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Review Article

Schizophrenia: A review of neuroimaging techniques and findings

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Abstract. Neuroimaging has been used in schizophrenia since the invention of computed tomography and new modalities are introduced as technology advances. Magnetic resonance imaging, magnetic resonance spectroscopy, diffusion tensor imaging, functional magnetic resonance imaging and radionuclide imaging are such techniques that are currently used in neuroimaging. Structural neuroimaging studies have demonstrated the association between auditory hallucinations and superior temporal gyrus volume loss whereas negative symptoms of schizophrenia were reported to be associated with prefrontal lobe volume loss. Functional neuroimaging techniques show that schizophrenia patients have diffuse functional disorders located in different areas and networks of the brain defined as the default mode network. The effects of chronic drug therapy affects neuroimaging findings by altering neuronal function via genomic expression and changes in the ultrastructural level. Although neuroimaging is an indispensible tool for psychiatric research, its clinical utility is questionable until new modalities become more accessible and regularly used in clinical practice. The aim of this paper is to provide clinicians with an introductory knowledge on neuroimaging in schizophrenia including basic physics principles, current contributions to general understanding and treatment of schizophrenia and possible future applications of neuroimaging.

Key words: Schizophrenia, neuroimaging, default mode network dysfunction, functional magnetic resonance imaging, diffusion tensor imaging

1. Introduction

Among all psychiatric disorders, schizophrenia is regarded as the most difficult to define. Schizophrenia is a syndrome hallmarked predominantly by delusions, hallucinations and thought interference in the acute phase and social withdrawal, apathy, slowness and lack of drive in the chronic period. However, it is also associated with many functional cognitive disabilities which are not solely psychotic in origin and thus is thought to be the final result of a diffuse spectrum of neurodevelopmental disorders. The etiology of schizophrenia remains to be unclear. Many researchers emphasize that focusing solely on the psychotic findings may result in inadequate comprehension of other areas of disabilities associated with the disease. The distinction between schizophrenia and other psychotic disorders, such as schizoaffective and delusional disorders, are also under debate (1,2,3).

Neuroimaging studies have shown that hallucinations and delusions have cerebral correlates with left medial temporal lobe and cingulate cortex; whereas disorganized thought and behavioral patterns are related to anterior cingulate, bilateral parietal regions and ventral frontal cortex. Psychomotor poverty, on the other hand, is shown to be associated with reduced activity of frontal cortex (4).

In this context, neuroimaging studies are not solely conducted to identify etiology of schizophrenia. Other areas in which neuroimaging is expected to aid are ruling out "organic" pathologies, foreseeing response to treatment and estimating prognosis, evaluation of accompanying neurodevelopmental pathologies, advancing drug development processes and identification of high-risk individuals.

The aim of this paper is to provide the practicing clinician with information on basic physics principles of various neuroimaging techniques which are used during diagnosis and treatment of schizophrenia with emphasis on current and possible future clinical uses.

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2. Neuroimaging in Schizophrenia

2.1. Computed Tomography

Computed tomography (CT) uses highly collimated x-ray beams. X-ray photons that pass through the patient are collected by detectors and their intensity shows variations which depend on the degree of absorption in the body. The x-ray beam is rotated over many different angles so that differential absorption patterns are obtained through a single slice of the body. X-ray absorption values for each point (pixel) within a CT slice is obtained by a mathematical analysis known as projection reconstruction and value of each pixel is demonstrated as a different shade in a spectrum of gray (5).

Most effective uses of CT in neuroradiology are ruling out hematomas and hemorrhage, detection of calcifications in lesions, evaluating acute head trauma and lesions of bony structures. Main disadvantage of CT is usage of ionizing radiation which limits its use in follow-up of patients (5).

In a patient with psychotic symptoms and signs, CT may be useful for ruling out stroke, tumors and hemorrhage. It is also used for evaluating cerebral volume loss, degree of hydrocephalus and traumatic sequel (6).

