Challenges in neuroscience*

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During the initial half of the 20th century, science and technology based on physics and chemistry achieved great advances in the arena of inanimate objects. However, developments in biology-based science and technology increased during the latter half of the 20th century and successfully approached the world of living creatures across the classic border between the inanimate and the living. In the 21st century, science and technology will turn to the human being, in particular to the brain that is the site of our mind. It is a thrilling question as to whether science and technology can close the gap between matter and mind or between non-human and human lives.

Century of the brain

I would like to define the 21st century as the century of the brain for the following three predictions:

1) Based on the knowledge accumulated and the technology developed until now, neuroscience has reached a highly strategic stage where breakthroughs are envisaged in the very near future. This is an area of science where many discoveries are still to take place, which are directly in response to the intellectual demand to uncover what we are as human beings.

2) Neuroscience can greatly benefit society through medical applications to cure neurological and psychiatric disorders and repair brain damage as well as prevent drug abuse and brain aging, which are threatening our society. In Japan, for example, 20% of the total government medical care expenditure is spent for brain and nerve disorders, and this figure may rise as individuals above 65 years of age will represent 1/3 of the total population in 50 years.

3) Neuroscience can also benefit society through technological applications to produce new information technology which will have great impact on the forthcoming highly information-oriented society. Brain-like computers and human-like robots are still dreams, but are becoming more and more realistic as neuroscience advances.

In contrast to this positive side, neuroscience also has a negative side as science inevitably contains. One should fear the possibility of abusing neuroscience in manipulating human mental capabilities and altering personality as well as impairing human dignity. It is such a problem that not only neuroscience but also any branches of life science rely upon animal experiments. I would urge all experimenters to make a careful choice of appropriate animal species and the number to be used in experiments. To reduce animal use to a minimum and to avoid uselessly painful procedures are absolute conditions for any animal experiment.

Promotion of neuroscience today needs special consideration because neuroscience is a highly interdisciplinary field investigated in numerous relatively small laboratories, often described as a distributed megascience as contrasted to a concentrated megascience which is based on highly concentrated facilities such as a nuclear collider or a space ship. For the diversity, removal of the barriers between university faculties and between administrative departments is vital. Although the 'decade of the brain' campaign started in 1990 in the USA, particularly aimed at medical applications, a research project called the Age of Brain Science has been launched by the Japanese government in 1996 supporting three subfields of neuroscience, i.e. to understand the brain, to protect (care for) the brain, and to create (model) a brain, in the next twenty years. Accordingly, special neuroscience grants have been created, and the Brain Science Institute was launched in RIKEN on 1 October 1997.

India has a long, brilliant tradition of neuroscience, and has numerous highly motivated researchers as organized in several national societies. Federation of Asian and Oceanian Neuroscience Societies (FAONS) has been established last year for promoting neuroscience in Asia and Oceania. I am sure that Indian neuroscientists will contribute a great deal to challenges in neuroscience in the 21st century.

Discoveries and innovations in neuroscience

Neuroscience is a unique field of science which not only requires reductionistic analyses but also synthetic inte-

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grations. So far, the reductionist approach has been successful in dissecting brains into nerve cells and glia cells, and these brain cells into molecules (Figure 1). Individual researchers tend to dwell at one of these hierarchical levels of brains, cells and molecules, without concern of the other levels. However, it now seems to be the time to take a turn towards integration, molecules to cells and cells to brain tissues and to begin to synthetically study behaviour and the mind.

Studies of the brain have been recorded since early history, and there were some outstanding discoveries made at the beginning of the 20th century, or even in the 19th century (Table 1). Studies of the brain continued to be fruitful through the 1960s and 1970s, and thereafter new developments were introduced by innovation of non-invasive measurement methods of brain activities such as PET (positron emission tomography), fMRI (functional magnetic resonance imaging) and MEG (magnetic encephalography), and also by developments in theoretical modelling and computer simulation techniques.

At the cellular level, a number of discoveries of cellular processes and technological innovations in the use of tissue culture and brain slices were made in the 1950s to 60s (Table 2). The recent years have been characterized by rich new technology for cellular neuroscience such as patch clamping to isolate activities of single channels, and various imaging techniques enabling us to observe cellular activities without cell penetration.

