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Radiologic Imaging in Psychiatric Disorders in the Light of Recent Developments

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1. Introduction

Psychiatric disorders account for a great majority of overall health problems. Therefore, psychiatric conditions have become of great importance for today's world. It is a known fact that quality of life is substantially determined by the mental health of an individual. A great number of physical diseases have also important mental component. As its importance has been defined here, psychiatric science has shown considerable change particularly in the second half of the current century, and making a diagnosis has become available not only via physical examination, but also by detecting underlying organic factors. In line with the advances in clinical psychiatry, neuropsychiatry and biologic psychiatry, considerable progression has been achieved both in diagnosis and also in treatment. In this process, structural and functional imaging techniques have remarkably contributed to the etiology of psychiatric diseases to be understood better, as well as to the development of diagnostic approach. Owing to the current development in radiological imaging modalities, certain anatomical or functional abnormalities could be assessed, from now on, in the psychiatric diseases that could have not been predicated upon any organic basis previously. In many studies conducted until today, diagnosis or follow-up in the course of the treatment has focused on development process of the disorder, pathophysiology, underlying progressive picture, and neural process, as well as potential factors, rather than imaging methods.

Since the invention of X-rays, available information due to the advances both in radiology and in computer technology has become sharable as well. With the new methods, other than old or conventional modalities, it has been possible to not only anatomically visualize but also functionally evaluate the tissues or organs. Exposure to ionized radiation is not a matter of question with such modalities developed in MRI field. Moreover, these techniques and experiences in this field are gradually becoming available day by day. Operator and software dependent variability of these methods that has been relatively going on would be solved in time and be standardized. Current advanced MRI modalities that can be used in addition to routine examinations include high resolution imaging (3Tesla), functional magnetic resonance imaging (f-MRI), perfusion MRI (p-MRI), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS). It is aimed to review the functional (f-MRI) or microanatomical structure (DWI, DTI) or metabolite (MRS) changes in imaging of the

psychiatric disorders. Moreover, metabolic alterations in structurally preserved normal areas can also be measured with PET/MRI fusion imaging. The next stage of brain imaging is estimated to be the molecular methods. Now, imaging at neuroreceptor level, as well as at neurotransmitter synthesis and transport stages, is aimed with advancing molecular imaging and is under research. All of the anatomic, metabolic or functional information obtained from all these modalities is helpful in directing the radiologists and/or psychiatrists to the origin of the abnormality, especially in the cases whose having normal conventional cross-sectional images.

In this section, firstly, the information about current approaches in psychiatric disorders and essential imaging modalities will be discussed completely, but briefly. Subsequently, innovational findings under the title of "advanced brain MRI findings in psychiatric disorders" provided additional new methods to the conventional MRI findings.

2. Information about basic imaging methods in psychiatric patients: Current methods and advances

Until today(now, bence), current psychiatric diseases have been studied under the topic of neuropsychiatry. Radiological modalities (**Table 1**) were used in the psychiatric diseases to investigate, eliminate, and to assess the prognosis of acute stroke, as well as to diagnose brain death, for trauma evaluation, to identify the focus in epilepsy, in the differential diagnosis of dementia, to investigate Parkinsonian syndromes, and to evaluate mass or recurrence, which are more evident pathologies with partially defined spectrum (Kwon et al., 2004). Before introducing the main subject, we thought that it would be necessary to summarize conventional modalities that have been used in the psychiatric and neuropsychiatric cases so far(in order to notice the contribution of advances discussed in this section). Of note, although the topic of this section has focused on "Advanced MR Imaging", general tendency in current technology is to perform all the examinations by multiparametric imaging until the pathology is detected before the patient leaves the radiology unit.

It should be kept in mind that, patients hospitalized for physical diseases or underwent invasive or non-invasive procedures experience fear and anxiety and these experiences sometimes lead to anxiety or depressive disorders (Krzyaowski et al., 1998). Considering that 30% to 60% of hospitalized patients were reported to have diagnosable psychiatric disorders, we should know that various stages of imaging might also cause psychiatric symptoms, in addition to the data mentioned up to now. Therefore, patients with anxiety, clostrophobia, or with known psychiatric disease should undergo radiological processes under the supervision of an auxiliary team including companion, consultant and security (Krzyaowski et al., 1998).

2.1 Computed tomography

The chance of imaging with multidetector subsecond systems has become available due to the acceleration in CT technology. This enables the completion of the process without problem in the patients with poor cooperation. In addition to being used for the elimination of urgent intracranial pathologies, it may also be used in the patients that are non-cooperated as a guide in placing special electrodes to stimulate ventral intermediate nucleus

of thalamus with high frequency stimulators (3D volumetric CT, **Figure 1**), which are used in the treatment of Parkinsonian symptoms (Schulz et al., 2005). Moreover, CT-perfusion may be an alternative problem solver in the cases, in who MRI is absolutely contraindicated (CT-perfussion, **Figure 2**).

Modality	**Explanation**
MRI	Magnetic Resonance Imaging 3 Tesla MRI unit Dynamic-contrast MRI, MR-Angiography MR-perfusion (MRP) MR-Spectroscopy (MRS-Proton, MRS-Phosphorus) Diffusion Weighted MRI (DWI) Diffusion Tensor Imaging and Tractography (DTI) Sensitivity Weighted Imaging (SWI) Magnetic Transfer Imaging (MTI)
CT	Computed Tomography Guidance to the surgical or radiotherapic ablation of local lesions via multidetector CT technology, advanced applications such as calculations at submillimetric level and navigation in neurostimulation therapies are its characteristics expected to step in standard routine. CT-angiography, high-resolution three-dimension imaging and CT-perfusion in the cases in which MRI is contraindicated are possible with this modality.
PET/CT	Positron Emission Tomography/Computed Tomography In this system, PET and CT are fused and the images of these two modalities can be either obtained separately or combined. This method as well presents anatomical data of sectional and functional activity. Changes in brain metabolism developed in the epilepsy, of which the focus could not be found with other methods, and in many other disorders can be investigated with this method. With the fusion of PET/MRI in the new systems, it is possible to obtain high resolution anatomic and physiologic images, and preoperative consultation is possible.
MEG	Magnetoencephalography In this system, it is possible to visualize action potentials, as well as the localization of the pathology magnetically. It is known as a current and new modality that spontaneously measures stimulated brain waves more sensitively than EEG and clinical examinations. Sometimes it may be more effective than the sectional analyses, and magnetically localize the abnormality and guides for successful epilepsy surgery.

Table 1. A summary of modalities which are used in a radiology unit to visualize psychiatric diseases and the modalities which are expected to make more contribution in the future with their main characteristics.

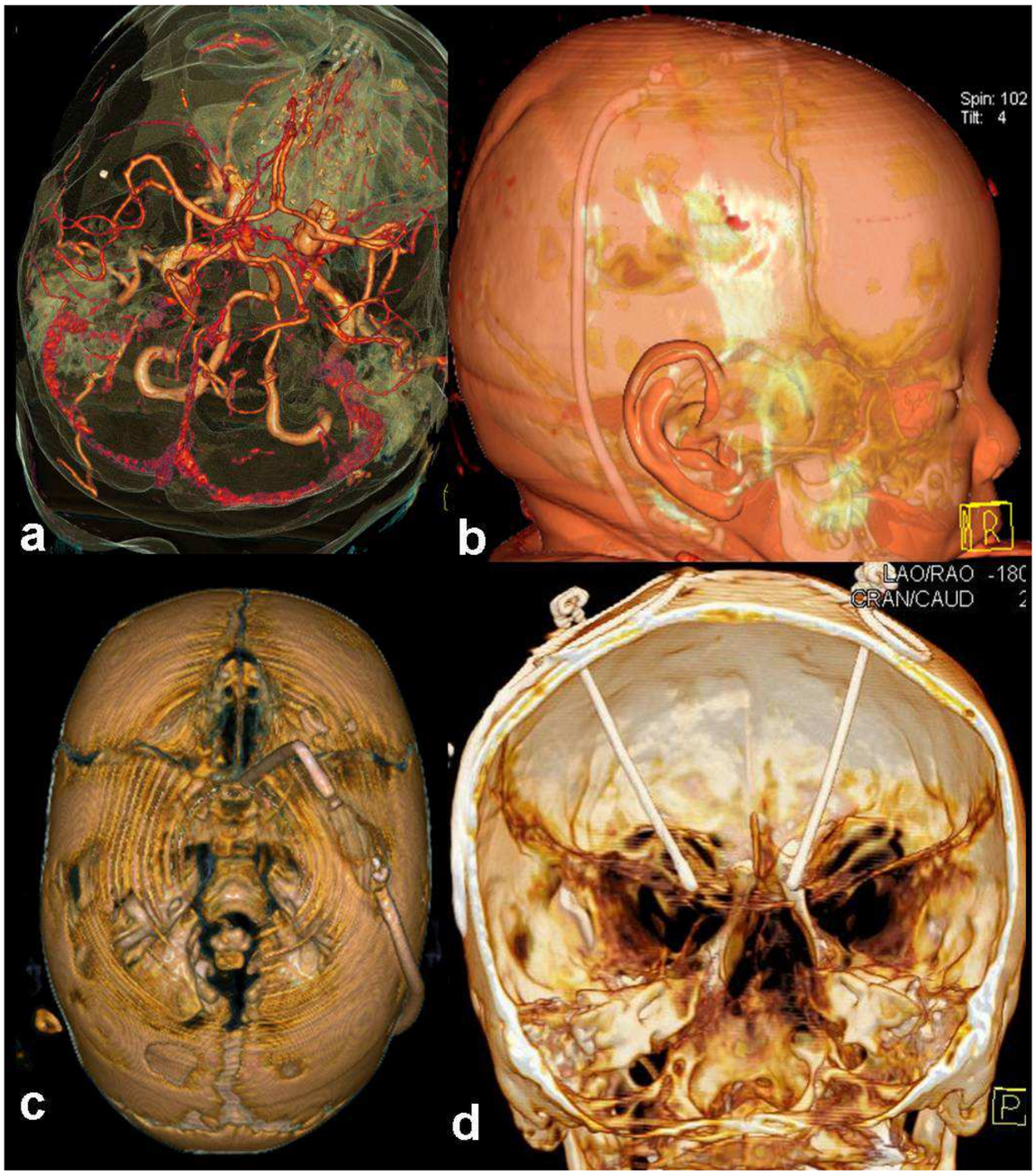


Fig. 1. Guidance in the surgical therapy using multidetector system with dual source CT (64x2). **a**) Main vascular anatomy is seen quite clearly on the three-dimensional computed tomography (3D-CT) image. **b-c**) These images were obtained by the same parameters with those of the previous case, revealed clear image of projection and trace of the ventriculoperitoneal shunt. **d**) Image of a case with Parkinson Disease, obtained by a virtually sliced section of the frontal half of the scalp. It shows neurostimulator electrodes.

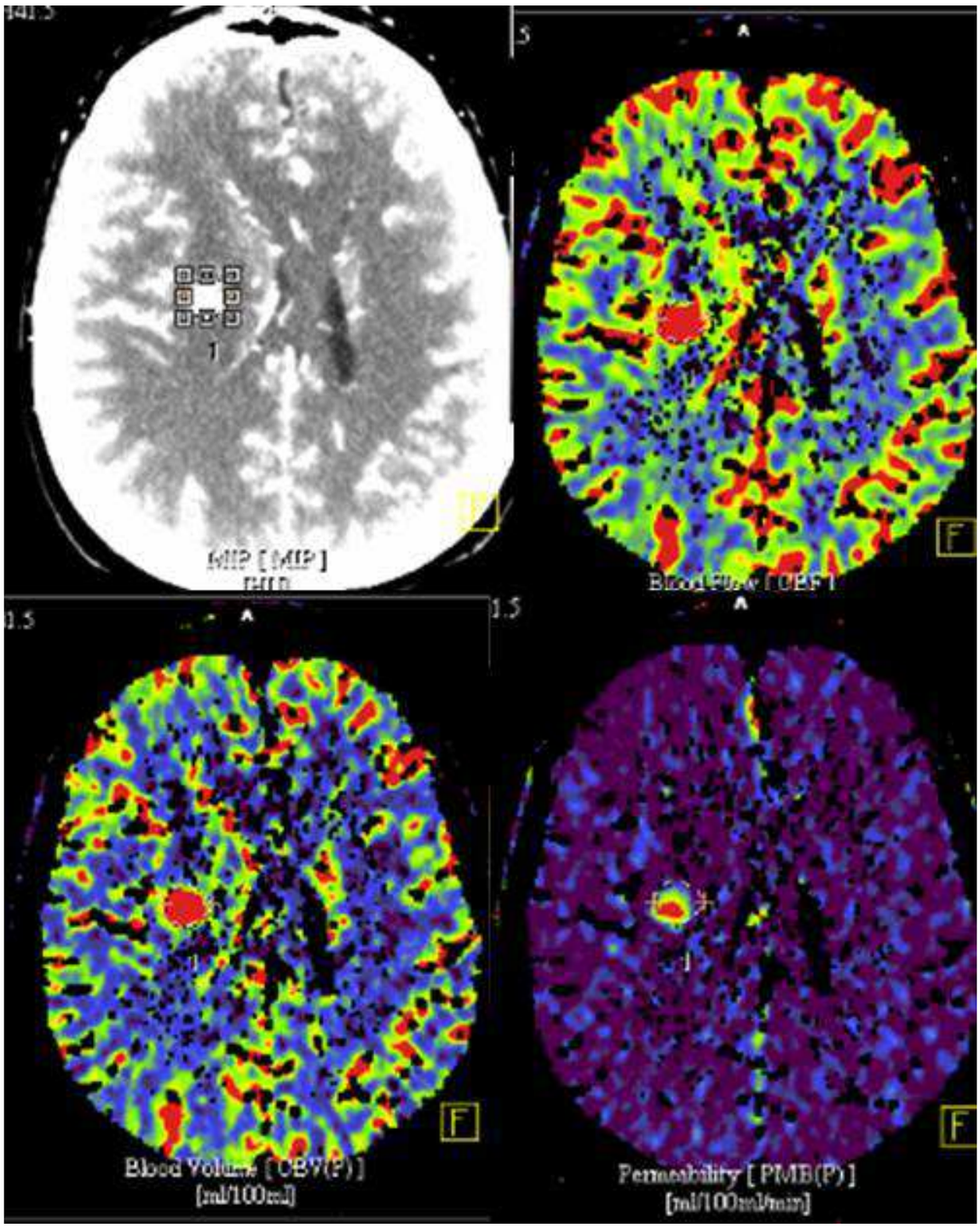


Fig. 2. Operated lung carcinoma. The case that presented with numbness, weakness and dullness on the 2nd year control. Right basal ganglionic mass has been detected on the contrast sections of the case that could not undergo MRI because of cardiac battery. The patient that could not undergo MR perfusion underwent CT perfusion in the same session, and the findings were consistent with right basal ganglionic metastasis.

2.2 PET, PET/CT, PET/MRI and other molecular-metabolic imaging methods

Recent studies show that it is possible to detect the neural progenitor cells in-vivo. This finding offers to foresee genetic therapy and to follow the outcomes in the near future (Seidenwurm et al., 1997). Along with the information at the level of neuromediator, transporter gene, and receptor that would be introduced by the studies on molecular neuro-imaging science, an expectation has appeared for finding an answer to the questions also in the field of biological underlying disorders of psychiatry (Sevin et al., 2007).

PET, which is an indirect metabolic imaging method, is commonly being used as PET/CT fusion modality. This method is usually used in early detection of Alzheimer's disease, in detecting the epileptogenic foci, and also in the evaluation of the effects of medical-surgical therapies (**Figure 3**). It detects the degree of uptake in the tissues, in which radioactive FDG (fluorodeoxyglucose) is injected via intravenous route to the patients with predicted pathology, and fuses this metabolic data on concurrent CT images.