A large cavum septum pellucidum is observed more commonly in schizophrenia patients, but it is not regarded as a causal factor (7). Such non-causal anomalies are more common in schizophrenia patients when compared to general population; 30-40% versus 5-12%. This may be regarded as an evidence of aberrant neurodevelopmental processes contributing to the development of schizophrenia (8).

Ventriculomegaly and cortical atrophy are also more common in schizophrenia patients; however, these are not secondary to chronic treatment with antipsychotic medications. Ventriculomegaly is shown to be correlated with age, deterioration of cognitive functions, decreased response to treatment and presence of negative symptoms (9 -11).

2.2. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has four-times the contrast resolution of CT (12). The contrast mechanism is different in MRI; it relies on a complex interplay of the different responses of tissues to applied magnetic fields whereas CT relies on differential attenuation of the x-ray beam (5).

Hydrogen atoms have a net spin and magnetic moment, so when it is exposed to a magnetic field it experiences a small torque. Its axis of spin aligns with the magnetic field direction and it rotates at a particular resonant frequency. If a pulse of energy in the form of radiofrequency which has exactly the same frequency as the resonant frequency, an interaction occurs. This external stimulus changes the hydrogen atom from an equilibrium state to an excited state. When this stimulus ends, the excited state spontaneously decays back to the equilibrium with time and the nucleus emits an energy which can be detected with receiver coils of the MRI unit and converted into gray-scale pixelated images via complex mathematical transformations (13).

MRI is advised in cases of first presentation of psychosis especially with unusual presentations, rapid or atypical development of psychosis, dementia and presence of focal neurologic deficits or symptoms. MRI is useful especially for ruling out possible underlying diseases such as epilepsy, multiple sclerosis, certain tumors and vasculitis (6).

A four percent decrease in gray matter volume is reported in schizophrenia while white matter is not affected. This structural change was evident from the first attack. However, the association between volume loss and duration of disease is still under debate (14,15). A three percent decrease in frontal lobe, 5-6% decrease in temporal lobe, 4% decrease in hippocampal and 10% decrease in parahippocampal volumes were reported which are all associated with executive function and cognitive deterioration such as memory loss (16-18). Auditory hallucinations are shown to be associated with superior temporal gyrus volume loss and negative symptoms were reported to be associated with prefrontal lobe volume loss (16,19).

2.3. Magnetic Resonance Spectroscopy

One of the most interesting features of magnetic resonance imaging is the ability to perform *in vivo* spectroscopy. Magnetic resonance spectroscopy is based on chemical shift phenomenon which may be summarized as the change in the magnetic field created by protons due to the presence of electrons in the vicinity. Precession of protons in complex molecules differs from one another due to their bonds with neighboring atoms. If the specific precession frequency of the protons in a given molecule is known, then the concentration of that molecule may be detected with MRI. This gives information about neurochemical properties of a selected volume of the brain (20).

With magnetic resonance spectroscopy, concentrations of different chemical species can be analyzed *in vivo* due to distinct precession

frequencies of bound protons. N-acetyl aspartate (NAA), creatinine (Cre), choline (Cho), myoinositol (mI) and glutamate - glutamine (Glx) are frequent markers analyzed in MRS studies (5).

N-acetyl aspartate is a marker of neuronal integrity and its low concentration *in vivo* indicates neuronal damage or axonal injury such as multiple sclerosis, Huntington's disease, Alzheimer's disease and encephalitis. Choline is a part of cell membrane and reflects cell membrane turn-over rates. Increase in choline levels reflects cellular hyperplasia. Creatinine is a marker for functioning energy metabolism and its levels decrease in hypermetabolic states. Glutamine and glutamate are components of neurotransmitter system and their concentrations can be measured as two distinct peaks. Lactate, acetate, aspartate and lipid molecules are indicators of pathologic conditions at a cellular level. Changes at molecular levels in the interior milieu are evident even before morphologic changes are observable (5,20-22).

A meta-analysis of 1200 schizophrenia patients reported decreased n-acetyl aspartate levels in hippocampal gray and white matter and prefrontal cortices. This decreased state is shown to be persistent during the whole duration of disease (21,22).