Studies at molecular levels have developed relatively late, and the 1980s were a particularly productive period (Table 3). At present, there are six categories of themes which need further elucidation at the molecular level (Figure 2): (1) first messengers (transmitters, modulators, hormones), (2) signal transducing molecules (receptors, second messengers, protein kinases, protein phosphatases, phosphoproteins), (3) neurotrophins (NGF, etc.) and adhesion molecules, (4) microstructural molecules (cytoskeleton, motor molecules, vesicle-associated proteins), (5) exogenous pathogens (slow viruses, prion), and (6) genes (immediate early genes, disease genes, triplet repeats, gene transfers).

Table 1. Advances in neuroscience at brain level

1861	Speech arena
1870	Motor area
1904	Classical conditioning
1906	Spinal reflex
1909	Brodman's brain map
1911	Neuronal diagrams
1914	Vestibular equilibrium function
1929	EEG
1929	Emotional function by hypothalamus
1934	Perspiration mechanisms (Kuno)
1940	Satiety center
1949	Auditory mechanism
1951	Food-intake center (Anand, B. K., *et al.*)
1955	REM sleep
1957	Self stimulation
1959	Human brain mapping
1962	Visual cortical feature extraction process
1962	Simple perceptron model
1966	Locomotion in thalamic cat
1967	Cerebellar circuit analysis
1968	Split brain
1969	Readiness potential
1971	CT-scan
1977	2-deoxyglucose method
1985	Brain blood circulation increase during thought
1986	Neurocomputer model
1990	Neurobiology of consciousness
	PET-scan
	MEG
	fMRI
1994	Frontal mental theta wave
2000	Age of human cognitive function

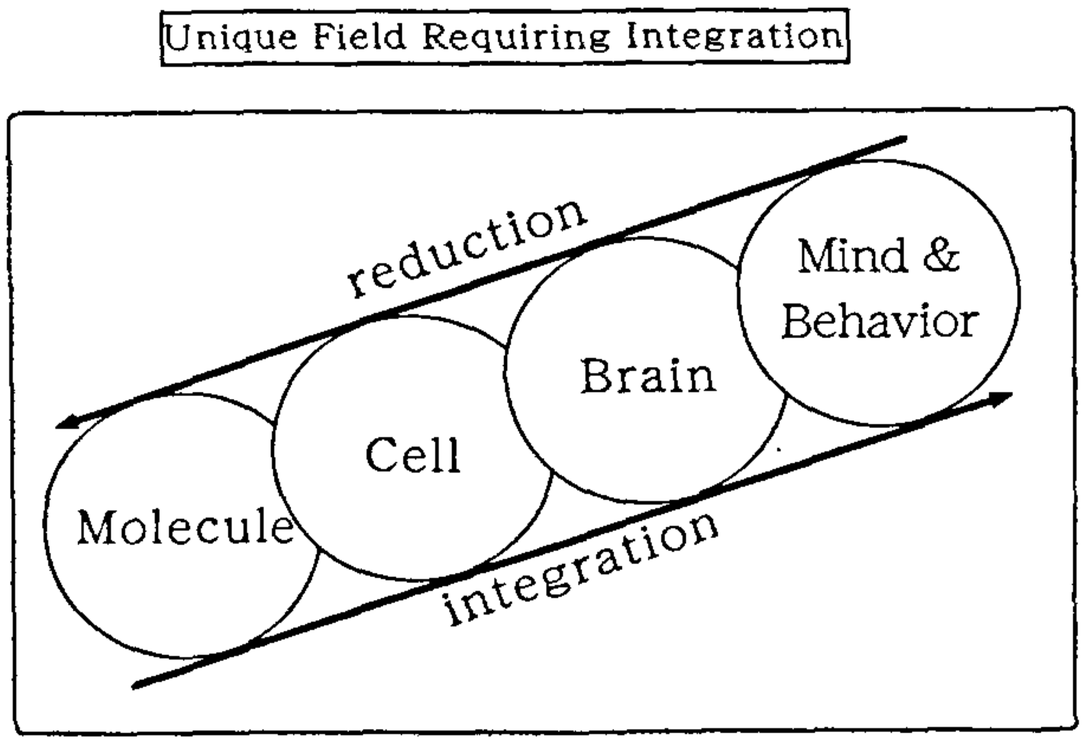

Figure 1. Unique feature of neuroscience.