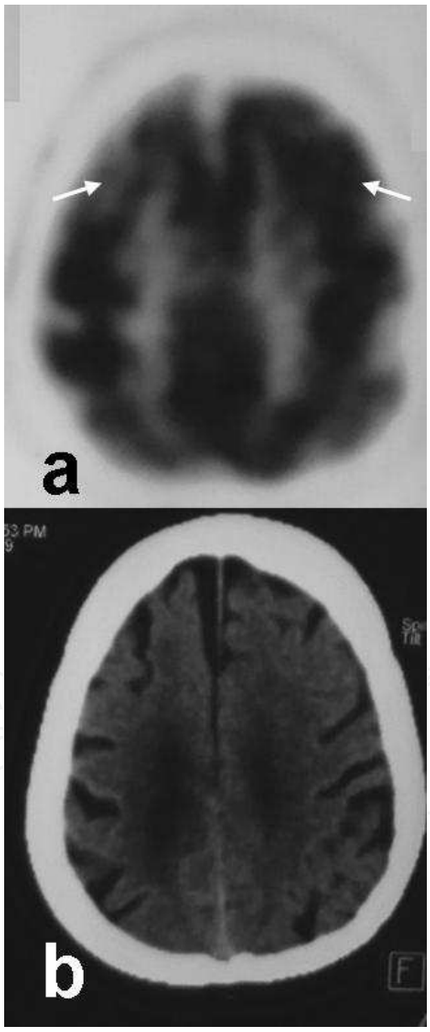


Fig. 3. PET (**a**) and related CT (**b**) sections of a case with Alzheimer's disease. There were lots of corticosubcortical asymmetrical FDG uptake areas (aroows) show "the hypoactivity" which is in harmonious with the clinical examination findings.

PET technology has been advanced such expeditiously that imaging reached to the receptor level. That is to say, experimental metabolite studies performed to lay speaking, memory, learning, cognitive functions and cerebral distribution of related receptors, as well as their activities have been successfully completed (Adachi et al., 2008).
The outcomes of the studies that focused on PET/MRI fusion modality, which has been theorized because of inadequate image resolution of CT, have ended positively and PET/MRI fusion systems are currently begun to be used particularly in the cranial localizations.
At this point, it must be emphasized that, multiparametric and fused systems, which are begun to be used extensively, require the multi-disciplinary collaboration (of a radiologist, psychiatrist, nuclear medicine specialist, physicist and molecular biologist) especially in investigating psychiatric diseases.

2.3 Magnetoencephalography (MEG)

Magnetoencephalography, which combines the high resolution anatomical images with electrophysiologic data can successfully test and visualize the dynamic cerebral functions. Thus, the focus that complex neural network shows dysfunction can be clearly localized and accordingly be treated; such that, a single region or action potentials produced by a single cell clump can be evaluated using this method. By this means, local neural effects of drugs with specific efficacy can be tested (Seo et al., 2011). The major disadvantage of this method is the fact that it remains to be able to evaluate only superficially localized cerebral pathologies.

2.4 Magnetic Resonance Imaging (MRI)

In line with the systems that perform very quick dynamic analysis in CT, techniques have been rapidly advanced and revised in MRI as well. In addition to the conventional sequences, MRI is able to analyze even anatomic-functional etiopathogenesis of various disease groups with numbers of modalities (**Table 2**). Here, the technical and clinical characteristics of the above-mentioned methods will be briefly discussed in terms of following topics.

MRI methods	Explanation	Psychiatric practicability
Conventional sequences (T1, T2, fat-saturated sequences, dynamic examinations)	Give opportunity to obtain high resolution anatomical information. Contrast patterns of the lesions can be shown with dynamic examination modalities.	Intracranial normal and abnormal formations can be detected with higher sensitivity than CT can. Moreover, it is easier with MRI to make differential diagnosis in the nervous system lesions.
MR-Angiography	Visualization of main vessels	It can be applied both with and without contrast. Availability to perform without contrast allows visualization of vascular anatomy without injection in the patients unable to coordinate and cooperate.

MRI methods	Explanation	Psychiatric practicability
Magnetization transfer imaging	It makes the basal signals, particularly those abnormal and those developed later, more prominent with a kind of subtraction.	By this means, abnormal contrast uptake foci that have not been exposed yet with conventional sequences can be detected early.
MR-spectroscopy	It allows the detection of metabolite content of a wide area, a lesion, or surroundings in the brain.	This method can detect the metabolite content of neural parenchyma without causing anatomic imaging anomalous. There are studies performed on many psychotic and neurotic disorders showing that metabolite concentrations show differences in various localizations as compared to the normal population.
MR-perfusion	A method that relatively introduces the differences in the vascularization of cerebral regions as different maps. Here, it is possible to detect the altered blood pool foci despite the preserved anatomy by forming rCBV (relative cerebral blood volume), rCBF (relative cerebral blood flow), MTT (mean transit time), and TTP (time to peak) vascularization mapping.	This method is able to differentiate malign tumors from benign, efficacy of medical-surgical therapy from radiotherapy, and the residue from relapses.
MR-diffusion	A method that detects micromolecular water motion and motion restriction.	A method that detects the nature of ischemic lesions (acute or chronic), as well as the cellularity of mass lesions. By this means, diffusion limitation of cortically localized lesions can be detected and dysplasia-cortical mass can be differentiated.

MRI methods	Explanation	Psychiatric practicability
Diffusion tensor imaging-tractography	A technique that identifies the nerve fiber traces via special software by changing the power of diffusion gradient and the direction of diffusion.	By this method, we can detect the nerve fibers and pathways by differentiating afferent and efferent fibers, although they have been considered normal via conventional examination modalities. DTI technology has been advanced to illuminate the etiopathogenesis of cognitive disorders (113).
SWI (susceptibility weighted imaging-high-sensitive imaging)	A modality that detects the abnormal foci in the brain quite before appearing on the known and routinely used sequences.	It is of great importance to early detect the calcific or hemorrhagic foci in the brain, although they are extremely small. This sequence will early detect the amyloidal angiopathy, or hypertensive encephalopathy, or calcification of basal ganglion, as well as the organic pathologies that might affect the cognitive functions in the diseases such as migraine.
fMRI cortical activation measurements (BOLD)	A method that monitors both motor and functional processes. The patients are asked to do the motor and sensorial paradigms they have been taught during special and rapid (EPI) sequences, and the cortical regions are detected, in which alterations (hemoglobin, loses O2 to become deoxyhemoglobin) are observed with blood oxygenation level dependent (BOLD) effect.	In the controlled trials, it is known that quite specific signal recordings (increasing and decreasing), different from the normal population, are obtained particularly in the prefrontal cortex in both the psychotic and affective diseases on the functional examinations that the activity created by word repetition and thought is recorded.

Table 2. Points that might contribute to the problem solving with psychiatric point of view in the MRI sequences, which have been frequently used in routine and in current MRI applications.

2.4.1 High resolution (3T) MRI analysis, dynamic contrast MRI (Dyn-MRI), diffusion weighted imaging (DAI), MR-angiography

Although its quality may vary due to the movement or other artefacts while investigating other organs, it is possible to early detect pathological process via high-resolution images obtained on the craniospinal axis by 3T. In addition to the conventional sequences, high

resolution images can distinguish the abnormal signal changes earlier (**Figures 4-6**). These anatomical structures or pathologies (infection, inflammation, and neoplasia) can be evaluated by contrast analyses, signal dynamics, and DWI. So the cellularity of the lesion can be detected. Main arterial and venous anatomy can easily be exposed noninvasively.

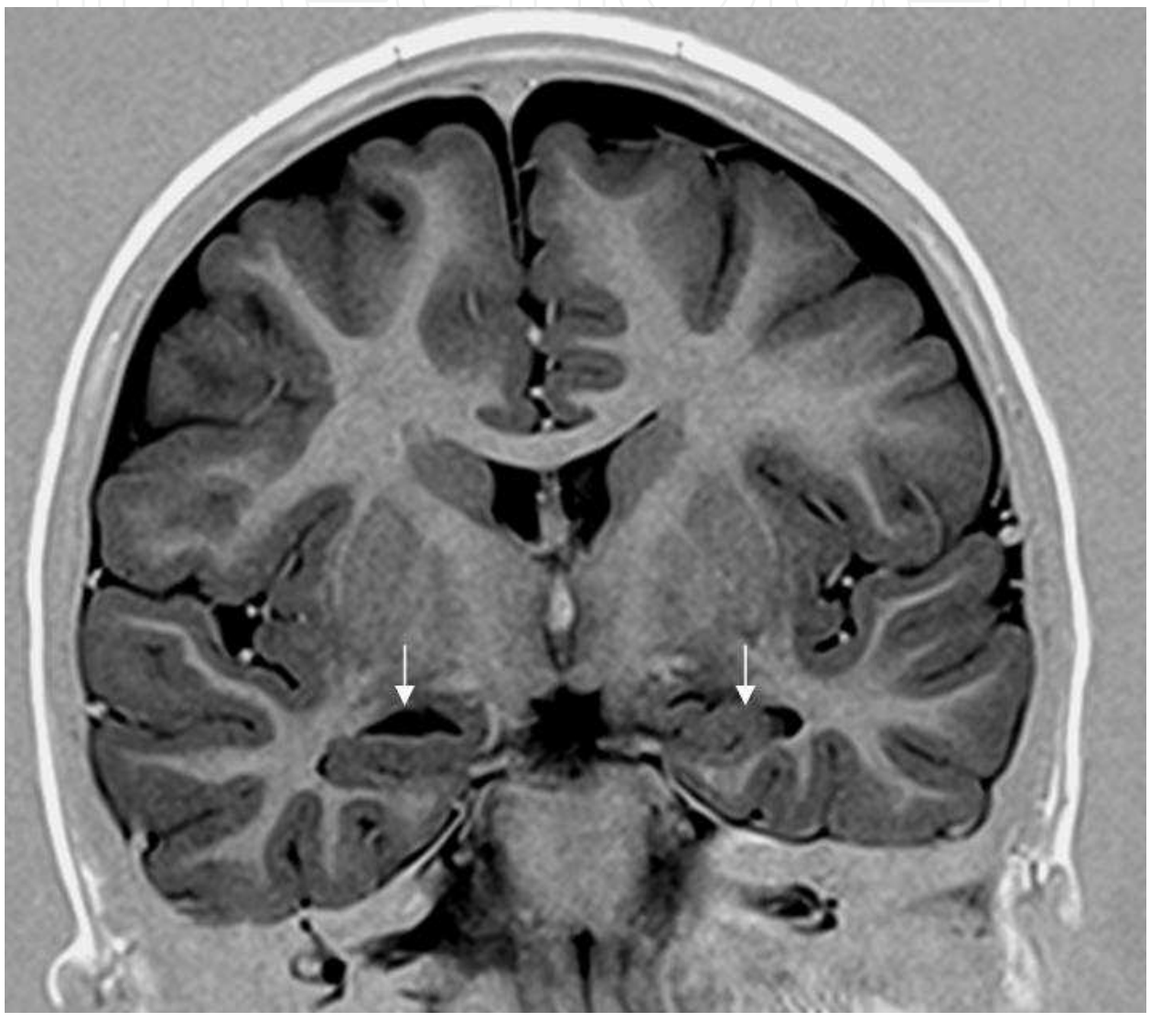


Fig. 4. A male patient with mild mental retardation and temporal epilepsy (age: 29 years). Coronal T1W brain MRI-1.5 Tesla obtained by high-resolution. Asymmetry between choroid fissures can be seen clearly (arrows).

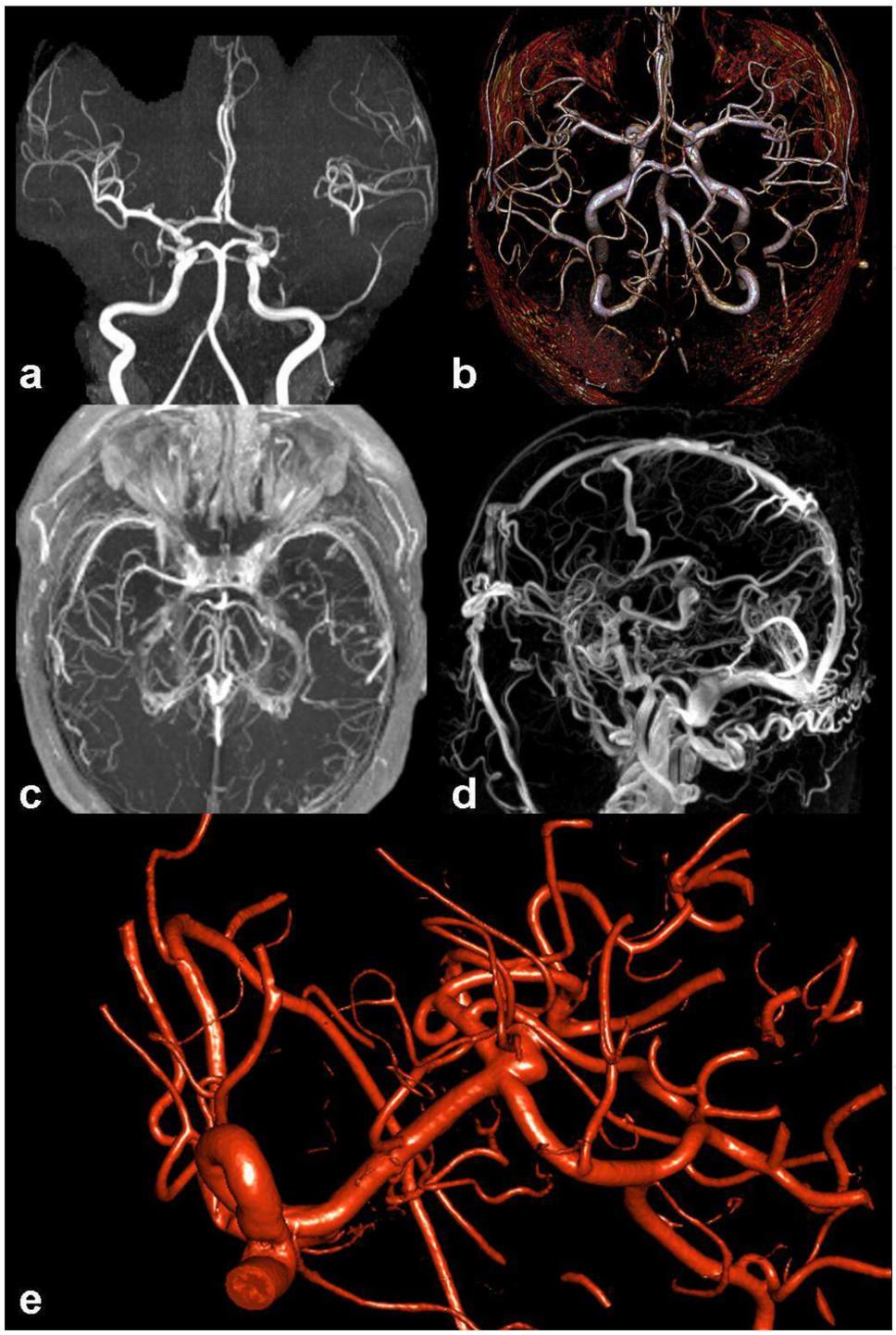


Fig. 5. On the coronal thick MIP (a), colored axial VR (b), posterior fossa axial thin MIP (c), sagittal thick MIP and (d) MRI imaging of different cases, it is conspicuous that extremely complex network can also be visualized in detail. Despite the advanced MRI technology, it is understood that more complex traces can be visualized with higher quality which is shown on the VR/3D biplane angiographic image.

