■第19回日本神経心理学会会長講演***

Clinical Neurophysiology for Memory and Intelligence

Kenichi Uemura* Yoko Imamura* Mistuo Kaneko**

INTRODUCTION

The neurophysiology of higher cerebral functions including memory and intelligence has recently remarkably progressed. A brief overview of neurophysiology of higher cerebral functions would certainly be useful to understand neuropsychological signs and symptoms in our daily clinical practice.

THREE BRAINS

Brodmann cytoarchitecturally divided the cerebral cortex into 52 areas (Brodmann, 1909). They are not only mutually connected by fibers but also are connected with specific thalamic nuclei. This indicates that each cortical area has a specific function. However, as shown in Fig.1, the cerebral hemisphere can roughly be divided into three parts (Uemura, 1986). The part posterior to the central sulcus integrates external sensory information for ideation and is the "sensory integrative brain". The part anterior to the central sulcus makes a decision based on the idea formed in the posterior part, induces a behavior via the motor system, and is the "expressive brain". The limbic system on the mesial surface is known to be related to emotion. The functions of these three brains will be explained in more detail.

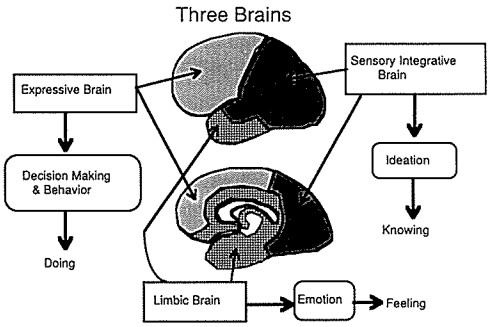


Figure 1 The three divisions of the cerebral hemisphere for higher cerebral functions.

1. Functional Organization of the Cerebral Hemisphere

As shown in Fig.2, the somatosensory information is perceived in the postcentral gyrus of the parietal lobe, the auditory information is perceived in area 41 of the temporal lobe, the vestibular information is perceived in area 2v of the parietal lobe, and the visual information is perceived in area 17 of the occipital lobe. The left hemisphere has Wernicke's speech area, and the parietal association area is related to verbal ideation. The right parietal association area is related to visuospatial orientation. These physiological functions have well been known for many years, but

*Departments of Neurosurgery, Hamamatsu University School of Medicine, Hamamatsu, Japan
**Hamamatsu Medical Center Hospital, Hamamatsu, Japan
***Presidential Adress by KU at 19th Annual Meeting of Neuropsychology Association of Japan.

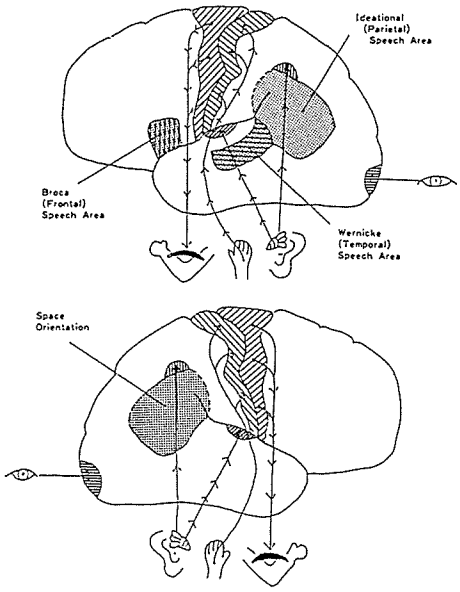


Figure 2 Early identified cortical functional localizations.

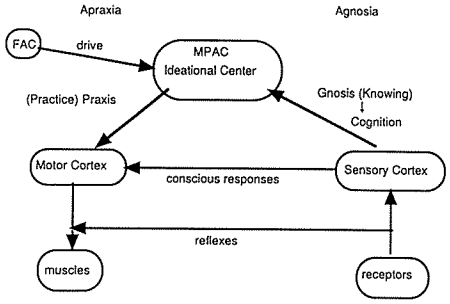


Figure 3 Shematic illustration of sensation, perception, cognition, and praxis in relation to agnosia and apraxia.

what are the functions of the large blank areas?

As shown in Fig.3, when sensory information from each receptor has reached the conscious level at the respective primary sensory cortex, it is said to have been perceived, and it is said to have been recognized when the meaning of the information is understood. The disturbance of this cognition process is agnosia. All the information must be gathered at the ideational center (areas 39 & 40, major parietal association cortex = MPAC) for ideation.

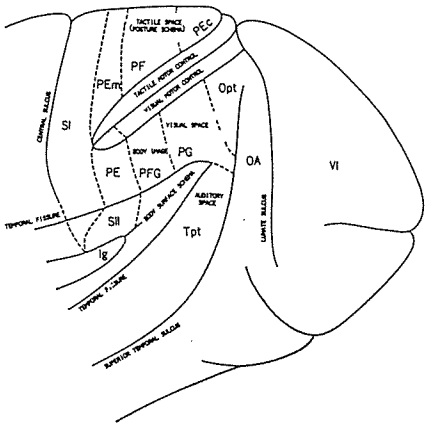


Figure 4 Functional localization in parietal association area in monkey (Modified from Sakata, 1985).

When we decide to respond to sensory stimuli under a drive from the frontal association cortex (FAC), a series of actions must be organized and transmitted to the motor cortex. This process is called praxis, and its disturbance is apraxia. The unconscious responses at the spinal cord, the brainstem, or other subcortical levels are called reflexes, and the conscious responses which bypass the ideational center are conscious responses.

2. The Sensory Integrative Brain

Sakata (1985) reported detailed processes of integration and cognition of somatosensory information in monkey (Fig.4). In man (Fig.5), the somatosensory information is topographically perceived at Brodmann's areas 3, 1, and 2 where 2-point discrimination becomes possible. This information is sent to the adjacent somatosensory association area (areas 5 & 7) where stereognosis, hylognosis, and posture scheme are recognized, and further sent to area 40 in MPAC where a body image is formed. A lesion in area 40 on the dominant side results in right-left disorientation and finger agnosia, and also apraxic agraphia as explained later.

Auditory information is sent to the audi-

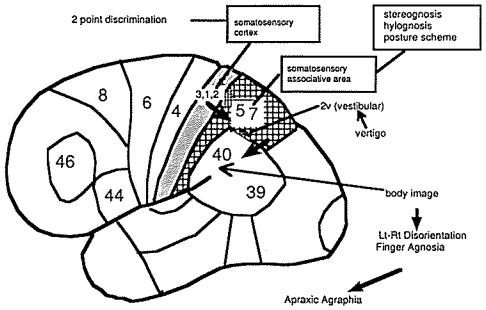


Figure 5 Integration of somatosensory information in the parietal cortex in man. Areas 39 & 40 constitute the major parietal association cortex (MPAC) or "ideation center". Area 4 is the motor cortex, area 6 is the premotor area, area 8 is the frontal eye-field, area 44 is Broca's speech area, and area 46 is for working memory.