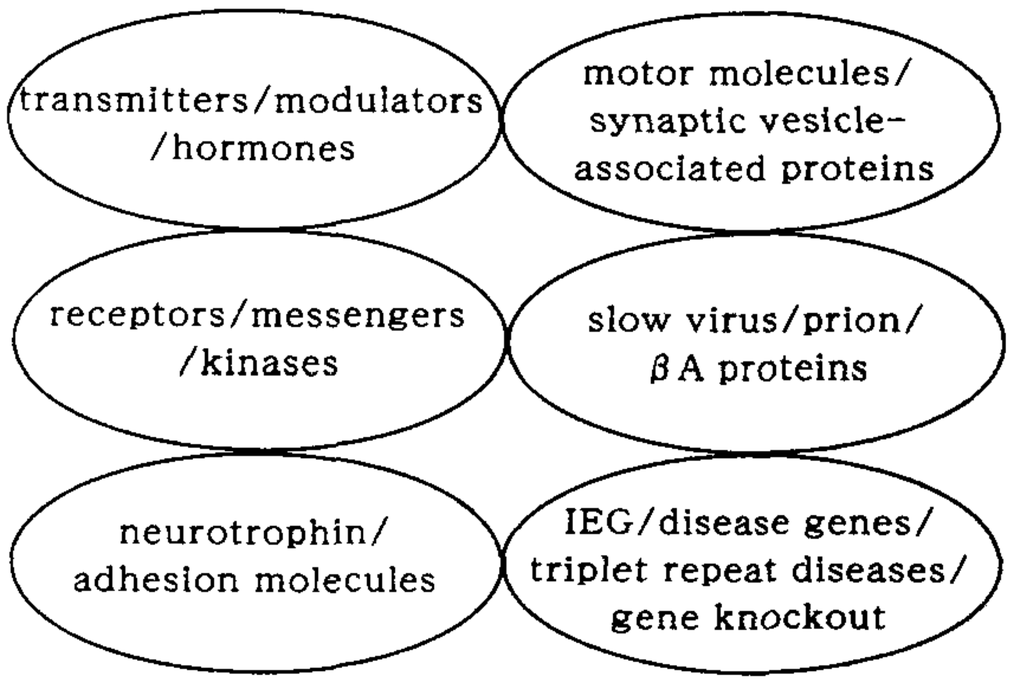

Figure 2. Six categories of molecules active in the brain.

Table 2. Advances in neuroscience at cellular levels

1838	Microscopic observation of nerve cells
1850	Nerve conduction velocity
1910	Neuron concept
1922	CRO observation of action potential
1932	Sensory signal transduction
1949	Hebbian synapse
1951	Inhibitory synapse
1951	Quantal release of transmitter
1952	Na theory
1957	Presynaptic inhibition
	Sensory receptor mechanisms
1960	Electrical synapse
1964	Ca^{2+} spike
	Tissue culture
	Brain slice method
1973	LTP
1976	Patch-clamp single channel recording
1980	Transplantation of nerve cells
1982	LTD
1990	Ca imaging
	Optical recording with voltage-sensitive dyes
	Dendritic function
	Axonomal targeting
	Apoptosis
2000	Age of developmental neuroscience on growth, differentiation, proliferation, degeneration, and death of neurons and glia

Table 3. Advances in neuroscience at molecular levels

1931	Substance P
1936	Ach as transmitter
1946	Noradrenaline
1950	Nerve growth factor
1952	Tranquilizer
1954	Posterior pituitary hormones
1962	Glutamate as transmitter
1963	Slow virus
1967	GABA as transmitter
1969	TRH
1971	LHRH
1974	Somatostatin
1975	Endogenous opiates
1980	Monoclonal antibodies
1980	NO
1981	CRF
1982	GRH
1983	Huntington disease gene
1983	nCAM
1984	Ach receptor and Na channel cloned
1984	C-kinase
1989	Glutamate receptors
1990	Prion
	Motor molecules
	Glutamate transporters
	Vesicle-associated proteins
	Immediate early genes
	Triplet repeat diseases
	Knockout mice
2000	Age of gene regulatory mechanisms in health and diseases

Perspectives of neuroscience

Extrapolating these recent advances, one would expect that early in the 21st century, neuroscience will uncover gene regulatory mechanisms of cellular functions, developmental mechanisms of growth, differentiation, proliferation, aging and death of brain cells, as well as brain mechanisms of human cognitive functions. Apart from infection by exogenous pathogens, most brain disorders are due to impairment of gene regulatory and developmental mechanisms in brain cells. The immediate challenge in neuroscience for the coming years is the development of effective medical care technology for diagnosis, medication, gene therapy and neurosurgery to prevent and cure neurologic and psychiatric disorders, brain damage, drug abuse and brain aging, which have so far been very difficult to approach.