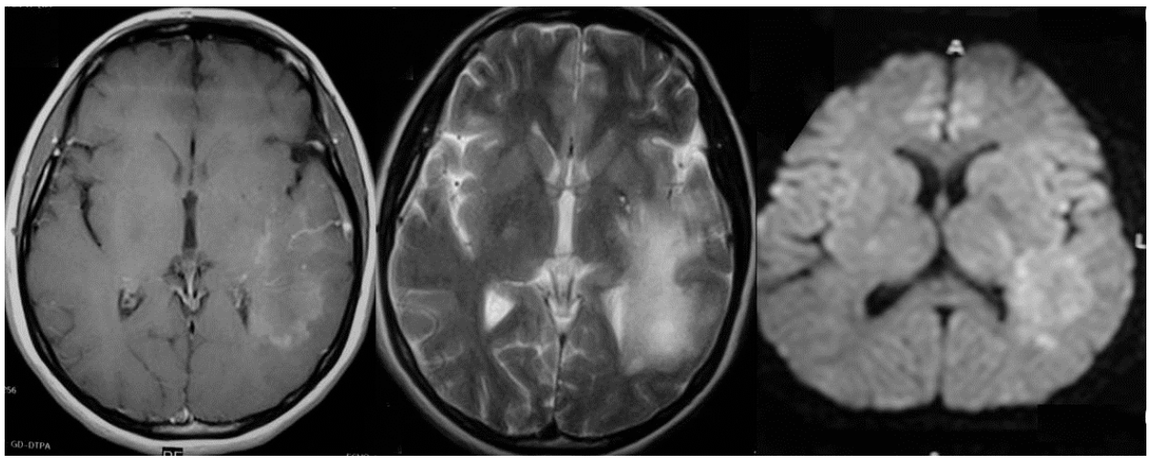


Fig. 6. Although it gives mass impression on the diffusion-based images, large heterogeneous contrast fields in the left temporal lobe of a case presented with atypical psychotic complaints has been considered acute-subacute infarction due to the limited diffusion in the vascular supply field.

2.4.2 Functional MRI (fMRI) and related sub-modalities

MRI spectroscopy that can measure certain cerebral metabolites.
Perfusion MRI can measure regional cerebral blood flow using different parameters such as time of arrival, time to peak, blood flow, transit time, delayed enhancement.
Blood-oxygenation level-dependent (BOLD) MRI measures regional differences in the oxygenated blood over time. Newer commercially fully integrated MRI systems are now available. With these units, it is possible to perform a variety of well-documented paradigms for motor, language, and visual mapping. Moreover, the possibility of fusing 3D DTI-BOLD and conventional images brings the development to its peak.
Diffusion weighted MRI, which measures random movement of water molecules through the axonal fibers. So, this method is capable to obtain tractographic images with additional tensor imaging software.

2.4.2.1 Magnetic Resonance Spectroscopy and basic principles

Proton MR-Spectroscopy is a useful in vivo examination for analyzing the metabolites of the human brain that are in small concentrations. The aim of this method is to detect the metabolite composition of the tissue. Particle content can be evaluated by a sensitivity one in a million, using the differences in Larmor frequency at horizontal axis caused by special frequencies. Previous studies have reported that the NAA level can be altered by neuronal cell death or other neuronal damage in the gray matter (Tzika et al., 1997). NAA is an amino acid, located exclusively in the neuronal cell bodies, dendrites and axons. In contrast, the Cho level has been regarded as a marker of cellular density, since Cho is the precursor for phosphatidylcholine, which is a major component of the cell membrane. Thus, the NAA/Cho ratio is regarded as a significant indicator in assessing neuronal activities, because it represents the relative ratio of neuronal density to cellular density.
1H-MRSI now offers the ability of directly correlating abnormal imaging findings with a presumptive measure of neuronal pathology. Quantitative differences in metabolite content can be investigated by whole brain MRS that can be obtained particularly in the new

technological systems (**Figures 7, 8)** (Bertolino et al., 2000). The status of different metabolites can be investigated by changing the parameters. As a neuron-specific surrogate marker of cellular integrity, NAA levels have been examined in numerous neurological disorders. In schizophrenia as well, reduced NAA in PFC (prefrontal cortex) has been shown to predict the abnormalities in dopamine metabolism (Callicott et al., 2000). Although, all the findings of the cases are seem sometimes as normal, but a pathology being reflected as low NAA ratio in PFC (Callicott et al., 2000).

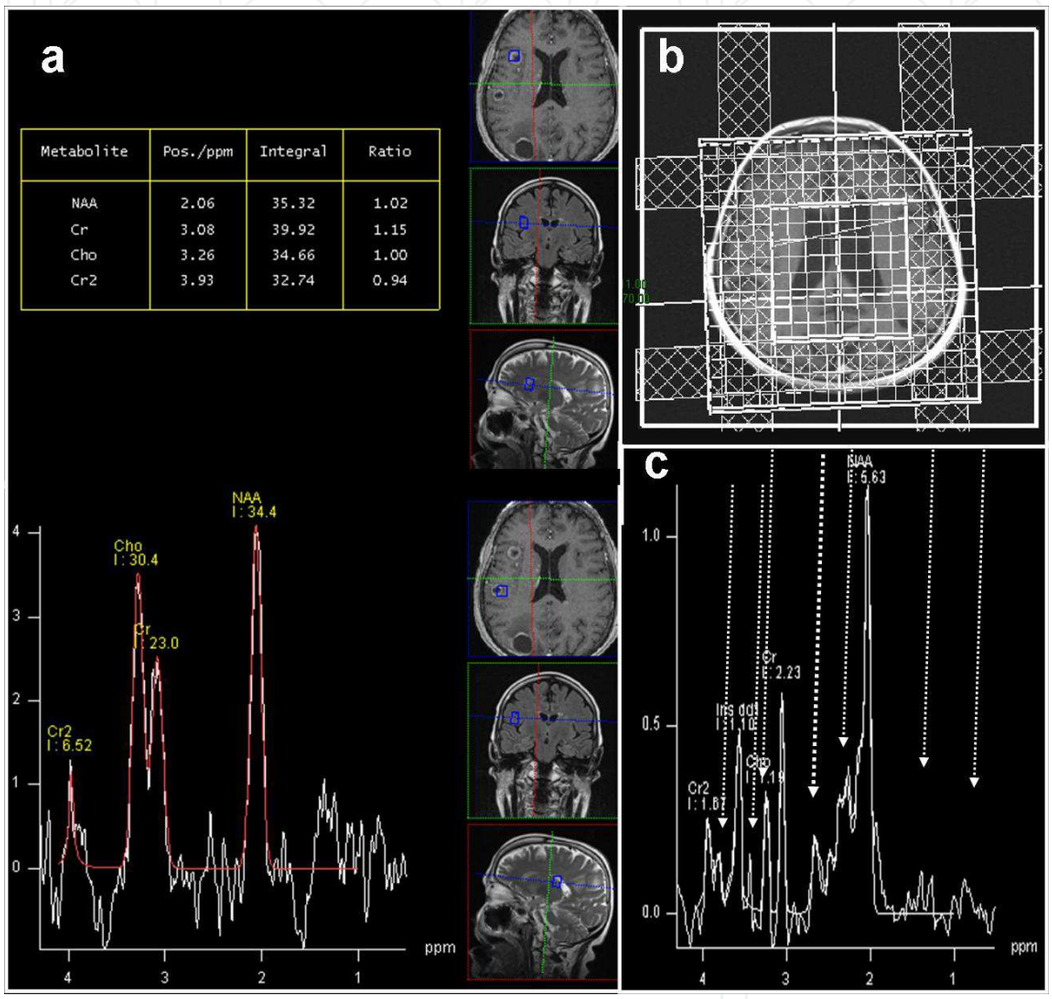


Fig. 7. **a**) It seems possible to evaluate various lesions and fields at the same time by whole brain spectroscopy, as well as to obtain metabolite peaks and proportional information concurrently with new software in the cases with multiple cystic intracranial lesions. Screening the whole brain via large multivoxel windows in that way may enable diagnosis of certain metabolic diseases perhaps along with the first psychiatric symptoms, as well as decreasing the dose and shifting to the treatment (such as dialysis for lithium toxicity). **b**) In this evaluation, in which all the fields that remained out of the investigation must have been suppressed, because increased susceptibility would lead to artefactual measurements. **c**) When the imaging is done using short "time of echo = TE" values, it is likely to obtain peaks of more metabolites (showed with long arrows).

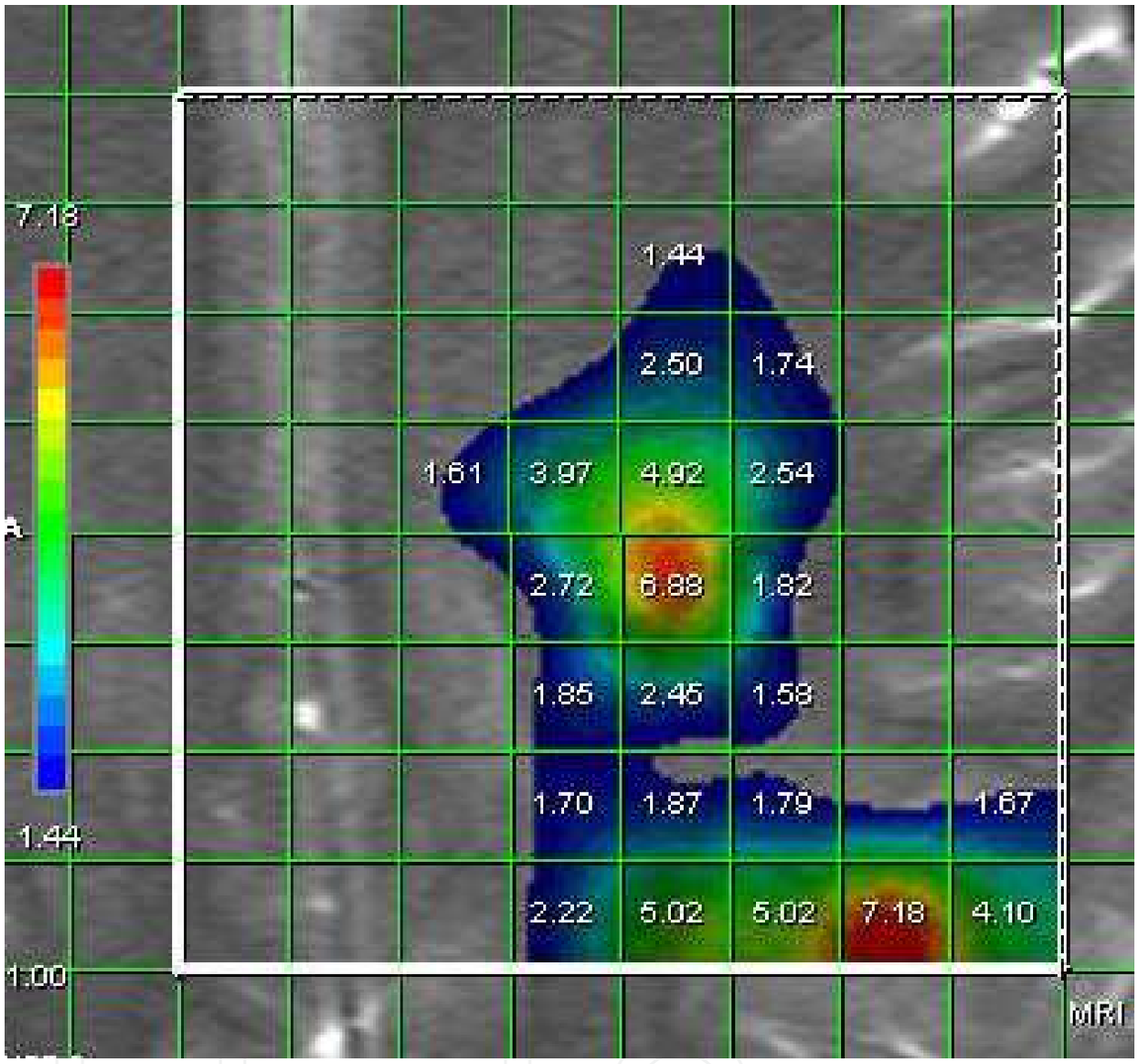
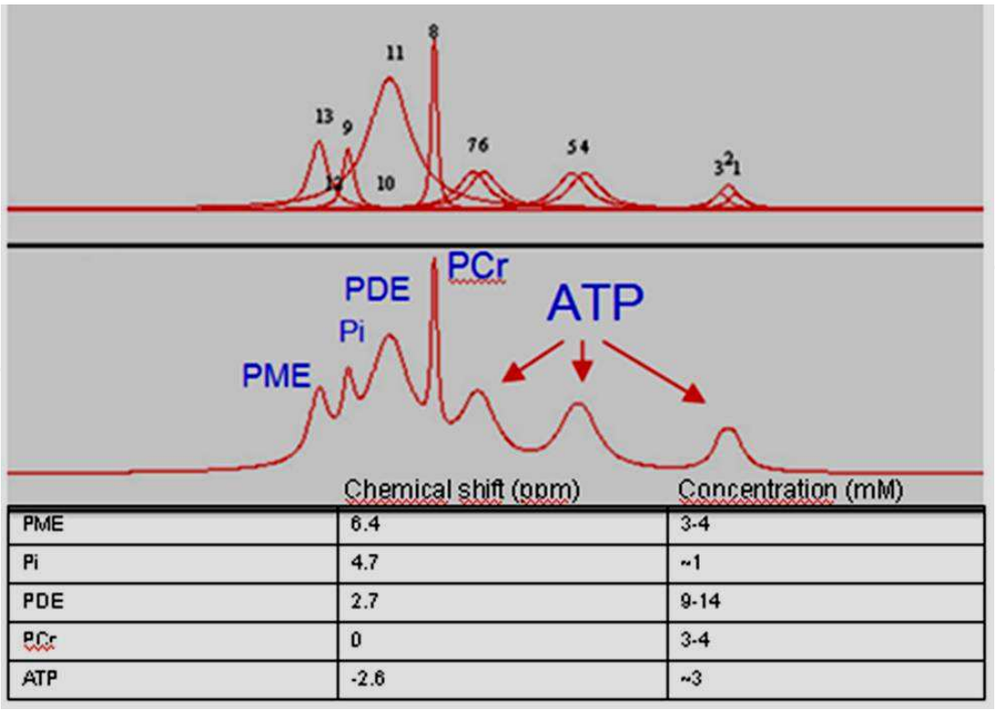


Fig. 8. Involvement of deep white matter in the left frontoparietal region that displays normal signal characteristics in a case with encephalitis. Cho elevation that indicates increased devastation on the color Cho/Cr maps; it may be changed into a more demonstrative form that a clinician could orientate him/herself.

It is known that spectroscopy can detect also the metabolites that contain phosphorus which play a role in energy metabolism. The basic elements of energy metabolism such as ATP (adenosine triphosphate), phosphocreatinine (PCr), inorganic phosphate (Pi), phosphomonoester (PME), and phosphodiester (PDE) can be measured by 31P-Spectroscopy (**Figure 9**) (17, 18). Beside the indirect information about energy metabolism, it is known that this method can also assess intracellular pH and Magnesium (Mg) levels via indirect ways (19).



PME	6.4	3-4
Pi	4.7	~1
PDE	2.7	9-14
PCr	0	3-4
ATP	-2.6	~3

Fig. 9. Distribution of the peaks obtained on a normal *brain-phosphorus spectroscopy*, and the resonance values and the amount of resonance are seen in the table attached.

Benefiting from the changes in this metabolite map, not only the grade of tumoral lesions or neoplasias is estimated, but also information can be obtained about the energy metabolism of a special region.

2.4.2.2 Perfusion weighted MR-Imaging (p-MRI)

Perfusion is the blood volume that passes through a certain amount of tissue in a unit of time. T1A or T2* type perfusion analysis can be done by labeling this blood volume with an exogenous marker including gadolonium. In more modern systems, which the studies are going on and which are newly being used in clinical practice (arterial spin labeling), blood cells are magnetically labeled with special radiofrequency bands, instead of using an exogenous agent, and are monitored. Again, in these systems, the degree of cerebral perfusion can be analyzed both qualitatively and quantitatively. Since all these signal recordings have to be done within a time shorter than two seconds, ultra-rapid software named EPI (Echo Planar Imaging) sequence are used in the perfusion weighted analyses. In the cerebral system, perfusion means oxygen delivery level to the tissue.

Tissue perfusion is an indirect indicator of metabolic activity. Physiologically, perfusion occurs in an adult's brain between 40-60 ml/100g/minute (Rostrup et al., 2005). At that point, it is important to make a shoot (particularly for perfusion and spectroscopy) including both hemispheres in ROI field in order to make a comparison between the symmetric regions. Consequently, distribution of cerebral blood flow can be calculated on the perfusion weighted MRI examination by certain automatic programs that use multiple parameters, such as CBF, CBV, TTP, MTT, and TOA, based on the changes in the microenvironment caused by the contrast substance while passing through the capillary network (**Figure 10**).