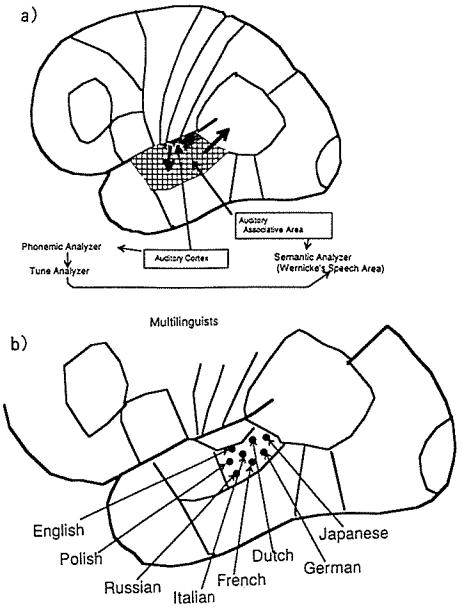


Figure 6 Integration of auditory information in the temporal cortex in man. a) The posterior portion of the auditory association area is Wernicke's speech area. b) Imaginary localization of seven languages used by one of the authors (KU).

tory cortex for phonemic analysis at area 41 and tune analysis at area 42, and then sent to the adjacent auditory association area for semantic analysis (Fig.6a). The left auditory association area has Wernicke's speech area, with separate speech areas for respective languages in multilinguists (Ojemann et al, 1978). Fig.6b illustrates imaginary localization of seven languages used by one of the authors (KU).

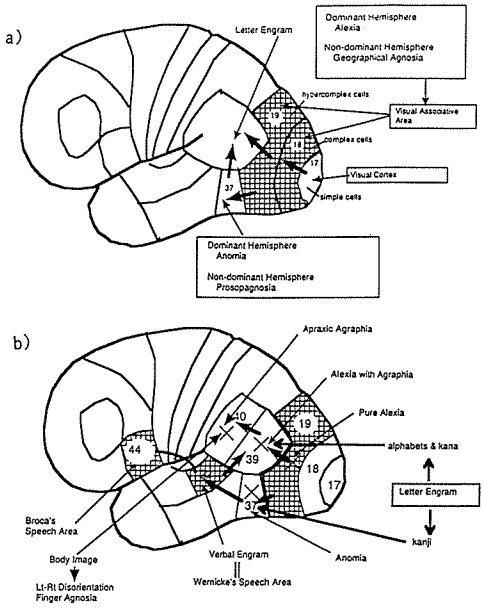


Figure 7 Integration of visual information from the occipital to parietotemporal cortices in man. a) Integration to the pariental cortex is related to visuospatial orientation of the object, while that to the temporal cortex is related to the object identification. b) X represents a lesion. For Japanese, kana (phonetic letter) is store in area 39, while kanji (ideographic letter) is stored in area 37.

The visual information is integrated through many stages in monkey. The object is recognized in the temporal lobe while its position in space is recognized in the parietal lobe. In man, visual information is perceived in area 17, and integrated in areas 18 and 19 (Fig.7a). A lesion in the dorsal area 19 of the nondominant hemisphere results in geographical agnosia. In relation to the object recognition in monkey, a lesion in area 37 just anterior to the ventral area 19 results in anomia in the dominant hemisphere, but prosopagnosia in the nondominant hemisphere.

As for the letter engram, phonetic letters as alphabets and kana are stored in area

a) Solution with the dominant hemisphere.

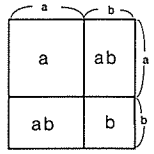
To solve $(a+b)^2$ wit left brain

$$(a+b)^2 = (a+b)\times(a+b) = a(a+b)+b(a+b) = a^2+2ab+b^2$$

How to solve with right brain?

b) Solution with the nondominant hemisphere.

To solve $(a+b)^2$ with right brain



$(a+b)^2 = a^2 + b^2 + 2ab$

Figure 8 Mathematic solutions in the dominant versus nondominant hemisphere. a) Solution with the dominant hemisphere. b) Solution with the nondominant hemisphere.

39, while ideographic letters as kanji are stored in area 37 (Fig.7b). Thus in Europeans and Americans, a lesion in area 39 wipes out all letter engrams, resulting in alexia with agraphia. Japanese cannot read kana but may still be able to read kanji. A lesion in the visual association area disconnects the visual cortex from the letter engram, and the patient cannot read, but can still write because the engram is connected with the motor cortex, thus resulting in pure alexia. A lesion in area 40 disconnects the motor cortex from the letter engram, and the patient cannot write, but can read because the letter engram is connected with the visual cortex. Right-left disorientation and finger agnosia are also seen as described earlier. The verbal engram is thought to be stored in Wernicke's speech area.

$(a+b)^2$ can be solved with the left

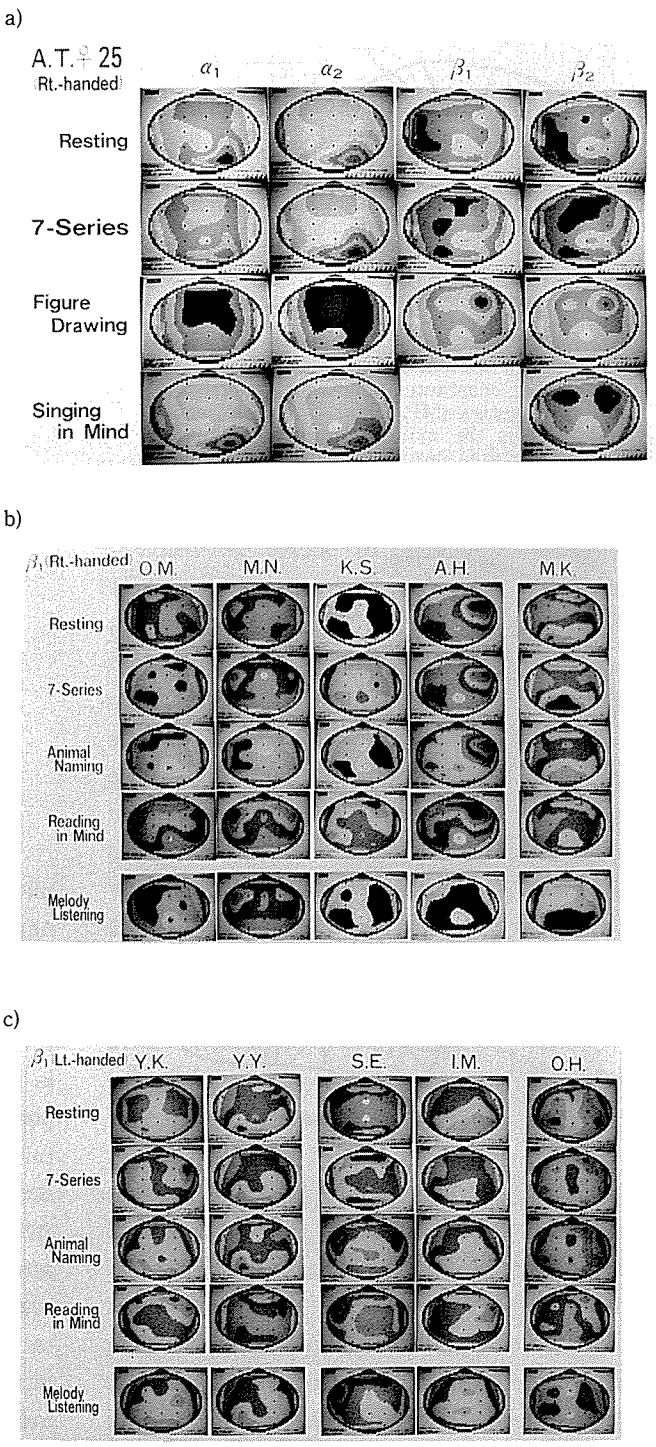


Figure 9 EEG topograms under psychological tasks. a) A 25-year-old female. 7' series activated β-waves more over the left hemisphere, while figure drawing and singing-in-mind activated them more over the right hemisphere. b) β-waves for five right-handers. c) β-waves for five left-handers.