The second challenge in neuroscience is to produce a brain-like computer and human-like robot. A neurocomputer mimicking the multilayered neuronal networks of the brain with incorporated synaptic plasticity as memory elements, would display substantial computational power for information processing. Nevertheless, the present neurocomputer is far from duplicating the brain's capabilities of inference, emotion, volition or self-awareness. There is still a large gap in our knowledge of brain mechanisms of these mental activities that might be filled before we can reproduce them artificially.

A third challenge in neuroscience is to understand how the brain works to conform with the mind. Studies at the behavioural and mind levels have been conducted primarily in the field of psychology, psychiatry and ethology rather than neuroscience. There remains a large gap in our understanding between the mind/behaviour components and brain function, but the gap is mostly due to very poor comprehension of the functions of brain tissues. The following sections present a scenario of neuroscience that might fill this gap by exploring the structure–function relationship of the brain.

It should be mentioned that the second and third challenges are interrelated. If we understand the structure–function relationships of the brain, it will help us produce a brain-like computer. On the other hand, theoretical modelling will help us gain insight into the complex structure–function relationships of the brain. Therefore, both these areas should be focused on together.

Evolution of the brain

One unique way to bridge the functions of the brain and behaviour/mind components is to observe the systematic evolutionary development of brain structures. The most

fundamental structure is seen in the lower vertebrates such as fish, frogs and snakes, where the brain stem and spinal cord implement three categories of functions (Figure 3), i.e. (1) reflexes, (2) compound movements such as locomotion and saccadic eye movement, and (3) innate behaviour such as food and water intake and reproductive behaviour. The center for innate behaviour is located in the hypothalamus at the rostral end of the brain stem, while centers for reflexes and compound movements are distributed throughout the spinal cord and brain stem.

To these three functional systems, four regulatory systems are attached, i.e. (A) the limbic system, (B) basal ganglia, (C) cerebellum, and (D) the wakefulness–sleep centers in the brain stem. In terms of evolution, the limbic system is an old part of the cerebrum that acts to modify innate behaviours by positive and negative reinforcement. An animal approaches water when it was perceived as sweet in previous tasting, but it avoids the seemingly same water when it was perceived salty previously. Therefore, the behaviour toward the same water is modified due to the animal's experiences so that the behaviour remains purposeful for animals' survival. The role of the limbic system can be defined as conferring purpose on innate behaviours.

The basal ganglia form a massive network lying in the deep interior of the cerebrum. Even though it is still under debate, the major function of the basal ganglia seems to be the following. Since numerous activities, competitive or even conflicting, may occur in the brain stem and spinal cord simultaneously, a mechanism of choosing one among them and suppressing the others is necessary for the stable operation of the functional systems. My proposal is that such selection is done at the basal ganglia to ensure stability in the system.

By contrast, the cerebellum contains adaptive mechanisms. A small compartment of the cerebellum equipped