In terms of convenience, the common unit for CBF is milliliters of blood per 100 grams of tissue per minute, and a typical average value in the human brain measured is approximately 50 mL/100 g per min., the gray matter being approximately three times higher than the white matter (Rostrup et al., 2005). For imaging applications, it is often convenient to express this as the flow delivered to a unit volume of tissue rather than a unit mass of tissue, because a signal is measured from a particular volume in the brain. Since the density of brain is close to 1 g/mL, CBF values expressed in these units are similar.

Cerebral blood flow is a measure of arterial blood delivery. Blood flow is controlled by varying vascular resistance. In the vascular system, the resistance is not uniformly distributed among all of the branches of the network but, instead, is dominated by the arterioles and the capillaries. The arterioles are the seat of vascular resistance control.

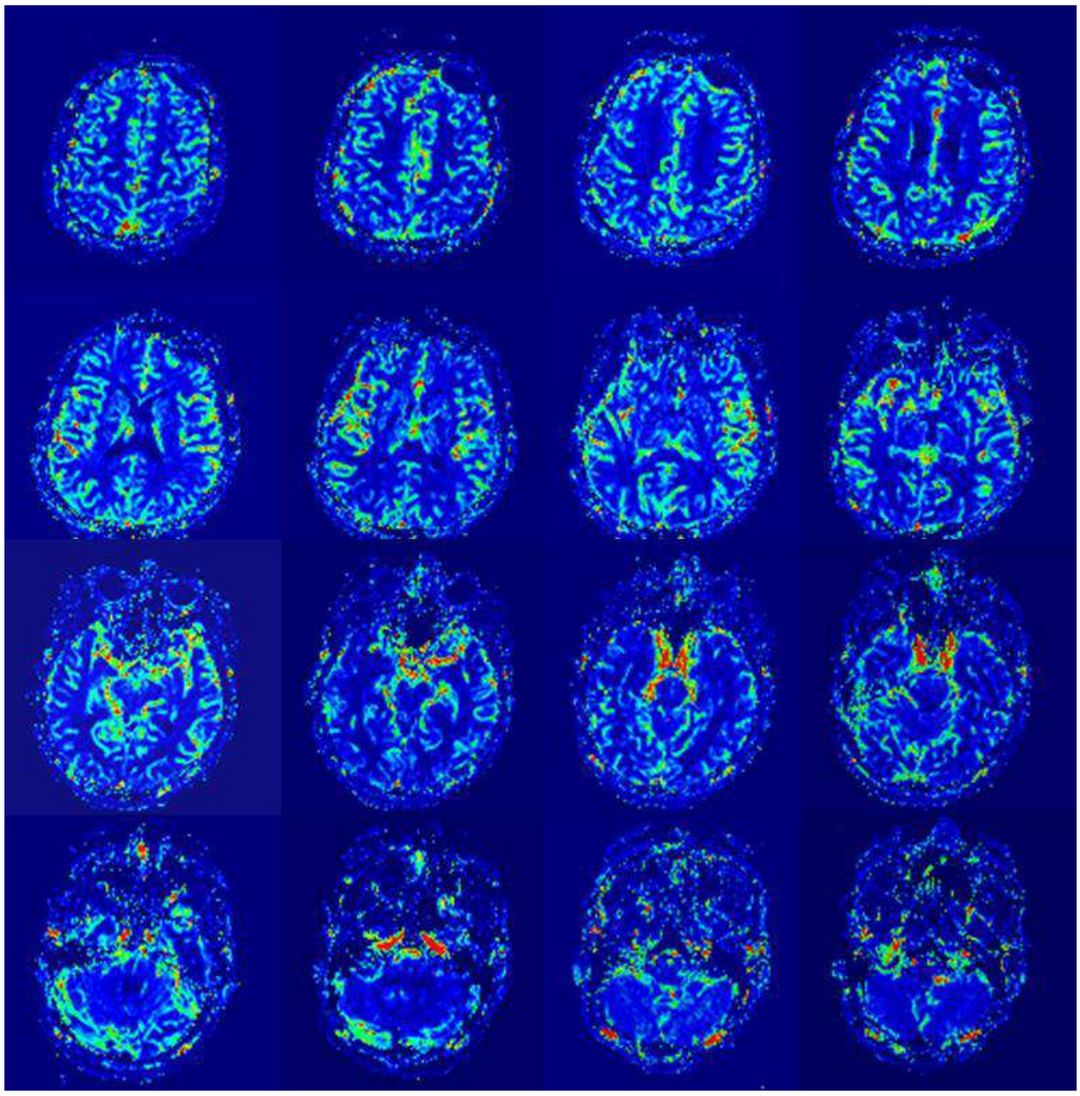


Fig. 10. Color perfusion images that show the rCBV map of a healthy subject. Here, signal decrease due to T2* effect gives information about the vascular bed in capillary network and is expressed as relative (r) because it indirectly reflects the perfusion.

Perfusion analysis has been mostly used for ischemic or tumoral cases since its first use (**Figure 10, 11**). Despite, in time, it was begun to be used in various psychiatric diseases for trial purposes including metabolic diseases, neurodegenerative diseases (Alzheimer), and attention disorder and hyperactivity, the fields in which it has been studied utmost due to its higher resolution than PET/CT and ability to localize better and offering quantitative information (Patrella&Provenzale, 2000). For example, decrease in rCBF has been reported in the anterior cingulate, temporal gyrus and precuneus, the fields associated with attention, in the attention disorder and hyperactivity syndrome. In schizophrenia, rCBV elevation has been reported in the occipital cortex, basal ganglia and cerebellar level (Leinsinger et al., 1997). Cerebral blood volume (CBV) is the fraction of the tissue volume occupied by blood vessels, and typical value for the brain is approximately 4% (CBV= 0.04) (Leinsinger et al., 1997).

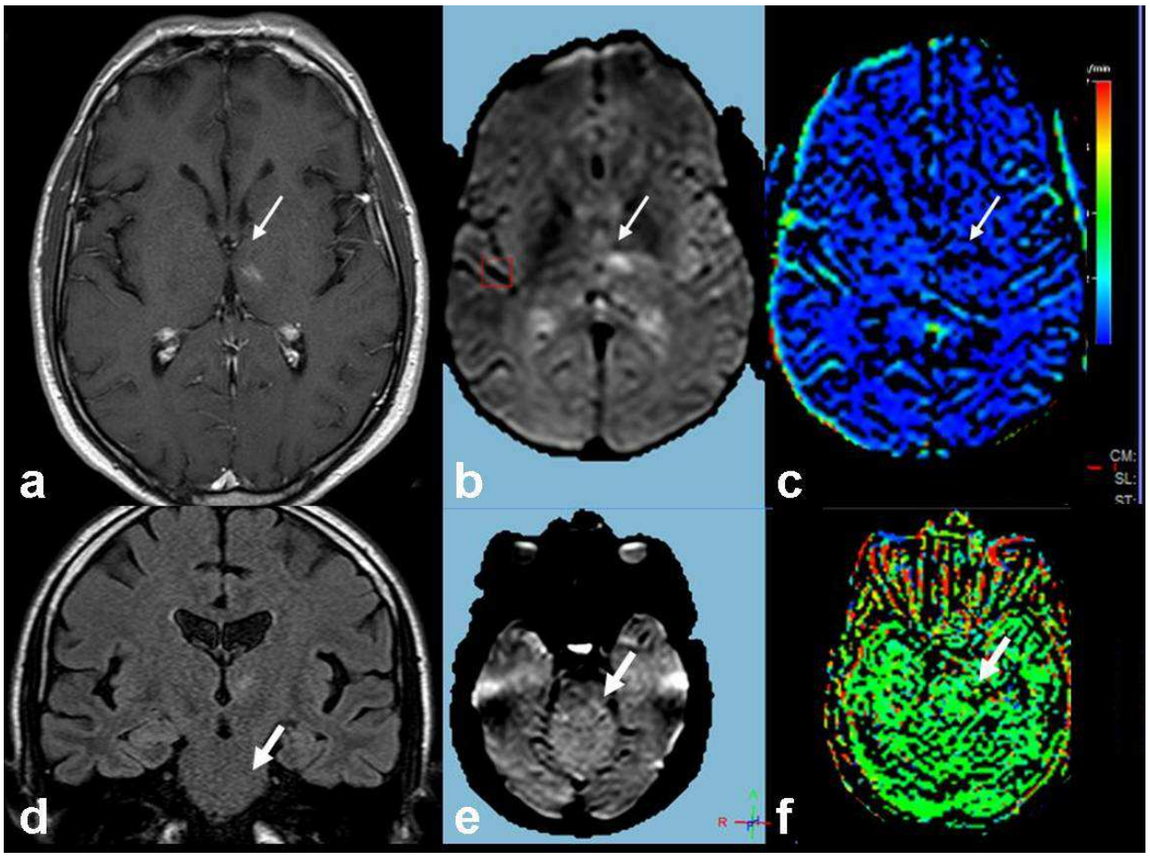


Fig. 11. Despite the presence of dullness and flight of ideas in the case presented with behavior disorder that developed recently, systemic and cranial screening is required because of concurrent attacks and sweating. On the T1W-C+ axial section (**a**), thalamic focus that uptakes contrast agent (arrow) has displayed T2-shine through effect on the perfusion sequence (**b**, arrow), and presented completely as non-perfused on the rCBV map (**c**, arrow). The same focus is visualized on the coronal FLAIR sequence (**d**). Although the pons is seen normal on this sequence (**d**, arrow), it is seen as a suspicious field on the basic perfusion image (**e**, arrow) and again as non-perfused on the rCBF map (**f**, arrow). Left thalamic subacute infarction.

The CBV roughly represents milliliters of blood vessel, regardless of dimension, per milliliter of tissue. Since an indirect neural activity indicator increases the local rate and products of energy metabolism, it in turn triggers increased flow to deliver more glucose and O2. That is to say, the process progresses backward. Instead of energy consumption first and then blood flow, increase in neural activity and metabolism products (NO is the most important trigger that increase CBF causing arteriole dilatation) occurs first and then increase in blood flow. A striking aspect of the brain is the relatively uniform Axygene Extraction Fraction = OEF at rest (Gusnard et al., 2001). This suggests that, during development, CBF to each region is adjusted to the basal level of energy metabolism (extraction fraction of O2 is the same, approximately 40%). What we summarized herein is that, this system seems to be affected, in fact, by numerous micromelocular, anatomic and sub-systems that have not been known yet (Perthen et al., 2008).
Recent studies have been focused on neurovascular unit and mentioned about the presence of more complex synaptic connection network of glial cells (Haydon&Carmignoto, 2006). It raised the thought that these astrocytes, which are in association with synaptic space and at the same time are located in the close neighboring of arteriole junction, work as hard as neurons and that have important functions in the regulation of neural activation. With these end-feet connections, astrocytes form a bridge between neuronal activity and blood flow (Filosa&Blanco, 2007). Considering that these hypothetic changes occur in a complex environment, neuronal cells should work patently together with overall neurovascular unit during the initiation and progression of neural activation, instead of working alone.

2.4.2.3 Functional MRI (f-MRI) with blood-oxygenation level-dependent (BOLD) technique

Failing to visualize underlying pathologies with old imaging methods has led psychiatric diseases to be considered medically only in the functional category and thus, the opinion that the absence of any organic pathology has been accepted (by mistake) (Rajkowska et al., 1998). This opinion has been confused with quite confirmed studies in the recent times; methods that can detect cortical thinning by 8% and the volume loss in postmortem schizophrenic brain as compared to the normal are in question (Selemon et al., 1998). In addition to this gross anatomic change, it should be known that perfusion abnormality alone, without the presence of any other micromolecular anomalous, is likely to cause abnormal potentials impairing the function. Functional MRI, which is a method that can illuminate the pathology by detecting perfusion abnormalities, steps in at this point.
In the beginning of the researches, positron emission tomography was the only technique that provide human brain mapping by measuring the changes in energy metabolism. But, more recently, fMRI methods have dominated the field of functional neuroimaging, primarily based on a phenomenon called as blood oxygenation level dependent (BOLD) effect (Bohning et al., 2001). In this frame, when hemoglobin loses O_2 to become deoxyhemoglobin, the magnetic properties are changed in a subtle way. When an area of brain is activated, the blood flow increases much more than the metabolic rate of O_2. This leads to a reduction in the extraction fraction of oxygen, seemingly a paradoxical scenario, in which the venous blood is more oxygenated. This phenomenon is known as BOLD (blood oxygen level dependent) effect, a local increase in the MR signal owing to a reduction in the OEF during increased neural activity (**Figure 12**). Recent research has emphasized the key role played by the astrocytes, cells that function projecting both neurons and blood vessels. This has led to the concept of the neurovascular unit, a close interaction between neurons, astrocytes, and blood vessels (Bohning et al., 2001).

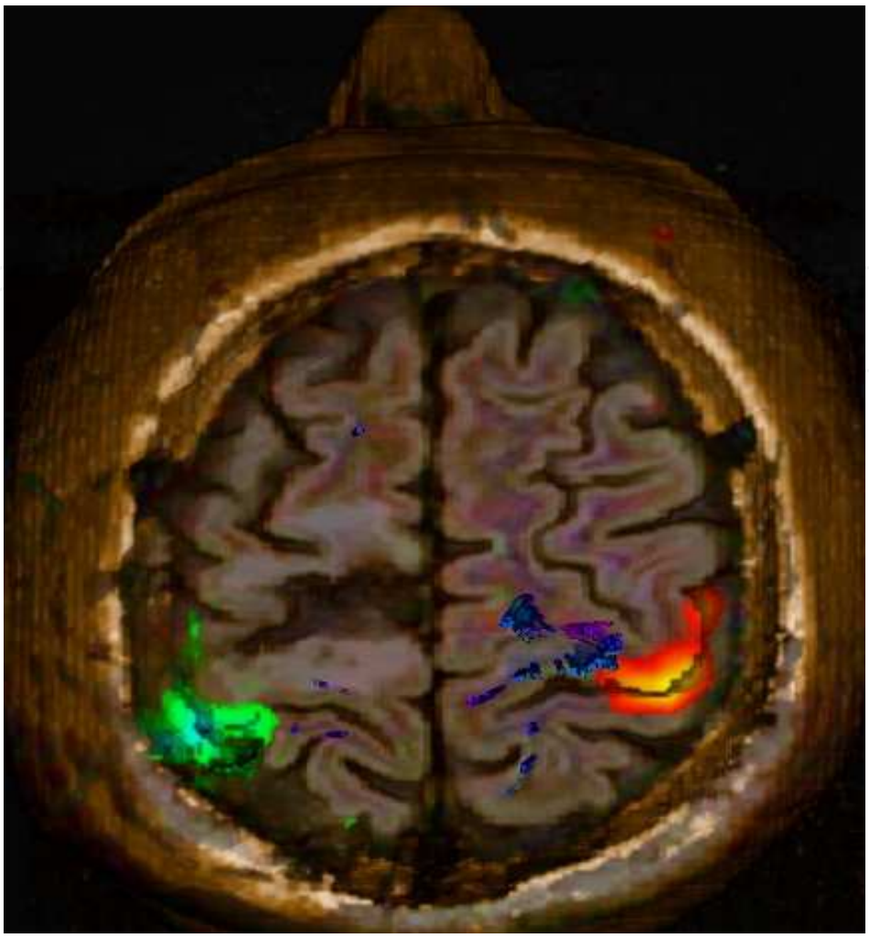


Fig. 12. Attention should be paid to the BOLD color scatter occurred on the right due to the contribution of remodeling that developed in time, in the motor area affected by encephalomalasic region, at the origin of the motor activity that occur during snapping. As the result, although this information gives simple impression on a color map, it, in fact, indicates signal decrease caused by the deoxygenation of the erythrocytes while passing throughout a capillary network with decreased diameter up to 6-8 μ and subsequent increase in the reactional blood flow.

Despite the relative difficulty for the patient in adapting to the MR gantry in the psychiatric diseases, non-invasiveness, no radioactivity, widespread availability, and virtually unlimited study repetitions make fMRI ideally suit to the study of in vivo brain function in psychiatry.