Table 1 Hemispheric dominancy of speech functions in 32 volunteers, tested by EEG topography under psychological tasks

Lateralization of Speech				
	Hemispheric Dominancy			
Handedness	Right	Left	Bilateral	Total
Right	2 (8.7%)	12 (52.2%)	9 (39.1%)	23
Left	1 (11.7%)	3 (33.3%)	5 (55.6%)	9
Total	3 (9.4%)	15 (46.9%)	14 (43.8%)	32

brain as shown in Fig.8a. But $(a+b)^2$ can be solved with the right bain as shown in Fig.8b.

We studied the language lateralization with EEG topography in many volunteers. In a sbuject shown in Fig.9a, 7' series (serial substraction of 7 from 100 (Hayman, 1941, 1942)) activated β waves in the left hemisphere, but figure-drawing and singing in mind activated them in the right hemisphere (Uemura, 1984b, 1986). Among 5 right-handers, the lunguage function was on the left in 4, but bilateral in one subject (Fig.9b). Among 5 left-handers, the language function was on the left in 2, bilateral in 2, but on the right in one subject (Fig.9c) (Uemura, 1984b, 1986). The result of our study of hemispheric dominancy of speech function is shown in Table 1. It is interesting that 52% of right-handers showed left hemispheric dominancy, whereas 56% of left-handers showed bilateral dominancy.

3. The Expressive Brain

The somatotopography is well known in the motor cortex which is the major source of the pyramidal tract. Fig.10 schematically illustrates the processes involved in voluntary movements based on the traditional physiology (Uemura, 1986). They involve the ideational center for motor planning, the premotor area with basal ganglia and the

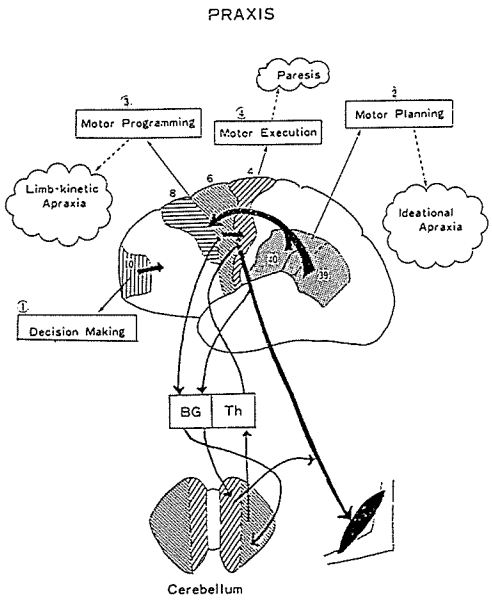


Figure 10 Schematic illustration of the processes involved for voluntary actions according to the classical neurophysiology. Motor planning occurs in the ideational center. Motor programming involves the premotor area, thalamus, basal ganglia and the lateral cerebellum (neocerebellum). For motor execution, the paravermian cerebellum is involved. The area primarily involved for decision making is not yet clearly identified.

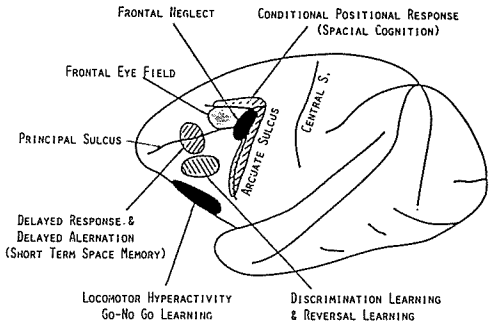


Figure 11 Functional localization in prefrontal area of rhesus monkey. (Modified from Kubota, 1976).

cerebellum for motor programming, and the motor cortex and the cerebellum for motor execution.

Kubota (1976) schematically illustrated the functional localization in the prefrontal area in monkey (Fig.11). Subsequent studies mainly on monkeys by Tanji et al (1994a, b)

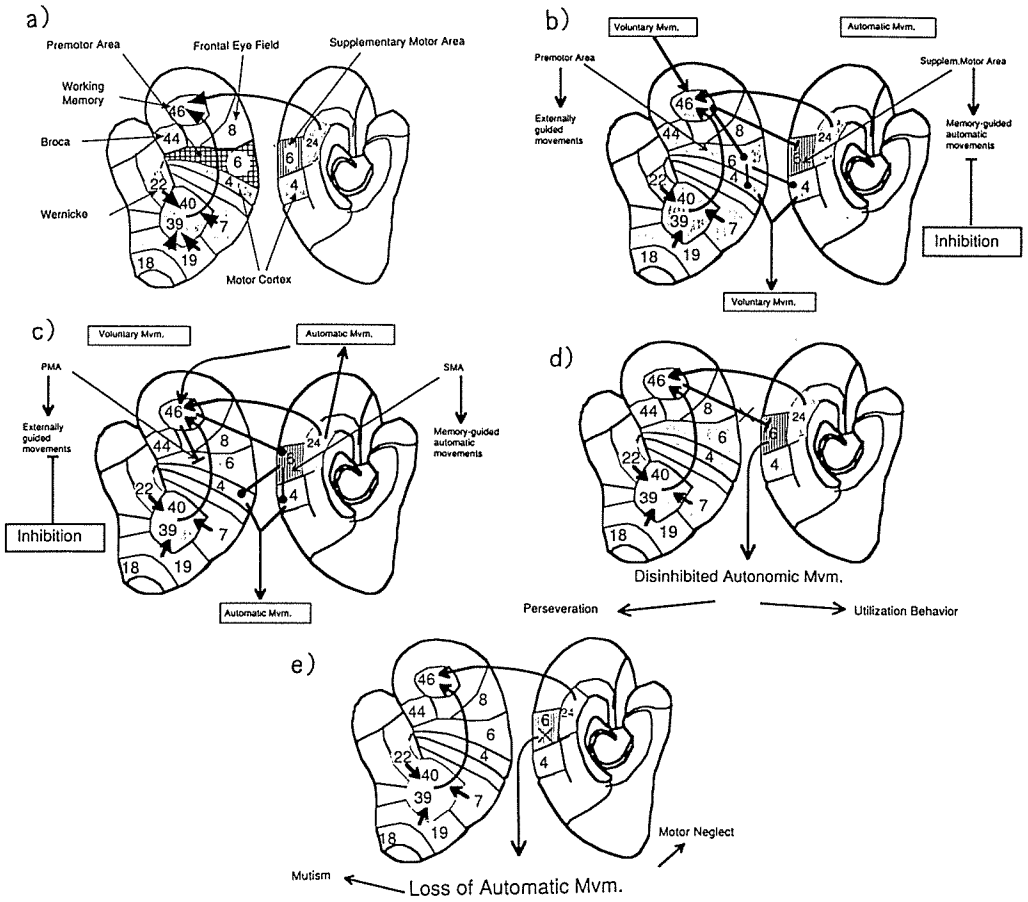


Figure 12 Schematic illustration of the processes involved for voluntary and automatic movements. a) Area 46 is now believed to be related to working memory. The supplementary motor area (SMA) (the medial area 6) is related to memory guided automatic movements, while the premotor area (PMA) (the lateral area 6) is related to visually or externally guided voluntary movements. b) Area 46 excites PMA and inhibits SMA for voluntary movements. c) Area 46 inhibits PMA and excites SMA for automatic movements. d) Disconnection between area 46 and SMA results in perseveration and utilization behavior. e) A lesion in SMA results in motor neglect and mutism.