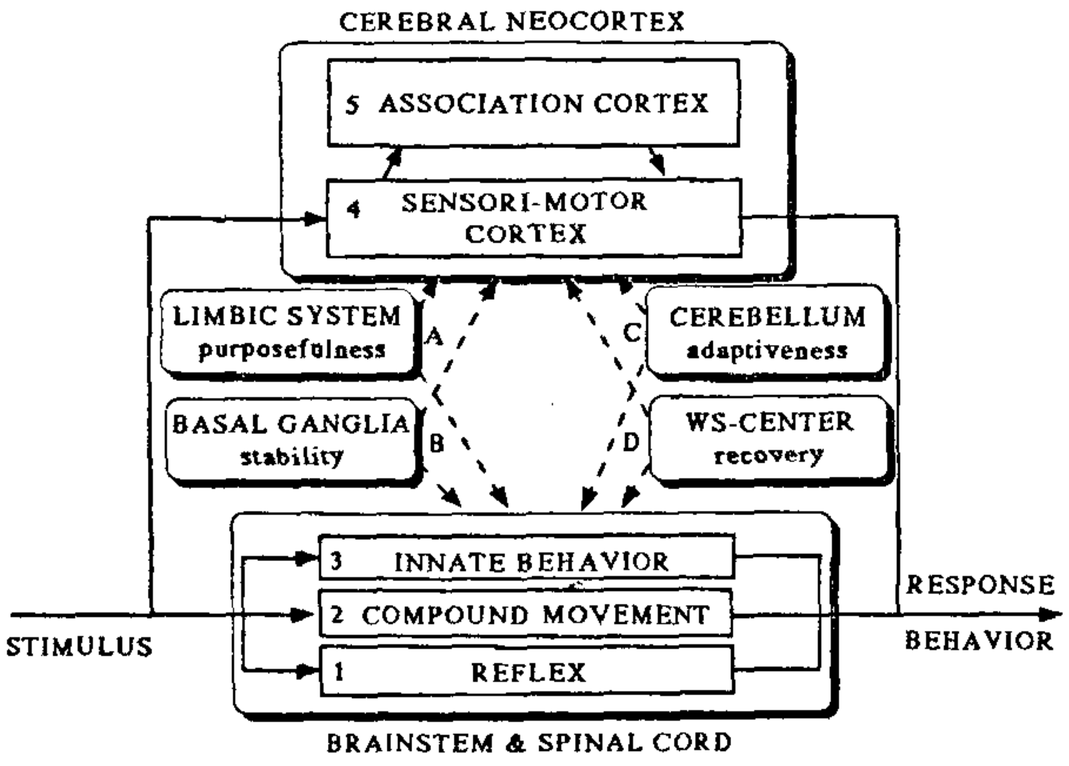

Figure 3. System structure of the brain. WS, wakefulness-sleep.

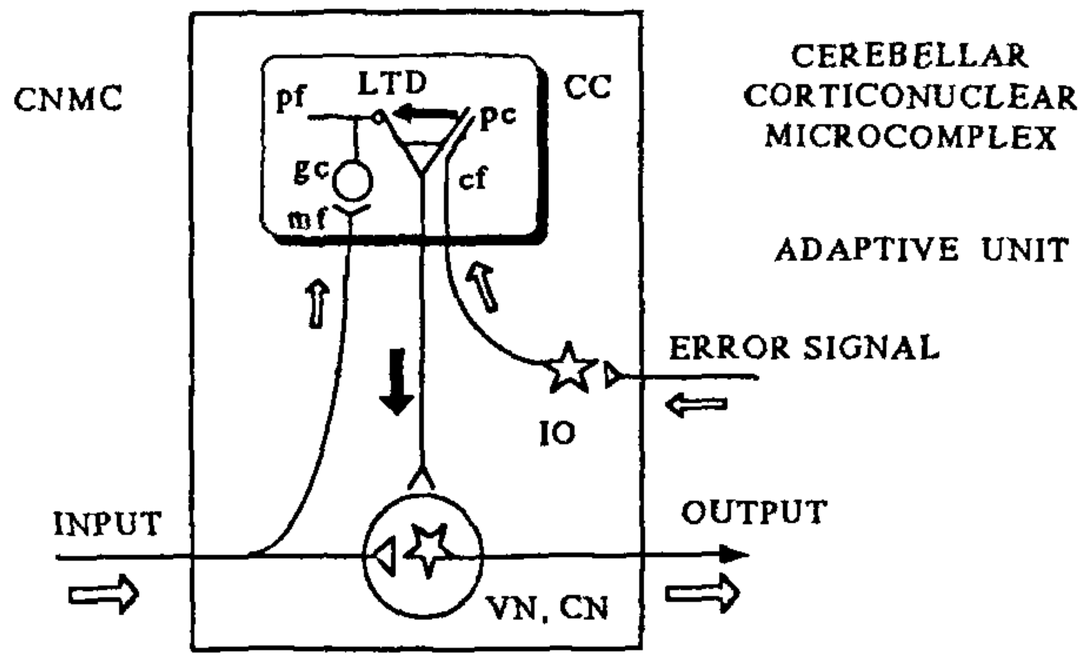

Figure 4. Structural compartment unit of the cerebellum. CC, cerebellar cortex; pc, Purkinje cell; gc, granule cell; pf, parallel fiber; cf, climbing fiber; mf, mossy fiber; LTD, long-term depression; IO, inferior olive; VN, vestibular nuclei; CN, cerebellar nuclei; CNMC; cerebellar corticonuclear microcomplex.

with adaptive mechanisms changes its input–output relationships through learning driven by error signals (Figure 4). A type of synaptic plasticity called long-term depression, LTD, is the major mechanism of this error-driven learning. When an animal faces a change in the environment, the cerebellum acts to adjust movements so that the animal is able to maintain precise and smooth movement.

The wakefulness–sleep centers in the brain stem may exert more general action than the other regulatory systems upon the functional systems (1)–(3), such as resting and recovery during sleep from the exhaustion caused by waking activities. In view of the neuroscientific data accumulated to date, it is reasonable to think that the three functional systems (1)–(3) and four regulatory systems (A)–(D) (Figure 3) together provide the central nervous system of lower vertebrates with the machinery for their behaviours.