In the controlled studies, the functional examinations, in which the activity created by word repetition and thinking has been recorded, showed a decrease in signals in the prefrontal cortex (sensorineural) in schizophrenic patients, whereas the signals associated with motor cortex remained the same and constant (Callicott et al., 1998). Additionally, in the uniparameter system, which is stimulated by sensorial stimulation (visual) such as photic stimulation and finger tapping and motor stimulation (finger motion), significantly increased regional cerebral blood volume was detected in the left occipital cortex and left caudate of schizophrenic subjects. Despite the sensorial asymmetry in this study,

schizophrenia-associated motor abnormalities (decreased magnitude of fMRI) have been reported more frequently (**Schröder J** et al., 1999). Although, in some of the studies antipsychotic medication was thought to cause this lateralization asymmetry, neuropathological examination of postmortem motor cortex has revealed both abnormal and normal cortex (Braus et al., 2000). In addition to the studies designed for the general hypoactivation of prefrontal cortex, there are studies performed with fMRI that have been specifically focused on the symptoms. For example, there are studies, in which abnormal temporal cortex activation in response to external speech was detected in some schizophrenia cases with auditory hallucinations (Woodruff et al., 1997). Moreover, some studies that have focused on the limbic system, other than the underactivation of prefrontal cortex, showed reduced amygdala activation in schizophrenic patients during sad-mood induction (Maas et al., 1998).

Along with the Ogawa et al.'s finding that deoxyhemoglobin has signal reducing effect on T2*, fMRI is first used in early 1990s and hundreds of studies have been performed on this subject since that time. In this system, fMRI is achieved via two methods. One of them is T1 perfusion effect; the other and more commonly used one is the BOLD (Blood Oxygenation Level Dependant) technique (Ogawa et al., 1990).

During functional MRI applications, staying still in a relatively narrow gantry unit and complying with the instructions in a dark medium with closed eyes are difficult, particularly for psychotic patients. Furthermore, the sensitivity of the region and the paradigm (motor, sensorial) may technically change the outcomes. Finally, a technical team and equipment qualified to perform shooting and a program able to process the images are required. Evaluation of function enables the activation in the motor pathways to be tested by finger movements. Since speaking will impair the quality of analysis due to "misregistration artifact" caused by head movements, it is performed as silent speaking and usually is maintained by word repetition and lexicalization. Despite the difficulty in evaluating the information about memory and limbic system, information about the pathophysiology of these systems can be obtained particularly by perfusion-weighted evaluation (Aksoy et al., 2000). At this point, it is obvious that fMRI evaluation in the pediatric age group would be difficult and post-processing evaluation of the parameters that are evaluated by the reactions such as anxiety, fear and crying would be artifactual in children. However, it has been reported in the literature that pediatric population over the age of eight years have similar results to those of adults (Patrella et al., 2000).

With its increased flexibility due to advanced technology, fMRI may allow us to map a sufficiently wide dynamic range. Thus, pathological cortical regions may be visualized more clearly during both rest and activation by evaluating all the measurements together. As seen on arterial MR-angiography on the Figure 5, major cranial arteries course decreasing from a calibration of few millimeter. They deliver glucose and O_2 to the brain with the blood they carry. Since they have been separated into thin branches, vascular system become more complex turning into an intensive collateral network with a diameter of generally 6-8 µ, and sometimes is decreased down to 2 µ. New MRI sequences have the sensitivity to show the reflex responses of capillary blood flow abnormalities against large-diameter venous system; thus, pathologies such as migraine, encephalitis and subarachnoid bleeding can be detected earlier as compared to the conventional sequences. Therefore, the aura, hallucination, or acute phases of these diseases can be recognized before overt clinical symptoms without being mistaken with panic attack and other conditions (**Figure 13**).

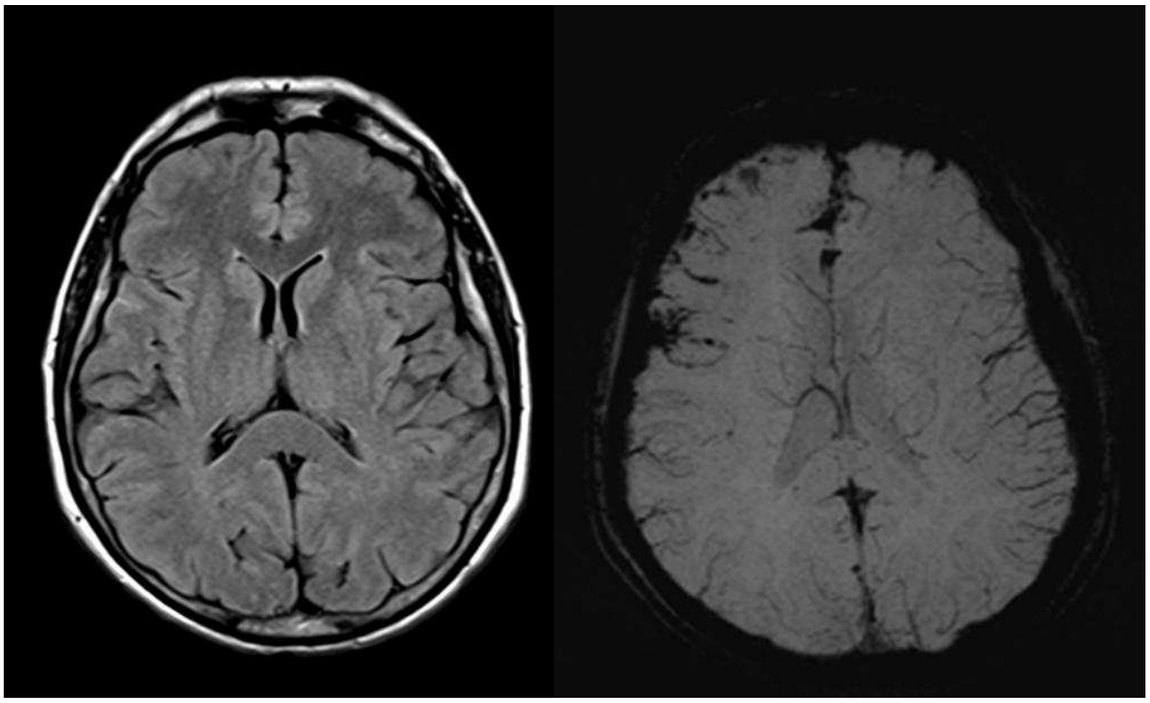


Fig. 13. In the case that has been brought to the emergency room with such an intensive headache that he could bump his head on the wall, FLAIR sequence image sensitive to the lesion and pathology showed no abnormality; however, axial section from SWI sequence showed signal loss in the right extra-axial spaces due to the presence of hemorrhagic products.

2.4.2.4 Fractional anisotropy and tractography, Diffusion Tensor Imaging (DTI)

Tractography can be made over fractional anisotropy maps that are obtained by applying diffusion gradient in multiple ways (varies between 6 and 30 directions). Diffusion tensor imaging is an MR technique that can be used to characterize directional properties of the diffusion of water molecules (Beaulieu, 2002). With the application of this technique, it is possible to obtain microarchitectural anatomy of white matter tracts exceptionally. So, DT fiber tractography has been reported to be robust for visualizing and evaluating connectivity in the brain (**Figs. 14, 15**) (Lee et al., 2005).

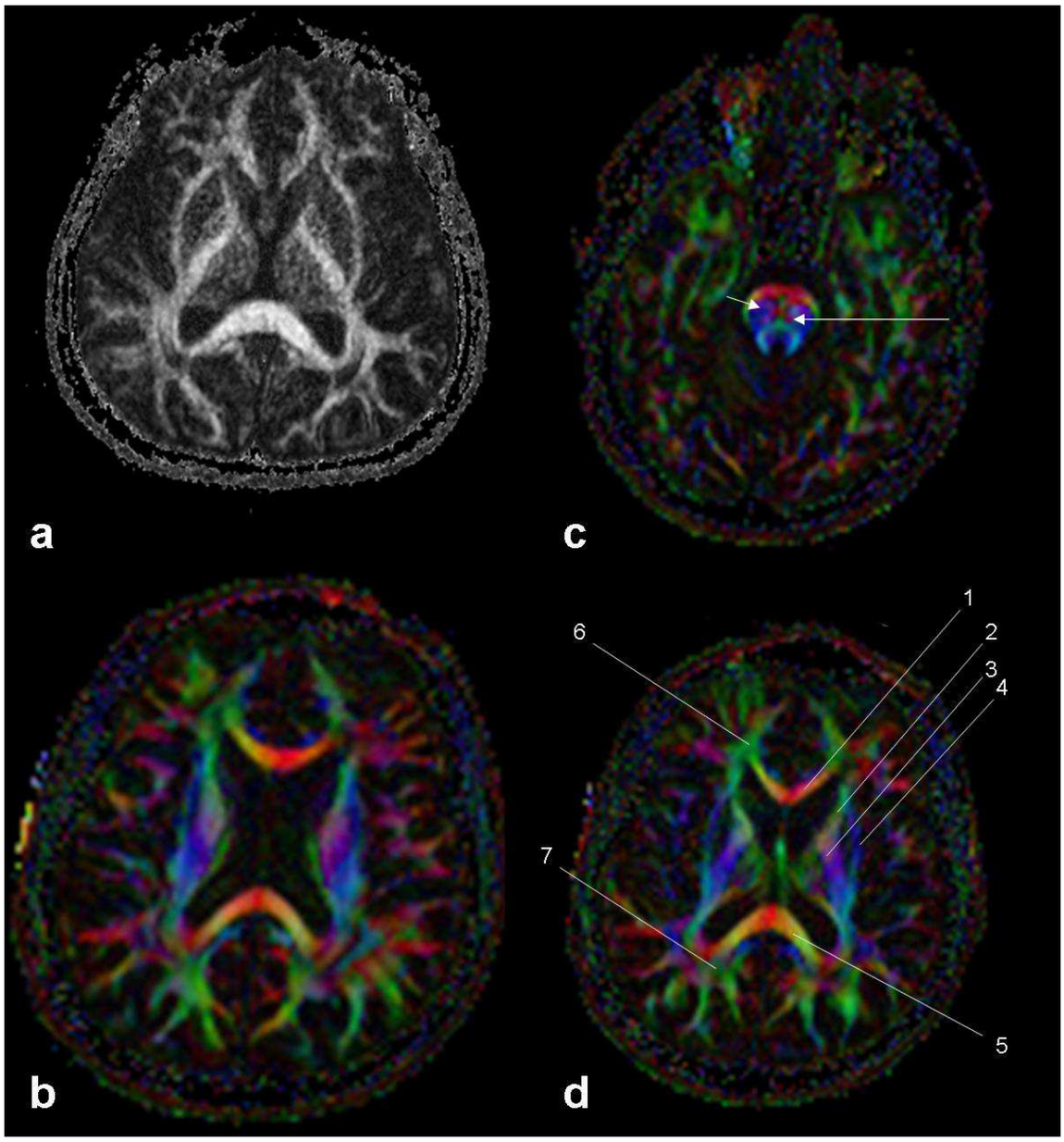


Fig. 14. Axial fractional anisotropy gray scale (a) and colored maps (b) show the restricted water diffusion crossing the fibers. Color-coded fractional anisotropy images of DTI. c) A section through the brain stem: pontine crossing fibers (long arrow) and corticospinal plus corticopontine fibers (short arrow) are shown. d) Supraventricular hemispheric section: genu of the corpus callosum (1), anterior (2) and posterior (3) limb of internal capsule, external capsule (4), splenium of the corpus callosum (5), forceps minor (6) and forceps major (7) are shown respectively. It may be possible to see the other minor fiber tracts also in detail.

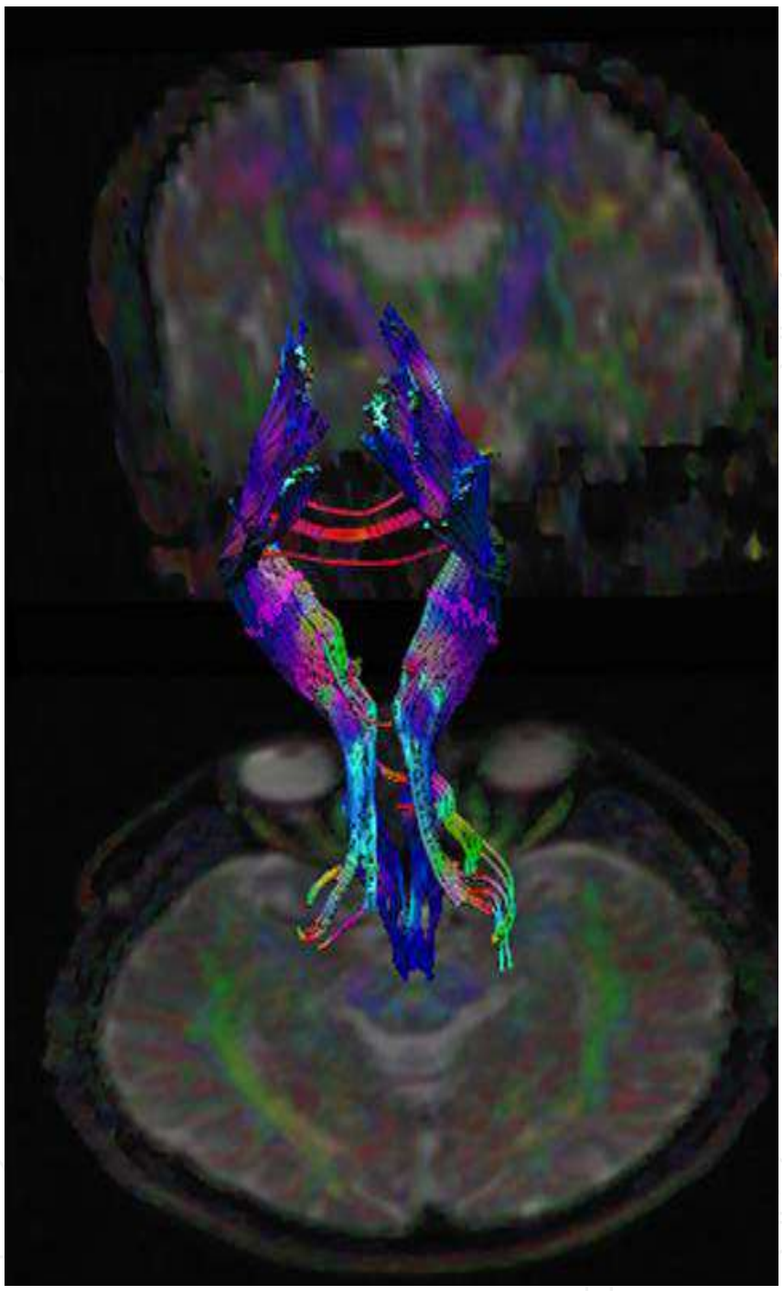


Fig. 15. After processing these fractional anisotropy maps with special softwares, it is possible to detect the tracts alone or as superposed on 3-dimension parenchyma floor labeled in different colors, as is seen in the picture.

The advent of diffusion tensor imaging (DTI) and fiber tractography has opened an entirely new noninvasive window on the white matter connectivity of the human brain. DTI and fiber tractography have already enhanced the scientific understanding of many neurologic and psychiatric disorders, and they have been applied clinically for the pre-surgical mapping of eloquent white matter tracts before resecting intracranial mass, also as a complementary metod fused with fMRI data (**Figs 16**).