have shown that the area 46 is related to working memory (Baddeley, 1992, D'Esposito, 1995), the premotor area to the externally (visually) guided movements, and the supplementary motor area to the memory-guided automatic movements (Fig.12a). If so, to perform voluntary movements, the area 46 must first inhibit the automatic movements from the supplementary motor area, and then stimulate the premotor area to induce desired movements (Fig.12b). On the contrary, the area 46 must first inhibit the premotor area and then stimulate the supplementary motor area to induce automatic movements (Fig.12c). Disconnection between area 46 and the supplementary motor area disinhibits automatic movements, resulting in perseveration and utilization behavior (Fig.12d). A lesion in the supplementary motor area wipes out automatic movements, resulting in mutism and motor neglect (Fig.12e).

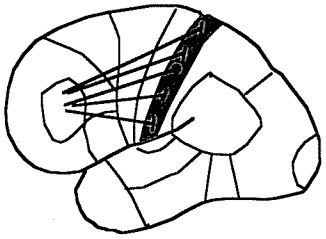
A patient with hemorrhage in the left prefrontal area showed perseverated writing. In the test of digit span, he could repeat 5 digits at the first trial, but in the test of

Digit Learning Test (Pt:Y.S.,Lt.F.Hem)

Examiner	Patient	Trial Times
723	723	1
4258	4258	1
36928	36928	1
715496	749641	1
715496	745691	2
715496	749691	3
715496	7456---	4
715496	745691	5
715496	745691	6
715496	745194	7
715496	745194	8
715496	745694	9
715496	765694	10

Figure 13 Results of digit learning test on a patient with a left frontal lobe hemorrhage, showing inability of learning 6-digit-number due to perseveration.

a) Attention: To augument interested sensation and to inhibit uninterested sensations.



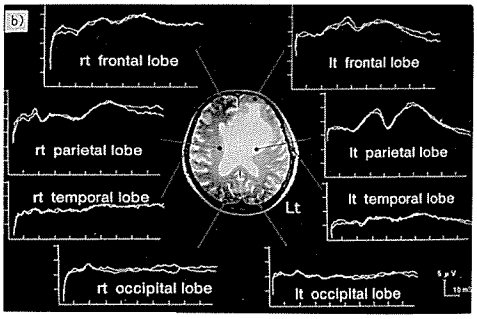
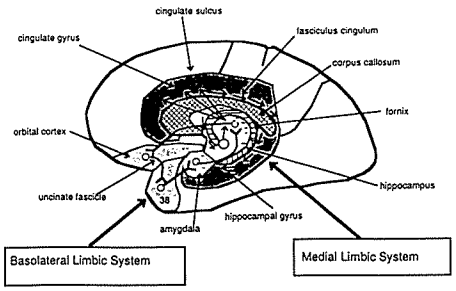


Figure 14 Prefrontal gating of somatosensory inputs. a) The prefrontal area auguments the area associated with interested sensory inputs while inhibiting the surrounding areas. b) The somatosensory evoked potentials (SEPs) recorded over the left parietal area (the second raw from the top on the right side of the figure) area were greatly enhanced. indicating that the preexisting on-going prefrontal inhibition had been eliminated by the left prefrontal glioma shown in MRI (center of the figure).

digit learning (Drachman et al, 1966 ; Hamsher et al, 1980) he was unable to learn 6 digits even after many trials. But this was not due to memory disturbance, but due to perseveration of the initial "7-

a)



b)

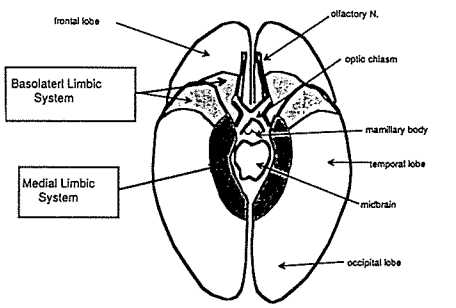


Figure 15 Medial and basolateral limbic systems (modified from Livington et al, 1972). a) The medial surface of the right hemisphere showing the medial and basolateral limbic systems. b) The basal view of the cerebrum showing both limbic systems.

4" instead of "7-1", as shown in Fig.13.

For attention, we must augument the interested sensation and at the same time must inhibit uninterested sensations (Ray et al, 1992 ; Yamaguchi et al, 1990). Thus the prefrontal area usually impose a strong inhibition as a whole to each sensory cortex as shown in Fig.14a. To account for this, the somatosensory evoked potentials recorded over the left parietal area on a patient with a left prefrontal tumor showed a higher amplitude as a result of disinhibition (Fig. 14b).

4. The Limbic System

The medial surface of the hemisphere contains the limbic system, which consists of the medical limbic system (Papez circuit) (Papez, 1937) related to emotional excitation and the basolateral limbic system (Yakovlev Circuit) (Yakovlev, 1947) related to

emotional depression (Fig.15a) (Livington et al, 1972). Bilateral injury to the basolateral limbic system disinhibits the medial limbic system, resulting in restlessness and violence (Fig.15b).

In summary, the cerebrum consists of three brains, namely the sensory integrative brain which integrates external sensations for ideation, the limbic system related to emotion, and the expressive brain related to decision making and behavior. These are the physiological bases for knowing, feeling, and doing, respectively.

MEMORY MECHANISM AND ITS DISTURBANCES

1. Three Stages of Memory in Man

The memory mechanism consists of three processes of memorization or learning, retention, and recall. The loosely used terms of short-term and long-term memories must first be clearly defined.

In 1953 Scoville performed bilateral amygdalectomy and hippocampectomy on Mr. H.M. with intractable temporal lobe epilepsy (Penfield et al, 1958 ; Scoville et al, 1973). His postoperative memory disturbances have been reported by Milner in detail which can be schematically illustrated in Fig.16 (Milner, 1970). Postoperatively, he demonstrates a total amnesia after surgery up to this date, although he can memorize for only 7 seconds. He can still learn manipulatory skills normally, although he cannot recall the skill training. He shows a partial amnesia for 1-2 years preceding the surgery, but his memory of events more than 2 years before surgery is quite normal.

This only one but crucially important clinical finding clearly indicates that the memory mechanism in man consits of

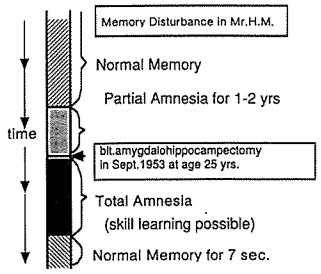


Figure 16 Schematic illustration of memory disturbances of H. M. following bilateral amygdalohippocampectomy in 1953.