Development of the cerebral cortex

In lower mammals such as rats, cats and dogs, the cerebral neocortex develops and constitutes a fourth functional system which consists of the sensory and motor areas of the neocortex as well as the thalamus. The fourth functional system in the cerebral cortex carries out elaborate sensori-motor functions. My hypothesis is that the four regulatory systems (A)–(D) act upon this fourth functional system in a manner similar to functional systems (1)–(3) with similar operational principles.

In primates, the association cortex has developed to such an extent that in humans it occupies two thirds of the entire cerebral neocortex, and together with the as-

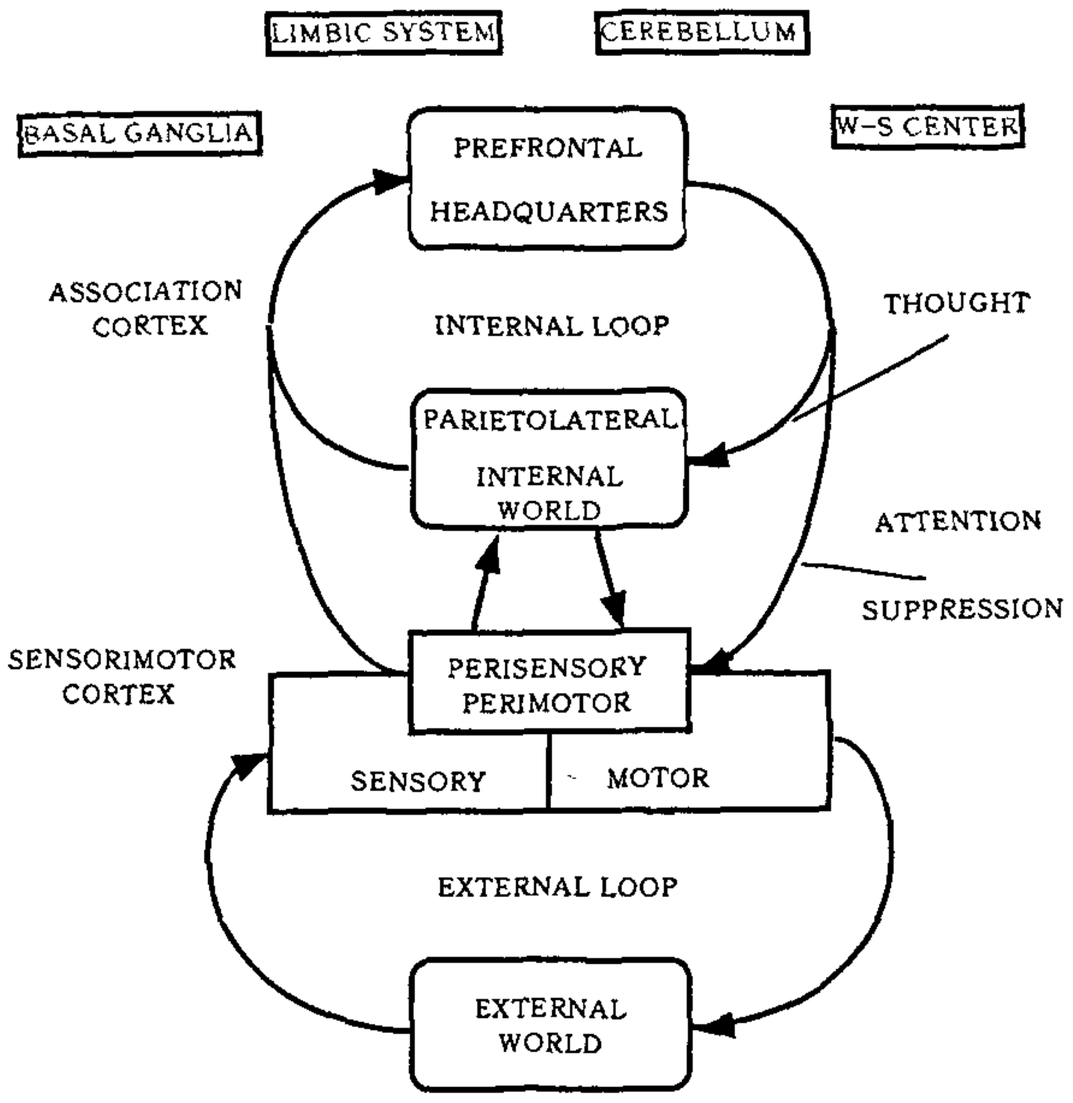

Figure 5. Internal loop structure in the brain.