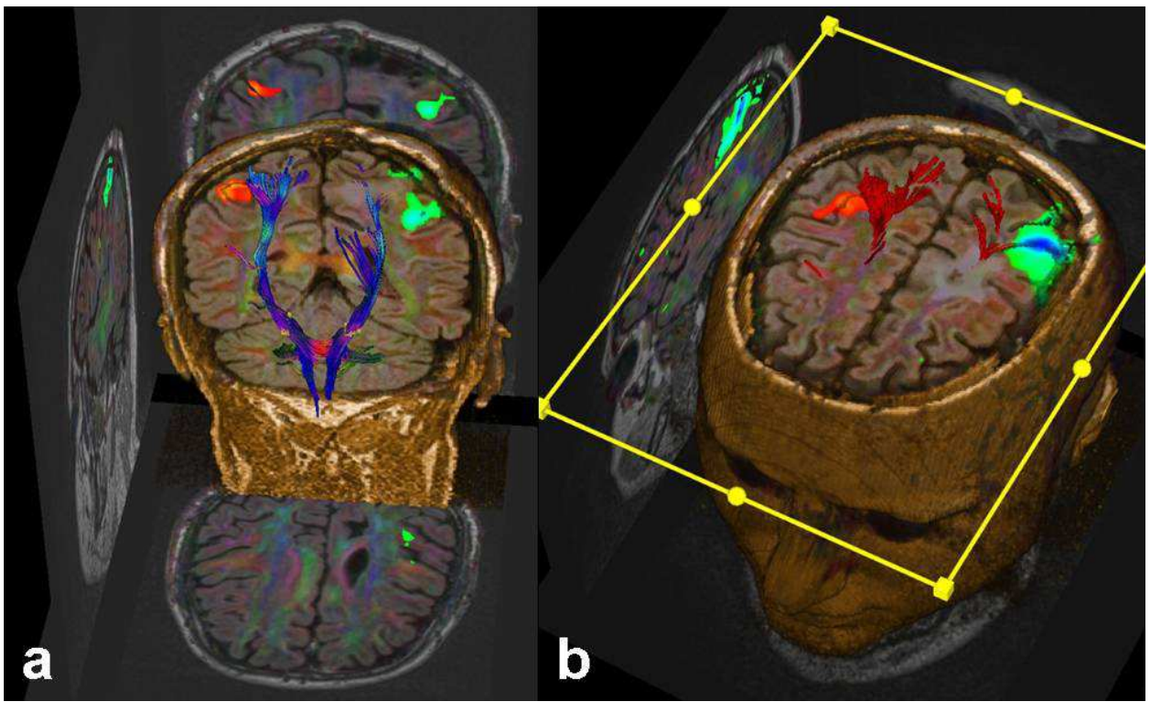


Fig. 16. fMRI-DTI fusion image. On the schema the BOLD signal characteristics that occurred during fMRI with sensory motor paradigms are recorded, the opportunity provided by three-dimensional evaluation of multiparametric data at the same time by coding the fractional anisotropy maps on DTI images offers quite advantageous information.

In this context, the basic principles of diffusion work according to the "Stejskal-Tanner Diffusion Encoding" system. A diffusion-weighted pulse sequence is constructed by adding a pair of diffusion-sensitizing gradients, also known as motion-probing gradients, to a T2-weighted spin-echo sequence. The diffusion gradients are applied along the same directional axis both before and after the 180° refocusing pulse (Stejskal&Taner, 1965). The objective of DTI fiber tracking is to determine intervoxel connectivity based on the anisotropic diffusion of water (Parker et al., 2003).
By this means, axonal traces are followed clearly and fiber tracking can be achieved in condition showing schematically on 3D images. DTI provides only microstructural information at relatively low spatial resolution. DTI fiber tracking is often combined with higher resolution anatomic images to delineate specific pathways. In this way, it is possible to depict virtual information about anatomic connectivity (which called virtual dissection) with 3D DTI tractography.
DTI Fiber Tracking is usually used before the tumor surgery to investigate the association between the mass and main corticospinal tracts (**Figure 17**). In general, if 1 cm space is left between the lesion and main corticospinal tract, there will be enough chance for the intervention. Besides, it can be used in certain developmental disorders as well (in scoliosis, absence of normally decussating pontocerebellar fibers). In addition to all these anatomical evaluations, quantitative DTI tractography studies have examined the microstructure of white matter tracts in pediatric individuals, in the patients with schizophrenia and in Alzheimer's disease (Hess et al., 2006).

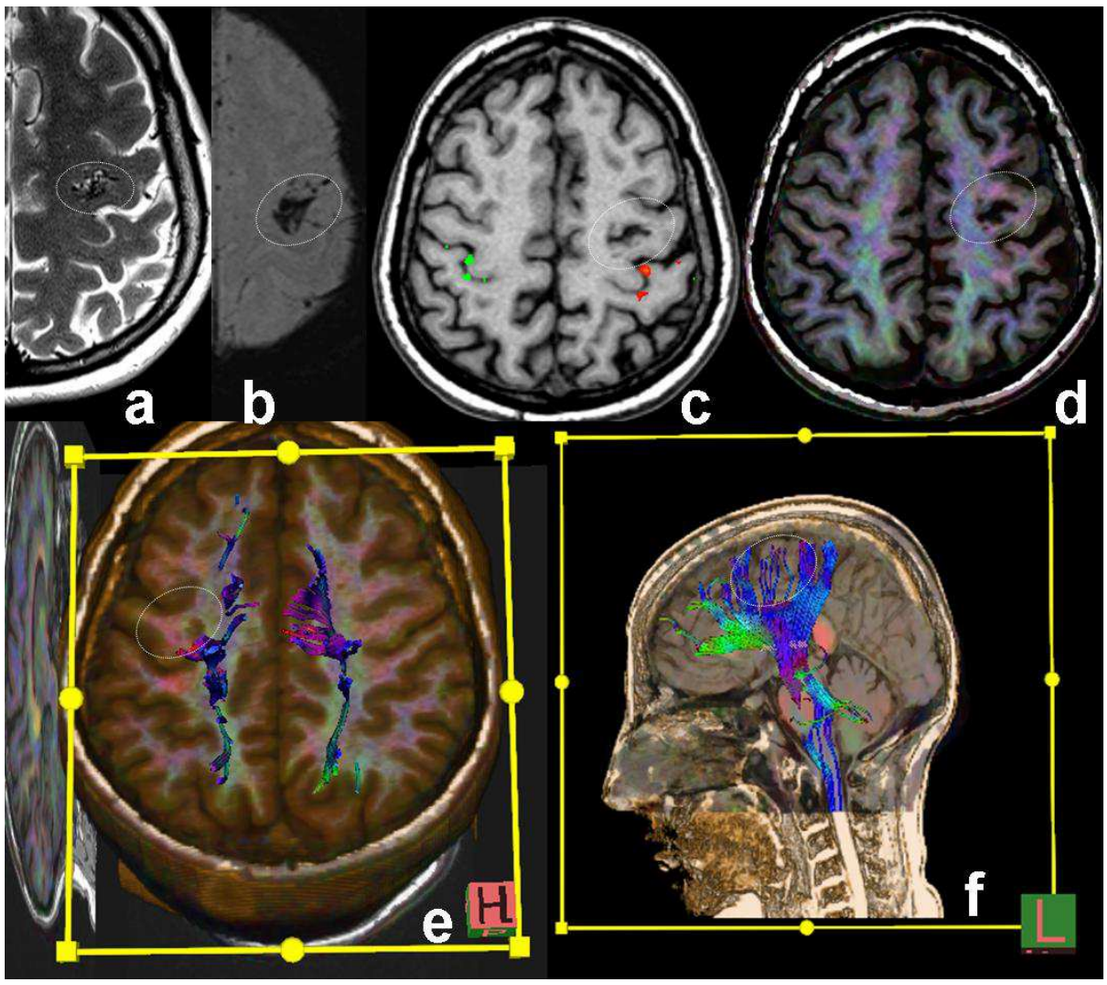


Fig. 17. A lesion localized in the left posterior frontal white matter is seen as hypointense on T2A images (a), and is more clearly visualized on SWI image (b) Cavernoma. This lesion, which is localized in the anterior aspect of motor speech region on the fMRI examination, superposed on the axial section (c), thins the related subcortical fibers on fractional anisotropy map (d), on MPR color VR image through superior vision (e), and on sagittal (f) DTI images. However, it does not cause a remarkable deformation in the course and arrangement of main corticospinal fibers.

Since the DWI principals are used in combination with advanced equipments in the fibertractography technique, microstructural information about biologic tissues, which could not be shown with other coventional techniques, can be obtained. However, even as sophisticated as a mathematical construct, this technique has limitations that affect the ability of DTI fiber tractography to fully delineate an axonal pathway and may lead to the generation of spurious tracks. These problems have led to the introduction of more advanced methods such as high angular resolution diffusion imaging and whole-brain connectivity networks. The asymmetry of diffusion anisotropy of the uncinate fasciculus between the subjects compared may reflect neurodevelopment-originated structural and functional differences between the two hemispheres. This asymmetry can be set forth demonstrating the course of DTI fibers (Kubicki et al., 2002).

In summary, functional MRI, 1H-MRS, Perfusion MRI, and DTI represent significant technical advances for functional neuroimaging. These tests, which yet require more experience about its usage, as well as observation of the results, should not be used for exact diagnosis, but used to confirm the diagnosis and to manipulate the treatment. Although their usage as the methods for exact diagnosis is not valid currently, both fMRI and 1H-MRSI are able to characterize statistical deviation from the normal. Under the light of 3T MRI systems and DTI, which is being advanced day by day with applicable properties, we think that radiological findings for psychiatric-neuropsychiatric diseases and the resolutions would be enhanced.

3. Advanced imaging findings in specific psychiatric disorder groups

3.1 Imaging in psychotic disorders

Initiation of the symptoms in cerebral diseases has been reported to be mainly within the frame of psychiatric picture (50). In fact, a single specific disease (such as encephalomyelitis, epilepsy, arachnoid cyst, Wilson's disease) has been associated with psychosis and there is information characterized by extensive studies and reviews only on this subject (Abbott&Bustillo, 2006).

The most consistent finding obtained from the brain imaging studies performed on schizophrenic cases is the decrease in brain volume and cortical grey matter volume and increase in the lateral ventricular volume (Kubicki et al., 2005). It has been thought that impaired connection between various parts of the brain is the main origin of pathology in schizophrenia (Stephan et al., 2006). Some literature data calculated by the ratios of MRS and DTI (diffusion tensor imaging) and MT (magnetization transfer) actually showed decreased neuronal content in corpus callosum in particular and decreased NAA (a neuronal marker) content in the frontotemporal pathways between the two hemispheres.

Studies on the cases with schizophrenia showed that such cases had changes in certain brain functions plus to structural alterations (Allen&Courchesne, 2003). In this field, it has been most commonly studied on the cellular, molecular and structural pathologies of temporal and frontal lobes (Allen&Courchesne, 2003). It was shown that N-acetylaspartate (NAA) levels were decreased in the temporal lobes of the patients with chronic schizophrenia. Moreover, it was reported that the asymmetric form of the brain was impaired due to the volume loss in the left temporal lobe in particular. However, the temporal lobe-associated neurobiological basis of schizophrenia has not been identified yet. Conflicting outcomes have been obtained from the temporal lobe 1H-MRS studies, in which schizophrenic cases were compared with the control groups. It was found that NAA/choline and NAA/creatinine levels were decreased in the right lobe in schizophrenia, whereas they were normal in the left lobe (Wong&Van, 2003).

In fact, different from the recent past, now we at least think that pathologies can be detected identifying the microstructural abnormalities with advanced techniques, in the studies, in which conventional sequence findings were normal (Kanaan et al., 2006). Despite a number of pervious conflicting studies, methods that measure brain glucose consumption have shown that, measuring glucose metabolism or blood flow during task performance have yielded more consistent findings. Hypofrontality has been demonstrated on Wisconsin Card Sorting Test performed on the schizophrenic adults (Kanaan et al., 2006). Hypofrontality is particularly associated with deficit symptoms, which is thought to result from the

schizophrenic patients' inability to activate frontal regions. Proton spectroscopy (1H-MRS) represents another in vivo imaging methodology that has been utilized to test the neurodevelopmental hypothesis of schizophrenia. With this technique, reductions in NAA levels in the hippocampal area and in the dorsolateral prefrontal cortex have been demonstrated in the patients with adult-onset schizophrenia.

In the recent studies performed with DTI, decreased diffusivity that involves whole white matter is in question. This is a consistent finding with loss of orientation and organization of fiber tract distribution; this technique requires to be developed more in order to obtain detailed in-vivo information in the further DTI studies (Huang et al., 2005).

Nonspecific hyperintense studies on the deep white matter and periventricular regions in psychiatric patients should be comprehensively performed using DTI or fMRI and be explained being purified from its current nonspecific nature.

Diffusion tensor tractography, combined with the information from conventional and functional MR imaging, can provide a powerful tool for neurosurgical planning, especially when surgery is performed close to the vital nerve fiber tracts. Particularly for the cases with signal abnormalities in the white matter, the guidance of tractography may be very necessary during radical operations in the name of preserving the critical fibers that were left in limited number. Using DTI, which offers indefinite but additional information to those from the conventional methods, may be beneficial in suspicious or overlapping symptomatology, as well as in manipulating pharmacological therapy that will be used in the treatment (Huang et al., 2005).

Atrophic volume changes in the various lobes of the brain or in the gyri of the schizophrenic cases have been discussed with speculative data that were contradictory sometime. In addition to these data, there is also a growing body of evidence suggesting a disturbance in the connection between different brain regions, which was just a theory, approximately 5 to 10 years ago. Here, with DTI, a technique that would roughly solve these connections at least for now, it is possible to evaluate the organization and coherence of fiber tracts of white matter (Peters et al., 2010). Although the techniques are insensitive to fiber tract, there are studies that DSI (diffusion spectrum imaging) could reflect the information about direction on the screen as differences in color-coding (Konrad et al., 2010).

DTI techniques are generally used to investigate frontotemporal connections in schizophrenia. Because, a number of studies have shown that functionally a disconnection is in question between frontotemporal connections, as well as volume loss and asymmetry in white matter. Some DTI studies have shown that involved tracts in schizophrenia include uncinate fasciculus, which is one of the greatest pathways, cingulum that enables connection in limbic system, fornix that connects hypocampus to prefrontal cortex and to thalamus, and arcuate fasciculus that connects the motor and sensorial speech centers. If we briefly talk about future directions concerning imaging in Schizophrenia, it should also be combined not only with other structural imaging techniques, but also with functional MRI and PET imaging in order to characterize and to understand more fully the relationship between functional and structural abnormalities in schizophrenia. Along with the standardization of multiparametric evaluations in neuroradiology field to put forward the lesion or pathologies in each organ, success in schizophrenia, which has been achieved within the last five years, would continue increasingly (Tang et al., 2007).

The onset of schizophrenia in childhood, usually defined as onset by age 12, is extremely rare. It has been estimated that the prevalence of childhood-onset schizophrenia may be 50

times less than that of adult-onset schizophrenia. When the structural brain imaging findings are primarily taken into consideration, lateral ventricle calibration in pediatric schizophrenia cases have been reported more stuffed than the normal in a study performed previously; however, later MRI studies did not corroborate this finding. Studies have shown decreased amygdala and temporal cortex volumes, but normal hippocampal, ventricular, frontal and total brain volumes (Shenton et al., 2001). In a study on childhood-onset schizophrenia, enlarged basal ganglia volumes at the beginning of the study were found normalized after patients were switched to atypical antipsychotic medication.

Very few functional brain imaging studies have been conducted in patients with childhood-onset schizophrenia. This can be attributed both to the fact that the disease is rarely seen and that it is difficult to evaluate pediatric cases via MRI. However, changes in favor of hypofrontality have been obtained in small study groups. Moreover, cerebellar hypermetabolism in childhood-onset schizophrenia, seen with these data analytic approaches, is notable in the light of recent evidence implicating the cerebellum in higher cortical processes (Akbarian et al., 1996).

As other functional imaging modalities, few 1H-MRS studies have been conducted previously in childhood-onset schizophrenia. As was observed in adult-onset schizophrenia, the ratio of NAA/Cr was significantly lower in the frontal lobes of the schizophrenic children in childhood-onset schizophrenia (Akbarian et al., 1996).

Functional imaging studies as well provide valuable evidence that the underlying pathophysiology in this disorder is similar to that in adult-onset schizophrenia. Studies on rCBF have provided evidence about task-related hypofrontality in early-onset disease, which were consistent with the findings in adult schizophrenia. MRS imaging findings in childhood-onset schizophrenia are in consistent with adult-onset schizophrenia that showed regionally specific reductions of NAA in mesial temporolimbic and prefrontal cortices suggesting neuronal involvement in these areas.