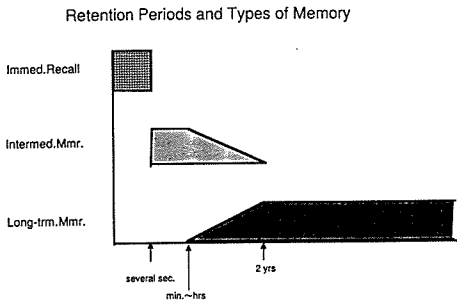


Figure 17 Immediate, intermediate, and long-term memories with respective possible retention periods.

immediate recall, intermediate memory, and long-term memory. As shown in Fig.17, the immediate recall cannot last longer than several seconds, but the intermediate memory can be retained thereafter up to 2 years at maximum. The transition from the intermediate to long-term memory can occur at any time from several minutes to 2 years after the event, probably depending on the content and formation of the memory. Therefore, the intermediate and long-term memories cannot be dichotomized simply by the longth of retention period.

2. Physiological Mechanisms of Memory

1) *Physiological Mechanism of Immediate Recall*

As shown in Fig.18a. each cortical area has bilateral connections with a respective thalamic nucleus, and between them exists a reverberating circuit (Chang, 1950) which

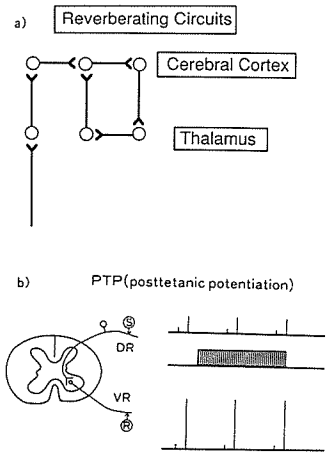


Figure 18 Electrophysiological bases for memory. a) Thalamocortical reverberating circuit accounting for immediate memory. A sensory input to the cortex is sent to an independent reverberating ciruit between the cortical and thalamic neurons for maintenance of the information for several seconds. b) Posttetanic potentiation of monosynaptic spinal reflex discharges. A certain stimulus to a dorsal root (DR) evokes a certain reflex discharge (top on the right). Following high frequency (tetanic) stimulation (middle on the right) to DR, the reflex amplitude is greatly enhanced (bottom on the right).

can maintain the received electrical activities for several seconds, which is convenient to explain the immediate recall.

2) *Physiological Mechanism of Intermediate Memory*

As shown in Fig.18b, an electrical stimulus to the dorsal root induces a spinal reflex potential. Following high frequency tetanic stimuli, the reflex potential will be amplified 3 times, which is called posttetanic potentiation (Lloyd, 1949). But this potentiation cannot last more than 2 hours, thus cannot account for the intermediate memory. However, the potentiation in the hippocampus was found to last more than several hours and at least up to several weeks, is called long-term potentiation (Bliss et al, 1973a, b), and is quite convenient to explain the intermediate memory. When an electric current of 600Hz, 300-400μA is given for the hippocampus 1 second daily, epileptic discharges will be induced in 2 to 3 weeks, which is called kindling phenomenon (Goddard et al, 1969 ; Ullal et al, 1989), and is also convenient to explain the intermediate memory. However, the mechanism of the long-term potentiation has not yet been adequately clarified.

The hippocampus is connected with afferents and efferents to almost all cortical areas, by which it can receive and temporarily retain the information from the sensory integrative brain and can return it to the sensory association areas for long-term memory.

3) *Physiological Mechanism of Long-term Memory*

As shown in Fig.19a, when impulses arrive at axodendritic synapses, a few impulses shown as A or B are not adequate to fire the neuron, and many impulses must be summed to reach the firing threshold of the neuron. As shown in Fig.19b, a presynaptic inhibition to an incoming axon terminal blocks the impulse of that particular axon, and an axodendrtic inhibition blocks the impulse of a particular dendrite, thus resulting in impulse selection. However, an axosomatic inhibition blocks all the impulses received by the neuron, resulting in total block.

As shown in Fig.20a, an axon terminal, upon arrival of an impulse, will secrete neurotransmitters which are taken up by the receptor of another neuron for synaptic impulse transmission, but in return receives neurotrophic factors which are sent back to the soma to maintain its activities. As shown in Fig. 20b, an increase in transsynaptic transmission results in an increased uptake of neurotrophic factors and sprouting of new axons for tighter synaptic connec-

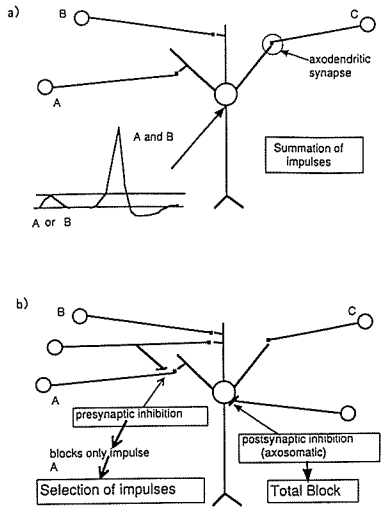


Figure 19 Electrophysiology of neuronal interactions. a) Summation of impulses. Impulse A or B is not adequate to fire the neuron, but simultaneously arriving impulses A and B are adequate to fire the neuron by summation of impulses. b) Selection of impulses. Presynaptic inhibition blocks only the impulse coming through the axon A, and an axodendritic inhibition by neuron B blocks only the impulses coming through that particular dendrite, whereas an axosomatic inhibition by C totally blocks the neuronal discharge.

tions between them. This indicates that the more the brain is used, the more neuronal networks will be formed.

On the contrary, as shown in Fig.21, the unused neuron cannot receive neurotrophic factors and must die by apotosis.

We are born with surplus neurons and axon collaterals, but the unused neurons will die and the unused collaterals will be eliminated. This is why infant education is important. Squire (1987) has schematically illustrated changes in neuronal networks by use and disuse.

The neuron will die when injured, and cannot regenerate. However, the axon can regenerate by 1 mm a day following injury. When axons are injured by cerebral hemorrhage or infarction, the scar tissue prevent the axons from regenerating and the function will not be recovered. In some

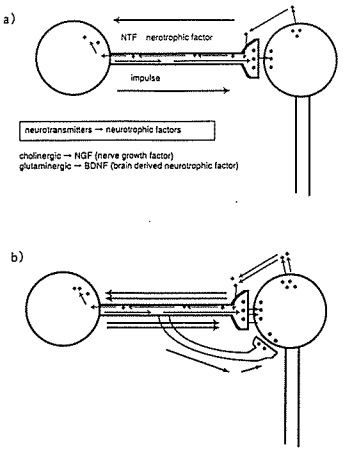


Figure 20 Neurotrophic factors(NTF). a) The presynaptic terminal secretes neurotransmitters to transmit the nerve impulse, when the postsynaptic neuron sacretes neurotrophic factors which are taken up by the presynaptic neuron to maintain its life. Neurotrophic factors are specific ; cholinergic neurons receive NGF, while glutaminergic neurons receive BDNF. b) The more neurotransmitters the neuron secretes, the more NTF it receives and the more axon collaterals will be formed.

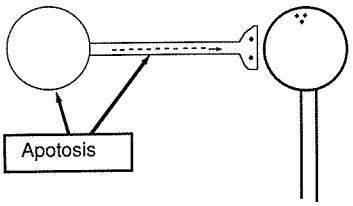


Figure 21 A mechanism of apotosis. If a neuron stops secreting neurotransmitters, it cannot receive NTF, resulting in the neuronal death (apoptosis).

cases, as shown in Fig.22, a bypass circuit may be formed by sprouting of collaterals.

