures.^{43,48} It is of interest to note that a most effective strategy to read another mind is to read the individual's lips. Nishitani and Hari⁴⁸ demonstrated elegantly that the cortical areas, including Broca's area 44, are activated sequentially from the occipital cortex to the temporal and inferior parietal areas, and finally to the fronto-central areas of each hemisphere, when subjects were shown still pictures that only implied motion.

The facts that the core regions of 'imitation' and 'speech' overlap around Broca's area, and that the core of reading another mind is to read another's lips may suggest that the evolution of this brain area might have contributed to form a fundamental basis of mind evolution. Indeed, syntactical-grammatical language and speech are the most advanced intelligence that has evolved in humans.^{16,21,22} Spoken communication is essential for further development of an ability to understand more complicated mind in teenagers and adult, whose mind is far more difficult to read than that of a 4-year-old children who has acquired the theory of mind. Therefore, we need to await 'another theory of mind' to be proposed.

"Look into yourself!": Recognizing self and the birth of self-awareness

What then would this alternative theory suggested by 'another theory of mind' deal with? It should at least explain the core mechanisms of 'self-awareness', the second important feature of mind. The most important stage in life for the acquisition of self-awareness would be in adolescents or teenagers. Before the establishment of his or her 'ego' in early teens, one experiences many 'thoughts' and 'beliefs'. There is some debate, but it seems that young children of elementary school age, understand what others might want, but not what they believe. Before children develop their own beliefs, they more often express 'desires' during the preschool period. Children then gradually develop the ability to control their 'desires', and establish 'thoughts' and 'beliefs' during their teenage years. They realize that their existence is independent from, but intimately related to, that of their parents, and also begin to distinguish best friends from other friends or classmates. This would be the time of life when one reaches the stage of recognizing self-awareness, a higher order consciousness. Descartes' phrase "*cogito ergo sum*" ("*I think, therefore I am*") seems to become reality at this stage.

A number of recent theories exist to explain the neural basis of consciousness and self-awareness, including the theories of Bogen,

Crick, Llinas, Newman, and Changeux (reviewed by Smythies⁴⁹). Those theories allocate different roles to various brain areas, in particular the reticular and intralaminar nuclei of the thalamus and the cortex. Crick's hypothesis is that awareness is a function of reverberating cortico-thalamic loops and that the 'spotlight' of intramodal 'attention' is controlled by the reticular nucleus of the thalamus.²⁰ Crick also proposed different mechanisms for 'attention' and 'intention' (or 'will'). Smythies argues about the possible role in awareness and intermodal attention and intention of the cholinergic system in the basal forebrain and the tegmentum; the reticular, the intralaminar, and the dorsomedial thalamic nuclei; the raphe and locus coeruleus; the reticular formation; the ventral striatum and extended amygdala; insula cortex, and other selected cortical areas.⁴⁹ Based on these considerations, it is assumed that the brain may work by large nonlinear parallel processing and much intramodal shifts of attention may be effected by intracortical, or multiple thalamo-cortical mechanisms. It is suggested that self-awareness would thus result from small local 'flashlights' rather than one major 'searchlight'.

Insights into the aging mind

Mind matures with age, but mind also ages. As we age, we may grow wiser, but we may grow weaker. Elderly people frequently experience memory loss and cognitive slowing that can interfere with our daily life. The functional loss may ultimately lead to Alzheimer's disease or a dementia of Alzheimer type, although a mild cognitive loss is usual in the normal aging brain.⁵⁰ Behavioral research on aging has mapped contrasting patterns of decline and stability in cognition across the adult lifespan.⁵¹ The cognitive neuroscience of human aging, which relies largely on neuro-imaging techniques, relates these cognitive changes to their neural substrates, including structural and functional changes in the prefrontal cortex, medial temporal lobe regions and white matter tracts.