Clearer images are available with newly introduced propeller (motion free) sequences to reduce extensive movement artifacts in pediatric cases; thus, child-related minor inconsistency is likely to be tolerated in this way. No doubt, an individual that the child can trust, who would be helpful in case of potential problems that could occur particularly during the examination (narrow MR gantry and high-decibel noise), is extremely advantageous and required, particularly in the cases who mainly have delusional and hallucinational symptoms. Although studies with current technologically advanced modalities have been going on, early radiological diagnosis might be possible by directing to the systems more molecular and with larger studies in the subjects with early and suspicious symptoms.

In summary; overall imaging findings within schizophrenia spectrum show that, deviation exists both in the early and late period of brain development, which begins from the childhood and continues along with the adult life, and that, advances primarily in functional and molecular imaging methods are required for the pathophysiology of schizophrenia. There are studies that used advanced modality and multiparametric facilities, in which fMRI, MRS and DTI reveal common and consistent findings (White et al., 2008).

3.2 Imaging in affective disorders

Along with the advances in MRI technology, particularly within the last 10 years, brain anatomy and pathologies have begun to be understood better both structurally and

functionally. In this context, it should be identified that adult depression needs different progress and intervention from that of geriatric depression, whereas psychotic depression needs different progress and intervention from that of nonpsychotic depression. In general, brain volume measurements have shown that subcortical white matter volume and the volume of basal ganglionic nuclei are decreased with age in addition to the cortical atrophy (Kumar et al., 1999). In the studies on total brain volume, no significant difference has been identified between the depressive and normal groups in terms of age-related volume changes. It has been reported that atrophy process was more prominent in the frontal and temporal poles in the normal aging population and developed secondary to the volume loss in the central white matter (Palsson et al., 2001).

On the other hand, studies have shown that, frontal lobe is mainly responsible for the emotion and executive functioning and that volume loss particularly in the orbito-frontal cortex and in the subgenually located prefrontal cortex is a common finding in the depressive cases. Furthermore, the prominence of psychotic component that accompany depression has been found to be associated with the degree of frontotemporal atrophy (Simpson et al., 1999). Despite the conflicting results in the studies concerning the whole temporal lobe, only hipocampoamigdala related bilateral minor volumes have been found to be associated with major depression (Sheline et al., 1996). In addition to cerebral volume calculations, the studies that investigate hyperintense lesions located in the white matter reported that these lesions are in close association particularly with cardiovascular and metabolic risk factors. However, despite this association, regression analysis showed that the intensity of such lesions is related to depression (Lenze et al., 1999).

Despite the extensive studies on depression, studies on bipolar affective disorders are limited. However, bipolar subjects generally exhibit no frontal or parietal lobe volume abnormalities. Major depression, as a quite common disorder (the lifetime prevalence is 4.4%), requires early diagnosis and treatment. In one hand, late-onset bipolar subjects may differ from early-onset subjects; increased left sylvian fissure volume and bilateral temporal sulcal enlargement have been observed in the late-onset subjects as compared to the controls (Rabins et al., 2000). Deep midline cerebral structures have been suggested as the mediators of affective experiences and thus "Emotion and Mood" (Palsson et al., 2001). There are neuroimaging studies performed on many affective disorders ranging from aggression to antisocial personality disorder. At this point, studies have been extended from brain imaging to exposing the temperament elements (Taylor et al., 2001).

Studies on mood disorders are usually nonspecific, and volume-related atrophic changes have been reported. Ongoing studies on mood disorders showed that neurobiological developments progress in terms of illuminating the physiopathology of the diseases. In addition to these nuclear medicine based studies performed by PET/CT using special metabolites, functional imaging technologies as well are begun to be used in this field for diagnostic purpose. As previous anatomical researches, these studies were also aimed particularly at the circuits that are important contributors in affective processing like prefrontal and anterior paralimbic basal ganglia-thalamocortical circuits (McGowan et al., 2004). Functional brain imaging studies have consistently yielded insights into the neural substrates of affective processes. Neuroanatomically oriented functional brain imaging methods include positron emission tomography (PET) with fluorine-18-deoxyglucose C8FDG), which can determine the cerebral metabolic rate of glucose (CMRglu), and with oxygen-15 water, which can assess CBF. Single photon emission computed tomography

(SPECT) with technetium-99m-hexamethylpropyleneamineoxime (99Tc-HMPAO) or technetium-99m-exametazime (99Tc-EMZ) can determine cerebral CBF. fMRI studies also yield data that was considered to be related to cerebral activity. Different from the type and distribution of transmitter, we can calculate the information of a complex network by use of fMRI based on the regional cerebral changes. For example, one of the interesting findings on MRI due to the facial expression was the fact that, activation of the amygdala was most consistently related to fear processing. The main circuit responsible for the facial expression is anterior cingulate-medial frontal gyrus-basal forebrain (Kiosses et al., 2000). In addition to the anatomical variations (volume loss, local-generalized atrophy, and white matter-related sequel signal changes) efficacy of treatment (psychotherapy, antidepressants, mood stabilizers, and sleep deprivation) of existent abnormalities can also be evaluated via fMRI (Kennedy et al., 2001).

Mood disorders may follow a unipolar course in which only depression occurs or a bipolar course in which normal mood alternates with both depression and mania. Co-morbid entities (such as anxiety) may alter the nature of fMRI findings. In appropriately applied tests, fMRI can detect the hypofunction in the ventral striatum, slowed motor manifestations in the dorsal striatum or thalamus, and amygdalar hyperactivity or hypersensitivity developed in anxious cases. In a study performed with fMRI, BOLD-fMRI has been performed with block design to reveal left amygdala activation during emotion. In the study, which has been performed by showing the photos of the actors taken in different facial expressions, it is found in general that medial prefrontal cortex, retrosplenial cortex and cingulum, and temporal pathways were involved in depressive patients and thought that hipoactivity might be the main underlying cause of hypoactivity (Dougherty&Rauch, 1997).

On the other hand, in addition to the standard motor or sensorial stimulations given by the technician, it is possible to stimulate noninvasively a brain region and to image simultaneously regional brain activity via transcranial magnetic stimulation (TMS) within the fMRI scanner, in the studies performed with more advanced systems. It was found in these studies that prefrontal brain TMS and thus the connectivity features showed variations in the depressive cases as compared to the normal control groups (Kito et al., 2008). On the other hand, vagus nerve stimulation (VNS) is a new technology that serves as an effective antidepressant. Moreover, the fact that activity shows an increase with VNS in the orbitofrontal and hypothalamus and in the prefrontal cortex may serve as a reference for the confirmation of fMRI data (Bohning et al., 2001).

In addition to this system, in which micromolecular system has been indirectly and noninvasively investigated without being exposed to ionizing radiation, brain imaging studies can also be done being oriented biochemically with a special radiotracer using PET and SPECT modalities. Data on this subject that is not within the scope of this paper can be obtained from the literature.

MRS studies in mood disorder showed that patients had metabolite alterations in prefrontal and anterior paralimbic basal ganglia-thalamocortical circuits. We can also calculate cellular construction and degradation products and metabolite contents with Phosphorus-31 magnetic resonance spectroscopy as well as conventional 1H-proton spectroscopy. In addition to the findings detected by 1H-MRS (Increased basal ganglia choline and decreased bilateral dorsolateral prefrontal NAA levels), studies that used phosphorus spectroscopy have found that bipolar patients had lower prefrontal phosphomonoesters (PMEs) (Yildiz et

al., 2001). This is an indicator of altered signal transduction putatively related to the pathophysiology of bipolar illness (Yildiz et al., 2001). Studies on adults, in whom affective illnesses have been developed after brain injuries, showed related abnormalities in the frontal or temporal lobes. Mania may be related to the right frontotemporal or left parietooccipital lesions, whereas depression is related to the left frontotemporal and right parietooccipital lesions (Castillo et al., 2000). Proton MR Spectroscopy provides information about tissue biochemistry and metabolic changes in vivo. MR Spectroscopy has been used with success in psychiatric illnesses limited to understanding some metabolic changes and to assessing the effects of lithium in the treatment of bipolar affective diseases.

White matter abnormalities are one of the components of the network dysfunction that underlies affective disorders. DTI can uniquely study the direction and integrity of white matter tracts and is thus an ideal tool to shed light on white matter abnormalities also in affective disorders. DTI studies on affective disorders consistently identify reduced anisotropy in the frontal and temporal lobes as well as reduced number of tracts in the patients with affective disorders as compared to the control subjects (Sexton et al., 2009).

Owing to the combination of fMRI studies and other neurostimulation methods such as TMS and VNS, it is thought that data obtained from the studies on this subject would be increased. Current techniques (BOLD fMRI, perfusion, diffusion, and spectroscopy) would be enhanced more in time; perhaps, more information about direct function would be obtained due to combined methods with the advances that we still could not predict. Organic data might also be obtained for the diseases, the physiopathology of which remained imaginable only, and the solutions would be put forward more clearly. This is not such a distant prediction, and in fact, appears frequently with simple mechanisms. For example, perfusion MRI of a case presented with depressive mood disorder and had contrasted nonspecific thalamic lesion on the MRI showed isointense millimetric non-perfusion foci in the left half of the pons on the above-mentioned contrasted focus; it was determined that atrial fibrillation and microembolus have caused the existing alterations. Although, numbers of symptomatic overlaps are likely between the two groups, the differences between mood disorders and schizophrenia in terms of anatomical changes of the brain are estimated to be clarified with detailed studies that would be performed on this subject. However, it should be kept in mind that current studies greatly have focused on the neurotransmitter and that in fact there are many numbers of transmitters and steps during the stages of forming and maintaining thought and behavior.

In summary, despite the advances that have rapidly been introduced to the routine use, estimations on the functional process are still being done indirectly by measuring blood flow and energy consumption, rather than directly via neurotransmitter formation and axonal conduction. Current studies investigate direct methods studying on the metabolites associated more directly. It has been suggested that clearer and adequate anisotropy maps and tractography imagings can be obtained in the future with high-resolution diffusion spectrum imaging due to the potential advances in DTI techniques. In this context, it is thought that adequate connections between the anterior cingulate cortex-basal ganglia and the frontal cortex could be identified by coding the afferent-efferent fibers in different colors with planned software.

3.3 Imaging studies in Attention Deficit and Hyperactivity Disorder (ADHD)

ADHD is a disorder of unclear pathophysiology mainly characterized by hyperactivity, impaired impulse control and attention deficit. ADHD is one of the most common

psychiatric disorders among children. Symptoms continue in the adulthood in 30-50% of ADHD cases diagnosed during childhood. As was shown in the studies that will be mentioned later, dysfunction of fronto-striatal formations and significant differences in metabolite concentrations in certain regions (such as caudate nucleus) have been put forward with fMRI and MRS in addition to the anatomic differences. Contrary to the autistic cases, decrease in total brain volume has been shown in many studies performed until today on the children with ADHD (99). In some studies, this volume decrease has been particularly stressed on (Critchley et al., 2003). In the studies with fMRI, differences have been identified between the children with ADHD and the control group in terms of the activations of prefrontal cortex, anterior cingulate cortex and striatum (Konrad et al., 2010). Some studies have revealed that differences in the blood flow prior to the therapy showed improvements such as returning to the normal levels after methylphenidate therapy, as compared to the normal population (101). It was shown with fMRI that both the clinical picture and decreased basal ganglia activation have improved in the cases presented with ADHD and learning difficulty as compared to the healthy subjects (Coryell et al., 2005). It was also shown with specific SPECT studies, which can obtain receptor-based information, that there was a decrease in the dopamine transportation intensity in the basal ganglia after the therapy (MacFall et al., 2001). All these studies showed that functions such as integrity of frontostriato-thalamic circuit and dopaminergic pathway are abnormal in the cases with ADHD and that, are improved with therapy.

Recent studies indicated a role for the basal ganglia (caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and ventral mesencephalon) in a variety of neuropsychiatric conditions involving motor and attentional dysfunctions. It is known that striato–thalamo–cortico–striatal loop is associated with motor, somatosensory, oculomotor, executive, emotion, and motivation functions in daily stimuli. Studies performed with fMRI suggested decreased perfusion in the dorsolateral prefrontal cortex of hyperactive children as compared to those nonhyperactive. Furthermore, asymmetry was found in the motor-timing and response phases of anterior cingulate activation during cognitive interference task in these hyperactive children as compared to those normal and non-hyperactive. Decrease in the perfusion of basal ganglionic region has been objectively demonstrated in the group including the children with ADHD. Attention-deficit and hyperactivity disorder (ADHD) is characterized by persistent inattention and/or situational excessive motor activity, and accompanying impulsive behaviors. It is the most prevalent childhood psychiatric disorder (3–11% of the school-age population). Some studies raised the thought that there is a problem with basal ganglia in some of the psychiatric diseases as well as in certain motor disorders. Ignoring molecular basal ganglionic communication cycle, which is out of the scope of this section, striatum is separated into two up to the cortical conduction type. The first is prefrontal cortical and associative areas including visual and auditory cortical regions projecting the dorsolateral head of the caudate and the anterior putamen. The second is extensive projections from the anterior cingulate and medial orbitofrontal cortex. This more complex cycle, which we have summarized, is the point, in fact, where the functional neuroanatomy is bound as would be in the future. As a general principle, examination must be suspended for 48 hours to 2 weeks prior to a functional imaging study in the children with ADHD.

Since the basal ganglia produce signals initiated by the commands of frontal-originated fibers, studies that investigated the activity and volumetry of DLPFC are not limited. In addition to these many conventional alterations, regional cerebral blood flow (rCBF) studies showed it is anomalous in both children and adult cases with ADHD. In these studies, greater frontal activation was found in the subjects with ADHD during response-controlled condition (Teicher et al., 2000). Decreased volume and altered asymmetries of the caudate nucleus in children with ADHD have been reported in several studies (Teicher et al., 2000). In addition to the volume loss, greater motor hyperactivity has also been found correlated with lower perfusion, assessed with resting state fMRI, in the right caudate of the children with ADHD. In some of these studies, the activation was measured increased in some brain regions, including the right caudate nucleus in the cases with ADHD, whereas no activation was identified in the normal cases receiving psychostimulant. Since putamen always plays an essential role in the sensorimotor activity, it has become a component studied in ADHD. Besides, an influence is in question also in globus pallidus and anterior cingulate region in the cases with ADHD (Filipek et al., 1998). On the other hand, cerebellum is an important organ, but neglected in ADHD. Despite the considerable number of evidences that indicate the role of dopaminergic system in ADHD, the underlying mechanism remains unclear. Although it is among the targets in current fMRI studies, PET methodology allows direct examination of dopaminergic function in vivo (Ernst et al., 1999). The current aim should be trying to visualize directly the functional pathology beginning from the "task development" stage, and to study with large series by standardizing the functions. The above-mentioned studies performed with fMRI were consistent with each other. The fMRI studies on children and adults with ADHD have shown that frontal lobes, basal ganglia and cerebellum are the regions most likely to be involved.

Current evidence suggests that ADHD involves dysfunction of a wide functional network of brain areas associated with attention and cognition. Cases with ADHD show greater fractional anisotropy in white-matter regions that underlie inferior parietal, occipito-parietal, inferior frontal, and inferior temporal cortices. Tractography may reveal that these regions generally form a part of white-matter pathways connecting prefrontal and parieto-occipital areas with the striatum and cerebellum. Again, when the information both from fMRI and from DTI studies is evaluated together, it was found that in ADHD some cortical regions that have previously been shown is dysfunctional or hypoactive (Silk et al., 2009). In another study, it was suggested that alterations in brain white matter integrity occur in frontal and cerebellar regions in ADHD. The pattern of decreased fractional anisotropy might implicate the corticopontocerebellar circuit in the pathophysiology of ADHD (Ashtari et al., 2005). In the ongoing studies of the same research group, it has been theoretically claimed based on the controls performed with DTI and MRI that these disorganized or spoiled grey matter pathways can be relatively repaired after appropriate treatments.