Glees et al (1950) clarified the mechanism of functional recovery following cortical neuronal injury. Following injury to part of the motor cortex, the monkey will develop paralysis on the contralateral side, but it will soon disappear. When the adjacent part of the motor cortex is destroyed, the once disappeared paralysis will recur, which indicates that the function lost by the previous injury had been compensated by the part

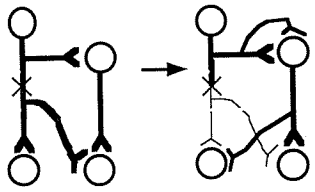


Figure 22 Fate of intracerebral axonal injury, showing a possibility of a bypass formation.

destroyed this time. But the paralysis will disappear again. The adjacent motor cortex is further destroyed to see recurrence and disappearance of paralysis. Such staged ablation of the entire motor cortex will still be followed by complete functional recovery. However, when the entire premotor area is ablated, the paralysis will recur but will never disappear this time. This shows that the function of the motor cortex can be compensated by the premotor area, but not by the other cortices.

We tend to easily forget stories heard from others and knowlege obtained by reading, but we may clearly remember a beautiful scene we have seen only once. This suggests that the transfer from the intermediate memory to the long-term memory occurs more easily in the non-dominant hemisphere. This is why the audiovisual education is more effective.

3. Two Routes in Memory Mechanism

In summary then, there are two routes in the memory mechanism (Fig.23). As for cognitive experience, the information perceived at respective sensory association areas is kept there only for immediate recall. It is sent to the hippocampus for intermediate memory, and finally returned to respective sensory association areas for long-term memory. As for manipulatory skills, the motor programs are sent to the cerebellum for intermediate memory by the long-term depression at Purkinje dendrites

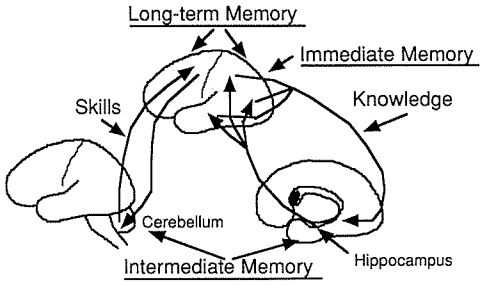


Figure 23 Two routes and three stages in the memory mechanism. Cognitive experiences are memorized in the posteior route as immediate memory at the sensory cortices, intermediate memory at hippocampus, and long-term memory at sensory associative areas. Skillful movements are memorized in the anterior route as intermediate memory at Purkinje dendrites, and long-term memory at the premotor and/or supplementary motor areas.

(Ito et al, 1982). They must be returned to the premotor and/or supplementary motor areas for long-term memory.

The mechanism for each memory can be speculated as follows. The immediate recall lasts only for several seconds, and may be related to the thalamocortical reverberating circuits. The intermediate memory lasts mainly for several hours to weeks and may be related to modulation of synaptic efficacy. Cognitive experience may be related to the long-term potentiation of the hippocampus, and manipulatory skills may be related to the long-term depression at Purkinje dendrites. Emotional experience may be related to the amygdala. The long-term memory for years may be related to synaptogenesis by sprouting. The cognitive experience will be stored at the sensory integrative brain, and manipulatory skills will be stored in the premotor and/or supplementary motor areas, basal ganglia, and the cerebellum (Uemura, 1984a, 1990, 1991).

4. Tests for Memory

Table 2 shows major tests for respective memories. Please note that the digit span

Table 2 Representative tests for respective memories

Tests for Respective Memories	
Immediate Recall	digit span immediate recall of 5 words
Intermediate Memory	digit learning 5 min. memory of 5 words, "What did you eat last night?"
Long-term Memory	more than 2 year old facts and experiences

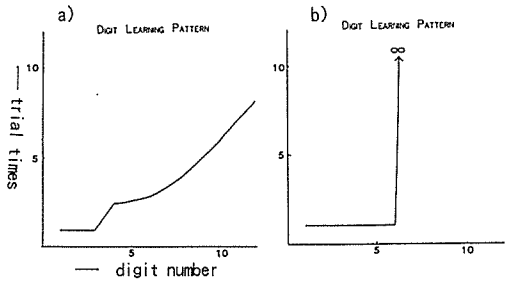


Figure 24 Digit learning patterns ; a) normal, b) abnormal.

is the most effective test for immediate racall and not a test for short-term or intermediate memory. To surely test the long-term memory, you must ask about the knowledge and experience that are more than 2 years old. Fig.24a shows a normal pattern of digit learning (Uemura, 1986). A person with the digit span of 6 can learn numbers with 6 digits at once, can learn numbers with 7 digits after one more trial. Thus the more digits are added, the more trials will be required for learning. Many brain injured patients cannot learn a number with only one additional digit beyond the digit span even after numerous trials (Fig. 24b). The most common cause is perseveration. This patient with a digit span of 6 could not learn 7 digits even after many trials, though there was no perseveration, as shown in Fig.25a. MRI (Fig.25b) showed a craniopharyngioma, which did not directly involve the hippocampus but has involved

a) Digit Learning Test
(Pt:HM 60f Craniopharyngioma)

Examiner	Patient	Trial Times
582	582	1
6439	6439	1
42731	42731	1
619473	619473	1
4179386	4137496	1
4179386	413968-	2
4179386	416938-	3
4179386	417698-	4
4179386	4397836	5
4179386	4319738	6
4179386	419738-	7
4179386	4319368	8
4179386	4173698	9
4179386	4137698	10

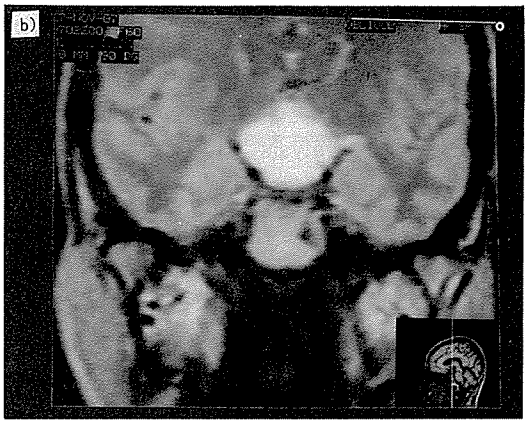


Figure 25 Digit learning pattem on a 60-year old female with craniopharyngioma. a) Inability to learn a 7-digit-number without perseveration. b) MRI demonstrating craniopharyingioma destoying the Papez medial limbic circuit.

the Papez circuit of the medial limbic system. Therefore the intermediate memory mechanism is thought to have been disturbed in this patient.

HAMAMATSU HIGHER BRAIN FUNCTION SCALE

1. Two Types of Dementia

Alzheimer's disease and vascular dementia constitute the two major dementias. The former is more common in America and Europe, while the latter is more common in Japan. Recent studies with PET (positron emission tomography) show that the regional cerebral metabolic rates and blood flow will

first decrease in the temporoparietal areas in Alzheimer's disease, thus called the posterior type of dementia, whereas they will decrease first in the prefrontal area in most vascular dementias, thus called the anterior type of dementia.