What neural mechanisms would the age-related differences in anatomy and functional activations represent? Anatomical neuronal volume losses in the aged brain could have several causes at the cellular level, including loss of synaptic density. The changes in blood flow observed with the positron emission tomography (PET) and fMRI are indirect measures of neural activity and could have several underlying causes at the molecular and cellular levels. Decreased activation with aging could be due to activity in smaller numbers of neuronal populations, greater variance or less synchrony in population firing, decreased neurotransmitter binding, decreased neuronal metabolism, or failures in afferent excitatory connections, and so forth. These connections between the findings of *in vivo* imaging and their underlying neural substrates, or matter, and mechanisms of mind and cognitive loss are most likely to be understood in animal models, where both molecular and cognitive methods can be applied in the same animal. Recent advances in molecular understanding of the genes controlling cognitive impairment during aging⁵² would provide some hints that will allow us to further explore and discover

the secrets of aging mind.

Toward the functional neuroanatomy of mind

Where within our brain is mind generated and stored? As overviewed here, the term 'mind' is used in different ways, but we defined 'mind' as the neural activity in our brain that forms our own self-awareness (or self-consciousness) together with the ability to read (or understand) the mind of other persons. To establish this self-awareness and the ability of reading mind, sub-components of mind, i.e., perception and cognition ("*Kan*"), learning and memory ("*Chi*"), sensation and emotion ("*Joh*"), motivation and consciousness ("*I*"), would need to be merged together and orchestrated into the unified concept of mind. Although mind cannot be assigned to a single locus of the brain, the loci of each sub-component of mind can be placed within several cortical and sub-cortical areas of the cerebrum. As discussed above, Broca's area 44 would be a crucial brain locus for the second aspect of mind, i.e., reading another mind. As to the first aspect of mind, i.e., consciousness and self-awareness, seems to be localized in other brain areas.

The most well characterized brain locus for consciousness is the brain stem.⁵³ However, this is only for the basic form of consciousness, i.e., core consciousness. The core consciousness is relevant for body regulation, playing an essential role in maintaining the homeostatic balance of a living organism. To maintain this activity of life, a somato-sensing structure is critical to report the current status of the organism. Core consciousness is conceived as the imaged relationship of the interaction between an object and the changed organism status that it causes. Neuroanatomically, nuclei in the brainstem reticular formation seem to represent the basic set of somato-sensing structures necessary for core consciousness and for the core self to emerge.⁵³ It is believed that the reticular formation modulates the electrophysiological activity of the cerebral cortex, thereby affecting higher order consciousness, such as self-awareness.

Finally, where and how is the more advanced state of consciousness such as 'autobiographical memory' formed in the brain? This is an advanced consciousness that mediates awareness of the self as conscious across the lifespan. Levine recently reviewed aging, lesion, and functional neuroimaging research on the anatomical substrates of autobiographical memory processes using autobiographical interview, and prospective collection of autobiographical material.⁵⁴ Results indicated that autobiographical recollection is mediated by a distributed fronto-temporo-parietal system, with the anteromedial prefrontal cortex positioned to integrate sensory information with self-specific information. The emergence of autobiographical recollection at around age four coincides with the timing of prefrontal regressive cortical and progressive white matter changes that may support the development of high-level capacity of human mind development. This would be the neural basis for an ancient Japanese tradition; "Three-year old child's mind (soul) stays alive until one-hundred years-old."

Conclusion

As overviewed herein, the human brain acquired special abilities such as mind during the evolution of hominids. Mind is represented not only by feeling, emotion, or intelligence, but also by the ability to recognize one-self as a unique individual being in the world, and also by the ability to read another mind, the mind of neighbors. With these abilities, humans are able to communicate, interact, love, envy, or fight, each other. Mind matures during the growing periods of childhood and teenage years, but occasionally during development or after maturation, the mind may fall ill. It also ages, and ultimately dies, with the brain. The first feature of mind, the ability to read another mind, develops by the age of four, and later the second feature of recognizing self matures in teenagers. In this context, it seems that reading another mind leads to self-mind. Thus, the acquisition of self-awareness seems to depend upon the ability to read other minds. The neural mechanisms of mind reading and formation are still unclear, but are believed to be generated by the harmonic activities of neural circuits or networks. Although sub-components of mind are known to be processed in different cortical and sub-cortical brain regions, further systemic neuro-anatomy and physiology studies are needed, combined with molecular and cellular neurobiology, in order to help elucidate the core mechanisms of the mindful brain.

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