sociated part of the thalamus, constitutes a fifth functional system in the brain. The primate association cortex has two major areas, i.e. the prefrontal area anterior to the motor areas and the parietolateral area surrounded by the sensory areas. The parietolateral area collects sensory information from various sensory and perisensory areas, and integrates this information to form images and concepts or ideas. In the case of attention or no-go suppression, the prefrontal area sends command signals to the sensori-motor cortex to interfere with the fourth functional system (Figure 5). The prefrontal area also sends command signals to the parietolateral area. A unique feature of the fifth functional system is that the prefrontal and parietolateral areas are interconnected to form an internal loop in the brain. The prefrontal cortex acts to manipulate images, concepts and ideas encoded in the parietolateral area via this loop, whose action seems to represent the process of thought. The fifth functional system also seems to be under the influence of the four regulatory systems (A)–(D) (Figure 3).

Roles and mechanisms of brain systems

The relationship between the brain and mind/behaviour levels could be uncovered if the roles and mechanisms of the 9 systems of the brain (Figure 3) could be identified. Reflexes represent essentially a classic type of control with a reflex center acting as a controller upon a skeletomuscular system as a control object. Compound movements involve a rhythm generator or other types of function generators in addition to the classic control system structures. Mechanisms of innate behaviours are more complicated than those of compound movements and include an internal program for complex behavioural responses.

Besides reflexes and compound movements, roles and mechanisms have been most thoroughly elucidated in the cerebellum. In modern terms, a cerebellar unit attached to a reflex or compound movement converts classic control to a modern type of adaptive control. When attached to the cerebral neocortex, which forms the fourth and fifth functional systems, a cerebellar adaptive unit appears to provide an internal model. Consider a cerebellar unit fed by input signals common to a system to be copied, with detected discrepancies of outputs determined as error signals (Figure 6). When the error signals are fed into the cerebellar unit to induce self-reorganization of its neuronal networks due to LTD induction, the signal transfer characteristics of the cerebellar unit are modified to result in minimization of the error signals until the cerebellar unit becomes a model having signal transfer characteristics identical to those of the system to be copied.

I interpret the loop connection between the motor area of the cerebral neocortex and the paravermal cortex of the cerebellum to serve a voluntary motor control utilizing such a model in the cerebellum (Figure 7). When the motor cortex sends command signals to a particular skeletomuscular system to perform a voluntary movement, the same signals may be sent to a model of that system, the output of which is returned back to the motor cortex. Thus, a voluntary movement may be performed without using the external sensory feedback in response to the actual movement, but instead by relying upon internal feedback through a model in the cerebellum. This control system explains why movement exercise increases skill; a cerebellar model of the skeletomuscular system in use is formed during the repeated exercise. This control system also explains dysmetria, a typical cerebellar symptom. While a healthy

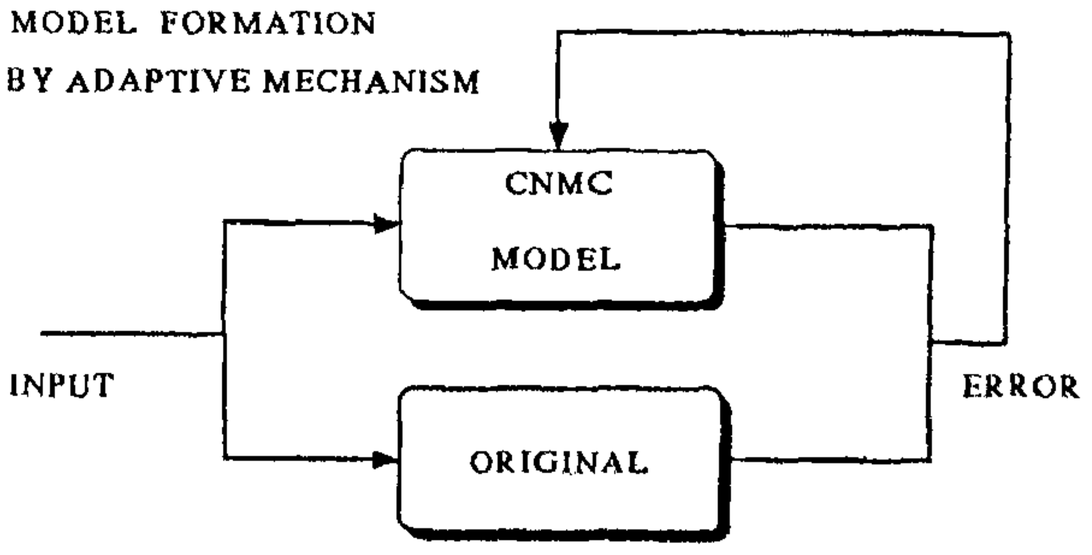

Figure 6. Model formation in a cerebellar unit by its adaptive mechanism.