Most tests for intelligence scale including Wechsler Adult Intelligence Scale (WAIS) and Mini-Mental Status Examination (MMS) measure the functions of the sensory integrative brain (posterior hemisphere) and not those of the prefrontal area. Thus for early diagnosis and management of treatable vascular dementia, a simple but effective test battery to measure the prefrontal functions is mandatory.

2. Kana Pick-out Test

The Japanese language is usually written with a combined use of both kanji (ideographic Chinese characters) and kana (phonetic letters). But it can be written only with kana, as shown in Fig.26a. Five kana represent five Japanese vowels, namely "a, i, u, e, and o", and all the other kana except the one representing "n" consist of a consonant and a vowel. So in this test, a story written only with kana is presented to the examinee, who is asked to circle only the 5 vowel-kana as many as possible within one minute and also at the same time to retain the meaning of the story. Thus two tasks must be conducted simultaneously and quickly.

This Kana Pick-out Test was applied to more than 300 normal volunteers of different ages. As shown in Fig.26b, the average scores were found to sharply decrease with aging with relatively constant standard deviations (SD).

The Kana Pick-out Test and

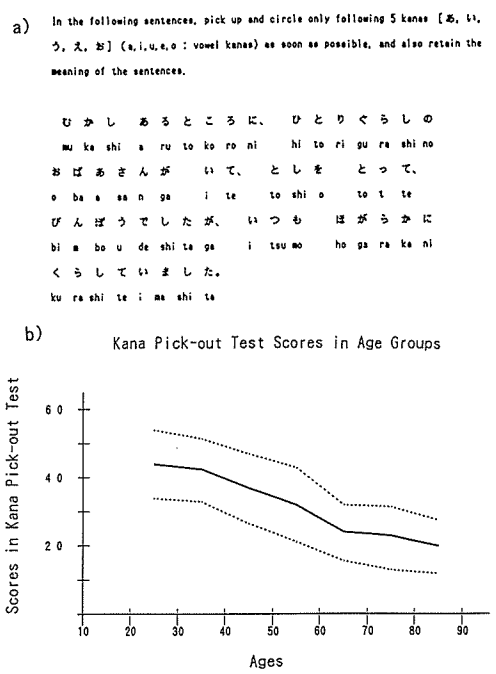


Figure 26 Kana Pick-out Test. a) The initial part of the test sentence written only with kanas (phonetic signs) from which the examinee is requested to pick-out only the five kinds of vowel kanas. The roman letters are shown here only for non-Japanese readers. b) The result of a study of Kana Pick-out Test applied to more than 300 normal volunteers with varying ages, showing the average scores and standard deviations.

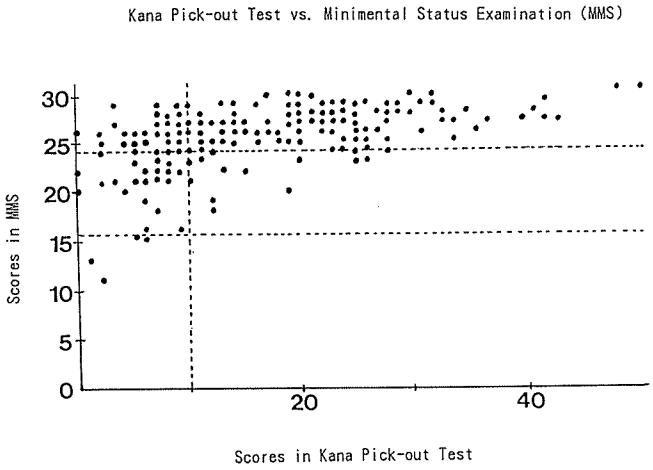


Figure 27 Results of application of Kana Pick-out Test and MMS to 150 normal volunteers aged 70th years.

Table 3 Screening of elderly volunteers for detection of early or predementia

Screening of Elderly Volunteers		
Normal	1,081	86.8%
Predementia	74	5.9
Mild Dementia	126	10.1
Dementia	14	1.1
Totals	1,245	100.0

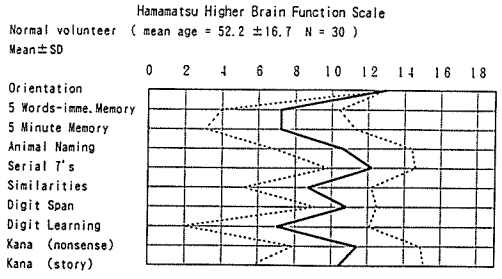


Figure 28 Normal scores (means ± SD) of Hamamatsu Higher Brain Function Scale (HHBFS) obtained by 30 normal volunteers (aged 52.2 ± 16.7 Yrs).

MMS were applied to 150 normal volunteers of the age of 70th. As shown in Fig.27, 24 subjects obtained very low scores (below 10) in the Kana Pick-out Test, even though they showed quite normal (24 or more) IQs. According to our criteria they are not normal and should be classified as "Prede mentia". These two tests were then applied to 1,245 elderly volunteers, finding predementia in 5.9%, mild dementia in 10.1%, and frank dementia in 1.1% (Table 3) (Kaneko, 1988).

3. Hamamatsu Higher Brain Function Scale (HHBFS)

We then added several other simple tests to form a battery of "Hamamatsu Higher Brain Function Scale" (Imamura et al, 1988 a, b, 1992). We applied it not only to dementia patients but also to the non-demented patients with localized lesions in the frontal or temporal lobe to see whether it can measure prefrontal functions.

Fig.28 shows the average scores with

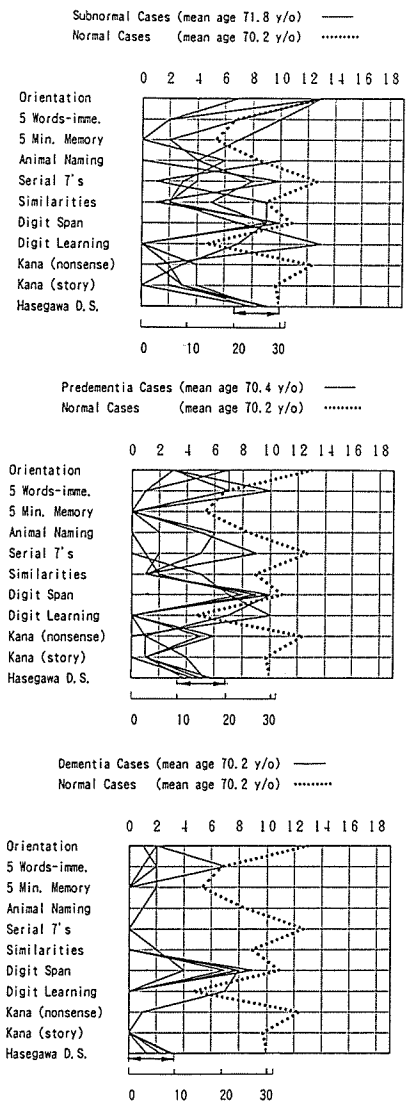


Figure 29 Scores of HHBFS and Hasegawa Dementia Scale in a) subnormal, b) predementia, and c) dementia cases.