2.4. Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) relies on the fact that areas of brain which are functional during a given task have locally increased cerebral blood flow. This increased cerebral blood flow is imaged with fast pulse sequences tailored to deoxyhemoglobin which is a paramagnetic molecule behaving much like gadolinium-based exogenous contrast agents. This is called blood oxygen level dependent (BOLD) imaging. With normal baseline brain activity, there is a mix of oxyhemoglobin (which is diamagnetic) and deoxyhemoglobin. Hemodynamic demand from brain activity first causes deoxyhemoglobin to form which reduces signal intensity; next oxygenated inflowing blood displaces the deoxyhemoglobin and signal intensity increases. The baseline and excited states are imaged in pairs and subtracted from each other. Often color is used for indicating areas of cerebral stimulation (12).

Clinical use of BOLD imaging includes defining motor and sensory cortical areas, Broca and Wernicke areas associated with speech and visual cortical areas; and surgical planning for tumor and epilepsy surgery (5).

Functional MRI studies in schizophrenia patients include research of executive and cognitive functions such as attention, memory, psychomotor function and basic stimulus processing. Among psychotic symptoms, auditory hallucinations are studied most extensively. Functional MRI showed that loss of superior temporal gyrus volume and functionality is associated with such symptoms. In a landmark study, McGuire et al (23) demonstrated increased activity of Wernicke and Broca areas and Heschl gyri during auditory hallucinations. Dierks et al (24) reported decreased responsiveness to external auditory stimuli in temporal lobes during auditory hallucinations.

Frontal cortex activation is extensively studied in schizophrenia patients and shows a pathologic left shift of the normal inverted U shaped curve of cognitive load versus frontal activation showing increased activation with cognitive load until a threshold is reached after which a gradual decrease in frontal activation ensues. There are however other studies which do not share the same results (25,26).

Functional MRI studies demonstrated that schizophrenia patients have diffuse functional disorders located in different areas and networks of the brain defined as the “default mode network” which includes bilateral precuneus and inferior - lateral temporal cortices, posterior cingulate and inferior parietal gyri (right sided) and right medial prefrontal cortex (27).

Studying the effects of drug therapy is also a very prominent fMRI research area. Meta-analysis of drug studies shows that specific neuronal regions normalize functionally over the course of anti-psychotic drug therapy while, though less frequently, some other regions denormalize. The effects of chronic drug therapy affects fMRI results by altering neuronal function via genomic expression and changes in the ultra-structural level (28).

2.5. Diffusion Tensor Imaging

In fluid environment water molecules normally move randomly and in all directions equally which is known as Brownian motion. In this case the diffusion of molecules is said to be isotropic. However when a barrier such as cell membrane is present, water molecules diffuse in a specific direction. This phenomenon is called anisotropic diffusion and is the basis of diffusion tensor imaging. The magnitude and direction of anisotropic diffusion in any structure can be detected by a mathematical process called the tensor. At least 7 measurements must be made in

order to construct a simple tensor, 6 with a diffusion gradient in all directions (simply up/down, left/right and back/forth) and one without a gradient. A tensor gives information on the direction of anisotropic diffusion of water molecules and this can be used for visualization of axonal pathways and white matter in general (20).

Diffusion tensor imaging is utilized in general neuroimaging to visualize association, projection or commissural fibers of white matter; to show white matter degeneration and myelin breakdown in demyelinating diseases; to demonstrate extent of tumor infiltration and mass effects of brain neoplasms and visualize axonal tracts in order to plan the extent of resection before tumor surgery. Diffusion tensor imaging also allows visualization of white matter tracts in colored three dimensional images and is called tractography (5,20).

A decrease in fractional anisotropy shows structural deterioration of white matter tracts and an increase in fractional anisotropy means edema, demyelination or axonal loss. Diffusion tensor imaging studies conducted as early as 1998 demonstrated decreased fractional anisotropy in corpus callosum and cingulum of schizophrenia patients. The results of such studies may be biased due to the fact that these findings may also be affected by various effects of age, gender and hand dominance of the subjects (29,30).