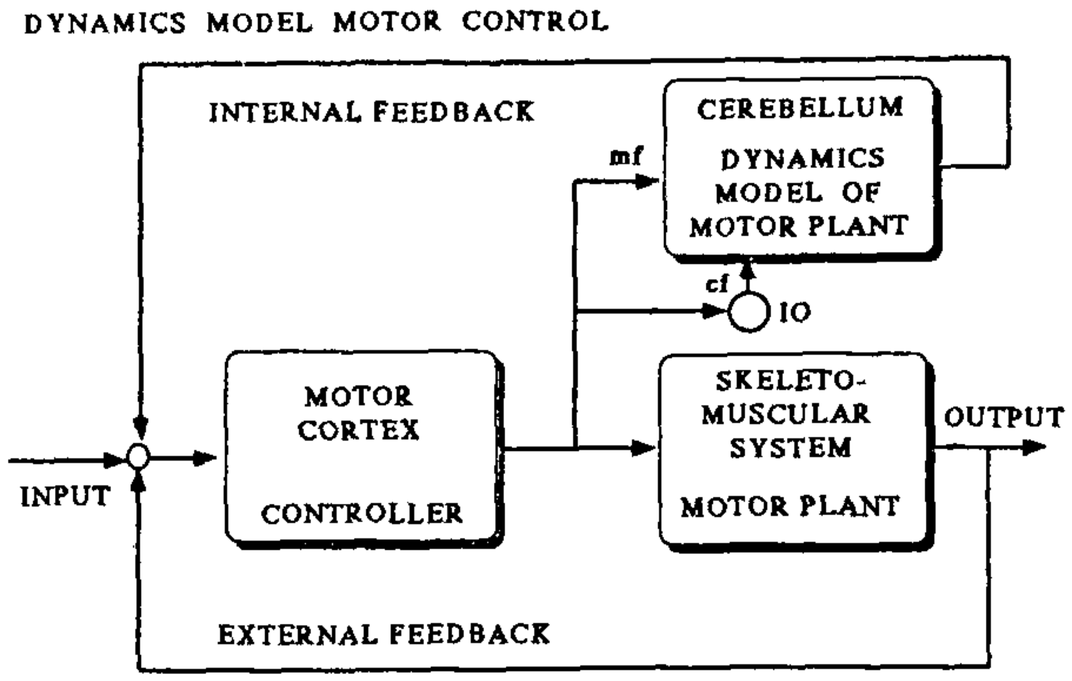

Figure 7. Principle of dynamics model control of movement. IO, inferior olive, cf, climbing fiber.

person can accurately touch his or her nose with a fingertip even with closed eyes, a patient with certain cerebellar diseases becomes unable to do so, apparently due to lack of a cerebellar model for the finger-to-nose pointing movement.

The above control system scheme for voluntary movements can be extended to explain thought processes for which the prefrontal association cortex acts as a controller to manipulate images, concepts or ideas generated in the parietolateral area as control objects. While the thought process is repeated, a model of images, concepts or ideas will be formed in the cerebellum so that the thought process can be performed in a feedforward manner without feedback. Here, an analogy is assumed between thought and movement. In the same way as we move arms and legs, we move images, concepts and ideas in our mind. The objects to be controlled are very different in movement and thought, but the operating control system principles may be identical in operation. The control system principles thus have wide application to problems of both movement and thought.

Problems of subjectivity

The psychology-divided components of the mind/behaviour such as perception, emotion, learning, thought, language, awareness and these are related to certain distinct areas of the brain. It is therefore possible to investigate their mechanisms by identifying these areas and studying the neural events taking place in them. In fact, an increasing number of mental functions have been topics of recent neuroscience research. Nevertheless, subjective components such as affect, volition and self-consciousness remain the most intriguing components for which related brain areas have not yet been clearly defined and consequently the identification of an effective neuroscience approach is currently difficult.

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