3.4 Imaging studies in the autism

Within the time from the first definition of autism until now, many structural and functional brain-imaging studies have been performed to investigate either the neuroanatomic disorders or the pathophysiology. In the structural brain-imaging studies, a decrease was detected in both the white and grey matter volumes mainly in the frontal, temporal and parietal lobes, as well as in the total brain volume, and this was attributed to an extensive

damage in the neuron networks that might have been developed in the early developmental period. In the functional brain imaging studies, efficacy differences have been detected in the temporal lobe and amygdala, which function in the language and social cognition fields, whereas an increase in the efficacy has been detected in the posterior cortical regions (Nugent et al., 2006). Despite this volume increase, some studies reported a decrease in the gray matter volume particularly in the ventromedial and superior temporal regions, in which emotional and sensorial stimuli are processed, and in the cingulate gyrus and superior temporal sulcus (Baumann et al., 1999). The studies on the autistic cases have been conducted within such a wide spectrum that one of the studies has reported an increase in the amygdalohypocampal volume in the parents of pediatric cases involved by the disease. There are studies suggesting that cerebral blood flow variation during language use in the autistic patients shows difference as compared to the normal population (Vostrikov et al., 2007). In the cerebral functional MRI studies that tested auditory data processing mechanism, it was found that the activity of left posterior insular region is less, but contrarily the right Wernicke homologous accompanies more activities. These data have led to the neurophysiological studies to understand why emotional component less accompanies speech in autistic subjects (Sanacora et al., 1999). Activations during human face identification and facial expression processing were found different in autistic children, adolescents and adults on the encephalographic fMRI studies (Hasler et al., 2007). Interestingly, it attracted attention in some fMRI studies that cerebellar functions as well showed an increase during motor activation (Filipek et al., 1997). Despite the conflicting results in the literature, studies performed with MRS reported that NAA concentration has been increased in the hypocampus-amygdala and in cerebellar level in autism (Durston et al., 2003). In a study that evaluated serotonin synthesis capacity via PET, it was expressed that this capacity was more intensive and long-termed in the autistic subjects (Schultz et al., 2000).

Although temporal lobe-originated abnormalities have been defined approximately and significant results have been obtained with these detailed data, it seems that DTI and molecular based studies that would be conducted on larger samples are needed to clarify the pathophysiology of autism. Studies have been performed on many topics in addition to these common, more extensive and perhaps popular study fields. Although the mechanisms were similar in all these extensive studies, patient groups and the focal region investigated were different. For example, FDG affinity was found lower in the medial temporal lobes of the cases described as aggressive on the psychiatric evaluations (Tamm et al., 2004). In many consecutive case reports or in the research papers, it has been reported that the symptoms mostly began within a psychiatric picture in congenital enzyme deficiencies, in metabolic or idiopathic cerebral diseases, or in systemic diseases (Shafritz et al., 2004). Furthermore, there is information characterized by large researches and reviews on this topic, in which an association between a single specific disease (such as encephalomyelitis, epilepsy, arachnoid cyst, Wilson's disease) and psychosis has been established (Barnea et al., 2004).

Autism is a developmental disorder defined by the presence of a triad of “communication, social, and stereotypical behavioral characteristics” with onset before 3 years of age. It is difficult to scan young children and to obtain appropriate age-matched controls. Studies have been mostly performed on mild and conformist autistic cases and thus, we have been restrained to obtain more current and extensive information (Heh et al., 1989). Although the

first results of the studies mentioned about increase in global glucose consumption of the brain, presence of basal ganglionic uptake imbalance has also been reported (Heh et al., 1989). Phosphorus-31-MRS showed that decrease in phosphomonoester levels, increase in phosphodiester levels and decrease in ATP levels were associated with increased ATP consumption (Minshew et al., 1993). On the other hand, proton (1H) MRS has showed that NAA is significantly lower in cerebellum in the autistic group (Prather et al., 2001). Since autism is most commonly recognized in the second year of life, later on during autism process, behavioral manifestations of autism change with age, and therefore, functional brain abnormalities as well might change in time, although autism is not a progressive disease. In the studies performed with DTI, white matter organization abnormalities were frequently detected particularly on frontal fractional anisotropy and apparent diffusion coefficient maps (Sundaram et al., 2008). Besides, many studies have mentioned about disappearance of normal asymmetric tract anatomy and reduced interhemispheric connectivity pathology between two hemispheres via demonstrative images.

3.5 Imaging in the extracranial pathologies that clinically present as psychiatric disorders

In this section, we are going to summarize the information in a table (**Table 3**). Findings about certain organic-extracranial diseases, the clues of which would be found also with other laboratory findings, as well as the psychiatric symptoms they caused, which would

Extracranial pathology	**Related psychiatric disease**
Hypothyroidism	Somatization, obsessive-compulsive disorder, anxiety, and paranoid thought are more common in hypothroidic cases (Vyas et al., 2010).
Hperthyroidism	Thyrotoxic encephalopathy (Brownlie et al., 2000).
Parathyroid malfunction	Mental dimness, imbalance and depression (Pollard et al., 1994).
Vitamin B12 deficiency	Depression, mania, psychosis, dementia (McCall et al., 2009).
Adrenal cortex hyperfunction (hyperplasia, adenoma)	As is known, hypercortisolemia is toxic for hypocampus and certain cortical regions, and may play a role in the development of psycopathologies such as posttraumatic stress, depression and dementia. Adrenal medulla-originated lesions may first present with fear and anxiety attacks (Schüle et al., 2009).
In most common endocrinologic diseases	Symptoms that mimic psychosis such as psychomotor retardation depersonalization and cognitive changes, depression, and anxiety (Roy et al., 1994).
In some extracranial tumors (such as lung carcinoma)	Some paraneoplastic substances may cause psychiatric symptoms due to their encephalopathic effect (Alamowitch et al., 1997).

Table 3. Certain organic extracranial diseases and related psychiatric symptoms they caused.

disappear when treated. To these brief data, psychiatric symptoms should be cautiously evaluated since they might be the reflection of underlying endocrinological disease or paraneoplastic syndromes with systemic signs, and the imaging spectrum should be widened if needed. As the result, such psychiatric symptoms that sometimes appear before the organic symptoms may have been used in early diagnosis.

3.6 Psychiatric symptoms and imaging of intracranial lesions

It was known also before the development of modern imaging techniques that intracranial space-occupying lesions and some other structural pathology lead to psychiatric symptoms. Based on their localization in the brain, space-occupying lesions cause personality changes, affective disorders and disorganization of intellectual functions. At least half of the cases with space-occupying lesion show psychiatric symptoms; furthermore, psychiatric behavioral changes appear as the first sign of the disease in 18% of the cases. In the postmortem studies conducted on the chronic patients or on psychiatric patients under treatment, cerebral lesion was detected by 3.5-5%. This rate is consistent with that found in the general population. However, in detailed examinations, change in mental status may appear as the initial symptom in 15-20% of the patients with space-occupying lesion. These are high cortical functions including attention, memory, emotion, personality, concrete thought and confusion. Symptoms such as a single epileptic seizure, change in the daily activities and interests, and not hearing high-frequency sounds may cause the physician to suspect space-occupying lesion. Using contrast MRI and CT, although the order is changed according to the centers, unveils the suspicious conditions in such cases. However, it is important to understand the underlying factor of the symptom; because, the association between space-occupying lesion and psychiatric symptoms may be developed primarily due to the direct invasion of the tumor, as well as secondarily due to the increased intracranial pressure caused by the edema and space-occupying character.

It is seen that the majority of space-occupying lesions that cause psychiatric symptoms are located in the frontal, temporal and limbic lobes (Feinstein et al., 1998). Along with the enlargement of the frontal lesions and disappearance of inhibition in time, personality changes such as irritability, impaired judgment and lack of interference, as well as neurologic symptoms, begin to appear. Whereas the right frontal ventral region is associated with manic behaviors, lesions of dorsolateral prefrontal cortex were found associated with apathy, lack of interest and psychomotor retardation (Feinstein et al., 1998). Temporal lobe lesions commonly cause complex partial (characterized by impaired conscious, repetitive psychomotor and autonomic motions) and simple partial (characterized by smell and taste hallucinations, deja vu, feel of fear) epileptic seizures. Lesions of temporolimbic region (likely due to the involvement of limbic formations such as hypocampus, fornix, mamillary corpuscle, mamillothalamic bundle, anterior thalamic nucleus, cingulate gyrus, and parahypocampal gyrus) are known to be frequently associated with psychosis and schizophrenia-like disorders (148). Parietal and occipital lobe lesions are rarely accompanied by psychiatric disorders.

Whereas, only localization of the lesion can be detected by tomography, differential diagnosis of the mass is available by MRI and functional techniques, and extremely beneficial information that might direct the therapy can be obtained. Tumoral metabolic activity can be identified by PET/CT, PET/MRI, and SPECT examinations. Examination by

DTI is a method that could identify the deformities of nerve tract caused by the edema-invasion-infiltration effects of the lesion.
In case of inconsistent mass lesion and psychiatric symptom, other likely anomalies that accompany the current psychiatric disorder can be investigated in the same session. The pathologies without mass lesion have been summarized under separate topics in the further sections of the review.
As a well-known entity; Alzheimer's disease: It is possible to differentiate the brain of healthy elderly from AD with conventional sequences. However, signal changes in the posterior segments of corpus callosum in early AD identified by DWI are consistent with pre-atrophy initial changes and are reasonable (Backman et al., 2001). On the other hand, DTI studies conducted in the early stages of the disease have revealed significant connection disruptions in the junction of white matter fiber tracts, including the temporal stem (uncinate fasciculus), cingulate fasciculus, corpus callosum, and superior longitudinal fasciculus, as well as the hippocampus (Volkow et al., 2000). The general rule up to now is; studies on AD have been performed with BOLD, and the degree of regional activity in mesial temporal lobe has been studied comperatively. In these studies, decreased mesial temporal lobe activity in mild AD cases, in which the volume loss was not manifest yet, as compared to the normal healthy population attracted attention (Kantarci et al., 2001). Additionally, magnetization tranesfer ratio measurements are more specific than visual analyses in detecting structural damage of the hippocampus in the patients with AD (Hanyu et al., 2000).

4. Conclusion

In conclusion, advances in molecular imaging technologies, in addition to the sectional radiologic imaging that provides anatomo-morphologic and functional information, have the ability to detect, diagnose and follow the neurophysiologic axis abnormalities that are reflected as psychiatric disorders. What is important is which of these methods are usable in what extent and which points the method would illuminate in the pathophysiology of the investigated disease. The aim of radiologic imaging in psychiatry should be to detect the specific findings of each disease and to allow differential diagnosis. Various algorithm templates that are appropriate for each clinic may be in question on this subject (**Figure 18**). For any of the imaging center, with routine or further radiological evaluation if needed, under the light of the literature information or experiences, this might be possible with the available modalities.
With regard to neuroimaging in psychiatry, numerous ongoing developments suggest that it may be possible to scrutinize the underlying anatomopathological or molecular abnormalities with radiologic imaging. By the emerging studies with 7 Tesla MRI, it may be possible to delineate subfield morphological abnormalities especially hypocampal regions. Besides, using DT-MRI in-vivo, under the ultra-high field MRI system, the tracts that form the white matter can be visualized noninvasively. Although, only the structural alterations have been studied previously, current technology aims to obtain metabolic, functional and consequently molecular information beyond the anatomic information. However, different from the other internal and surgical fields, the process in psychiatry is more complex and variable. Since there might be a severe metabolic-functional underlying organic etiology without presence of anatomomorphologic alteration, it is impossible, at least for now, to make the diagnosis easily with a "gold standard" imaging modality. With further advances,

optimization and standardization of radiological diagnostic systems for psychiatric diseases may be required in the near future.

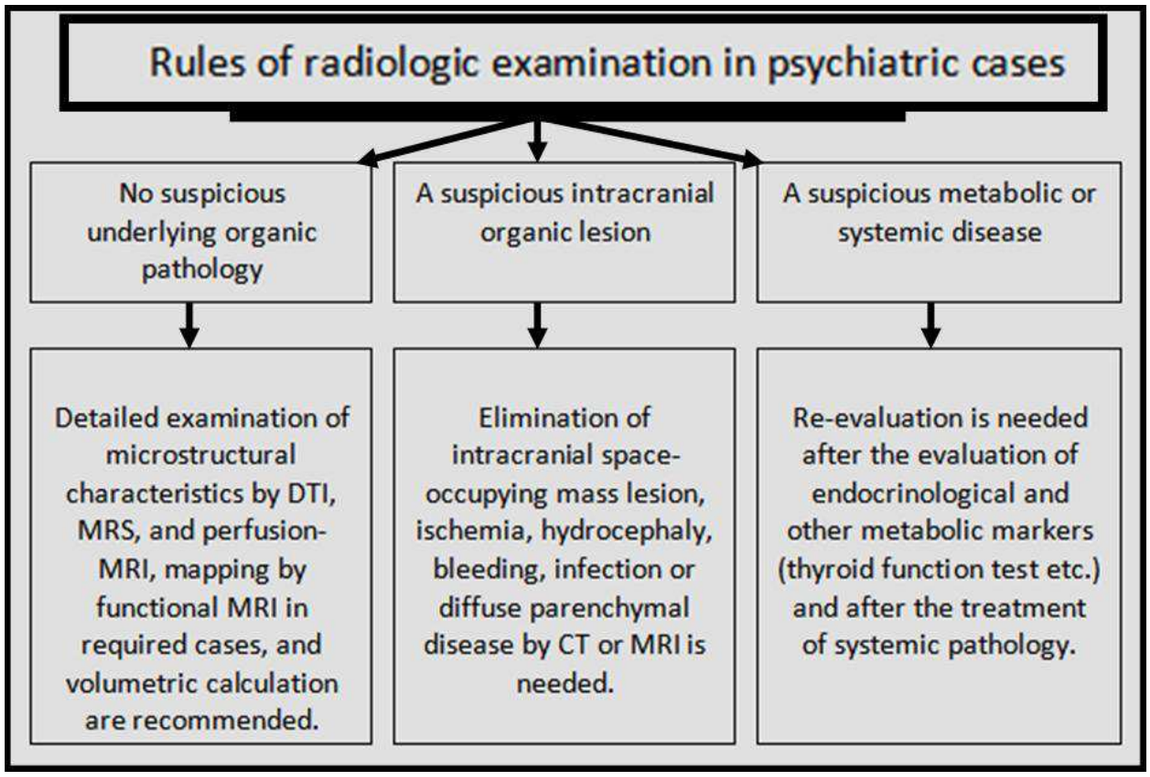


Fig. 18. A practical and applicable schema that indicating the simple algorithm that can be applied to radiological evaluation in psychiatric disorders.

With new modalities, the distribution of psychiatric medications that are considered relatively serious can be investigated by giving marked medications, in terms of not only the disease could be foreknown, but also potential toxicity and which organ it would affect most. It is already possible to measure the concentration of lithium or fluoxetine metabolites by detailed MRS examination.

Since the course of the fibers can be known and predicted in the examinations performed with DTI in particular, it can be used as a guide in stereo-ataxic neurosurgery that is used in the treatment of therapy-resistant obsessive-compulsive disorder or major depression. DTI guidance can be used to preserve the risky tracts prior to the procedures such as anterior cingulotomy, anterior capsulotomy, and limbic leucotomy. Moreover, efficacy of therapy (particularly in epileptic cases) can also be evaluated with this method. At this point, therapy-resistant obsessive-compulsive disorder and depression can be treated more appropriately with transcranial magnetic stimulation (TMS) for the regions that abnormally matched DTI/fMRI. It can be said in all contexts that knowledge about imaging in

psychiatry would be improved and, as in many fields, routine use of MRI sub-modalities for diagnosis might be in question in the near future, although not so close.

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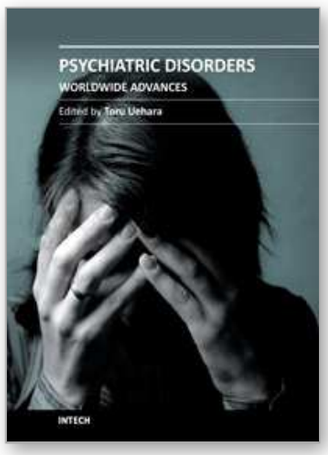

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