2.6. Single Photon Emission Computed Tomography and Positron Emission Tomography

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are radionuclide neuroimaging techniques. SPECT detects gamma rays emitted from the radionuclides. Radionuclides are introduced to the patient's body in various molecular forms which accumulate in the target organ or tissues. Gamma radiation is emitted when radionuclides disintegrate into more stable isotopes or isomers and this radiation is detected and mapped by detector systems called gamma cameras. SPECT is basically an assembly of gamma cameras with a computed tomography system (20).

Positron emission tomography, as the name implies, relies on positrons for image construction. Positrons are basically positively charged electrons which are emitted from a radionuclide when a proton is converted into a neutron. Fluorine-18 is one such radionuclide and is used for tagging glucose molecules to form F-18 deoxyglucose (FDG). FDG PET is mostly used in oncology, however it has also been extensively used in neuroimaging studies (20).

There are two types of radionuclide studies in schizophrenia patients: Blood flow - glucose metabolism studies and neuroreceptor research.

Blood flow and glucose metabolism studies are conducted in two phases; resting and active states. During activation with Wisconsin card sorting test, schizophrenia patients exhibit less pronounced increase in blood flow to dorsolateral prefrontal cortices (31).

Abnormalities in blood flow to temporolimbic tracts were shown to be associated with disorders of inhibition of subcortical dopamine release and positive symptoms of the disease. Auditory hallucinations were proven to be associated with increased blood flow to medial temporal and limbic areas (32).

Radionuclide studies are an important part of novel drug research. The pharmacokinetic properties of the drug, such as passage through the blood-brain barrier, and interaction with other molecules and neuroreceptors *in vivo* can be investigated. Radionuclide studies in schizophrenia patients demonstrated increased dopamine in synapses. Each anti-psychotic drug has different receptor affinities which can be demonstrated by PET and SPECT. Second-generation anti-psychotic drugs were shown to have regional specificity, higher affinity for Dopamine receptors and more reversible receptor-binding properties compared to first-generation drugs. These are seen as the reasons for clinical superiority of effectiveness and more favorable side effect profiles. In future practice, radionuclide studies may be used for predicting side effects and guide drug selection for individual patients (6,33-35).

3. Conclusions

Neuroimaging techniques have provided the scientific community with an immense body of knowledge on the pathophysiology of schizophrenia. This body of knowledge is rapidly growing and there are also ongoing new studies in search of new neuroimaging techniques. Molecular neuroimaging with novel imaging probes targeting very specific neuronal receptors and co-agonists is one of the many areas of ongoing studies with very promising preliminary results. N-methyl-D-aspartate receptor hypofunction is believed to play an important role in schizophrenia pathogenesis and the development of PET imaging probes for GlyT1, a co-agonist receptor for N-methyl-D-aspartate receptors, is an example having a great potential for increasing the pathophysiology of schizophrenia and may aid in novel drug research (36).

Data from neuroimaging studies yield results that may not always be applied to individual patient care. One of the main objectives of future studies must be to develop an algorithm of obtaining neuroimaging findings which may be used in individual patient assessment and treatment. In the future, a baseline neuroimaging study, be it MRI or other newly developed technique, may be used to rule out other possible disorders and to guide treatment regimens.

Neuroimaging techniques must be able to aid in patient follow-up by giving information on progression and prognosis in order to be incorporated into clinical practice. There is also a need for novel neuroimaging techniques for screening high-risk individuals to estimate the probability of advancing to overt schizophrenia.

When looked at a historical perspective, neuroimaging studies have shown us that schizophrenia is an organic mental disorder. More frequent use of state of the art neuroimaging techniques in clinical practice will make otherwise incomprehensible neural processes visible to both clinicians and patients. This, hopefully, will result in less stigmatization of schizophrenia patients and may lead to more patients and families seeking help.

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