SD of HHBFS in normal subjects. The thick solid line represents the average normal score for each subtest. Fig.29a shows the results obtained by the subjects classifed as "subnormal" by the Hasegawa Dementia Scale (HDS) (Japanese mini-mental status examination similar to MMS). The thin solid lines represent the scores obtained by HDS-subnormal but our predementia subjects. The Kana Pick-out Test is the most

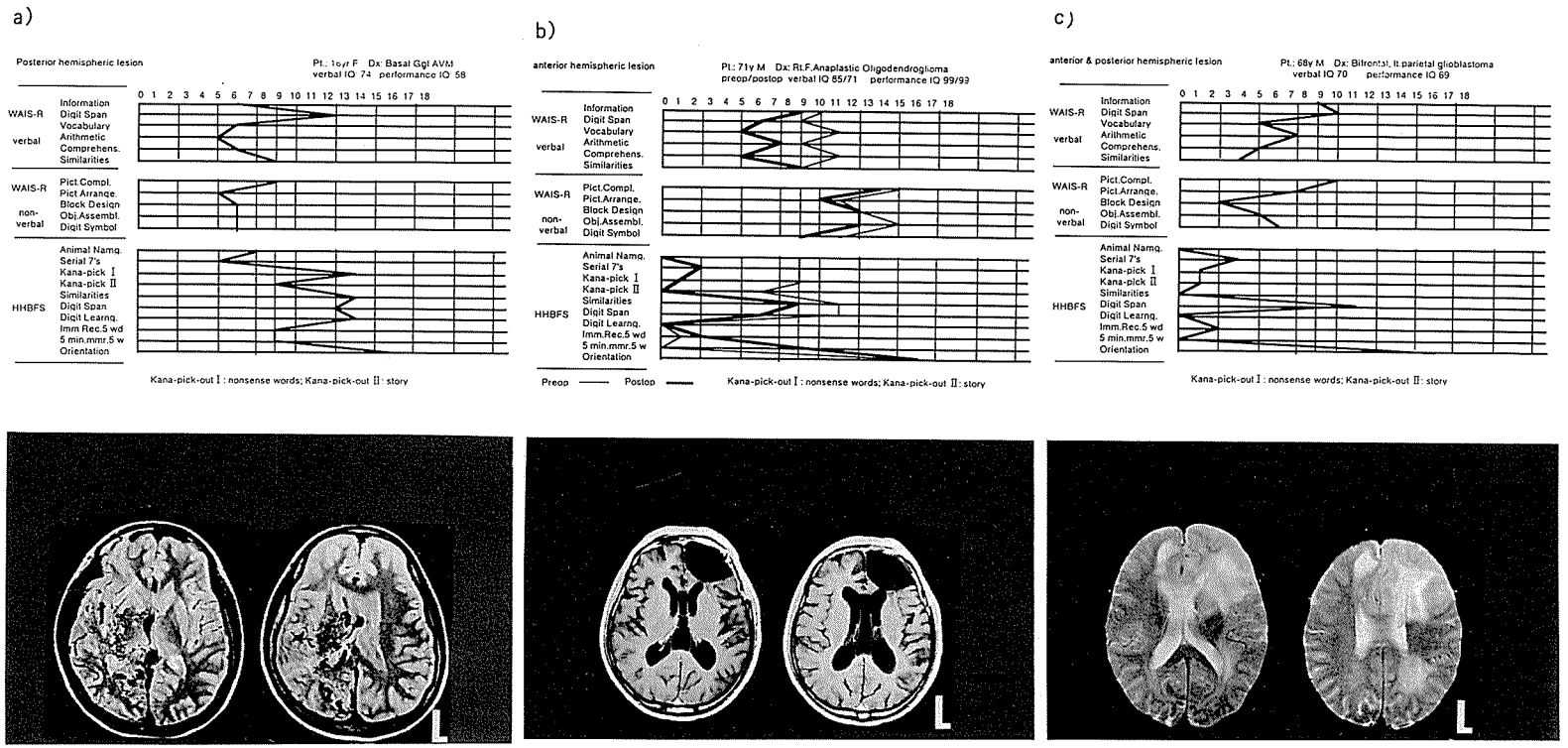


Figure 30 Comparison between WAIS and HHBFS in 3 representative cases. a) A 16-year-old girl with a large AVM in the right posterior hemisphere, showing lower scores in WAIS but normal scores in HHBFS. b) A 71-year-old male with a large anaplastic oligodendroglioma in the left prefrontal area, showing normal scores in WAIS but lower scores in HH BFS. c) A 68-year-old male with a large glioblastoma involving both anterior and posterior hemispheres, showing lower scores both in WAIS and HHBFS.

sensitive. Fig.29b shows the scores obtained by HDS-predementia but our mild dementia subjects. They showed lower scores not only in the Kana Pick-out Test but also in the subtests of 5 minute memory of 5 words, serial sevens (7' series), and similarities. Fig.29c shows the scores obtained by HDS-dementia but our frank dementia subjects. Only immediate recall of 5 words, digit span, and digit learning are preserved.

Representative Cases (Imamura et al, 1996)

In a 16-year-old girl an AVM has widely destroyed the right posterior hemisphere (Fig.30a). WAIS which is believed to measure the functions of the posterior hemisphere or the sensory integrative brain showed lower scores in many items, but our Hamamatsu Higher Brain Function Scale which we have reported to measure the prefrontal functions showed normal or even higher scores.

This 71-year-old male had a large anaplastic oligodendroglioma in the left prefrontal area (Fig.30b). The preoperative data are shown with the thin line, which showed normal scores for WAIS, but lower scores for Kana Pick-out Test, digit learning, and immediate recall of 5 words in our HHBFS.

In this 68-year-old male, glioblastoma destroyed not only bilateral frontal lobes but also the posterior hemisphere (Fig.30c). He obtained moderately lower scores for WAIS, but extremely lower scores for all items except those items not specific to the prefrontal functions in our HHBFS.

In 6 cases with lesions in the dorsolateral prefrontal area, the average score was lower only for animal naming (Frith et al, 1991 ; Parks et al, 1988) and Kana Pick-out. In 3 cases with lesions in the mesial prefrontal area, the average score was low only for digit learning due to perseveration. In 4 cases with lesions in the orbital surface, the average score was low only for Kana Pick-out.

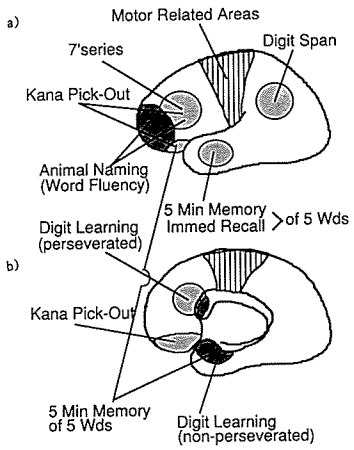


Figure 31 Localization of functions tested by HHBFS. a) The lateral view of the left hemisphere. b) The medial view of the right hemisphere.

Functional Localization in Prefrontal Area

The functional localization in the prefrontal area in relation to our HHBFS is as schematically illustrated in Fig.31. Animal naming is related to the frontal tip, 7' series and Kana Pick-out are to the dorsolateral prefrontal area, the disturbed digit learning due to perseveration is to the mesial prefrontal area, the disturbed digit learning without perseveration and recall of 5 words after 5 minutes are to the hippocampus, immediate recall of 5 words is to the temporal lobe, and the digit span is to the parietal area.

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