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A Biomedical Imaging Analysis of the Prevalent Neuropsychiatric Disorders

Ayden Jacob[1]* and Sharon Cohen[2]

[1] Oxford Institute for Radiation Oncology; University of Oxford, UK
[2] St. Lukes Hospital, USA

Abstract

The utilization of various neuroimaging modalities to illuminate the structural and functional abnormalities detected in neuropsychiatric brain disorders has reached an unprecedented stage of evolvement in the medical community. Advances in structural and functional brain imaging technologies enable the medical community to discover the neurobiological basis of neurological illness in a very precise and dependable manner. Neuroimaging tools such as PET, SPECT and MRI have been better developed in order to further the neuroanatomical and neurophysiological basis of mental illnesses and cognitive disorders. With the advent of radiological innovation in neuroimaging, the focus in the medical community has shifted from the examination and study of single brain regions perhaps responsible for a specific psychiatric illness, to the critical examination of integrated brain systems which may be responsible for the phenotypic expressions of these illnesses. Imaging techniques have now made it quite clear that we must begin to investigate the neural networks involved in the pathophysiology of neuropsychiatric disorders. This paradigm shift, due to the innovations in brain imaging technologies, will likely facilitate the diagnostic reclassification of these complex heterogeneous disorders, enhance our understanding of genetic and environmental causes of the disorders, and improve our ability to treat these patients.

Introduction

Historically, the ability to examine the internal mechanisms of the human body was limited to the mere study of cadavers. Medical imaging technology has transformed various arenas of medicine over the last 30 years by providing scientists and physicians with a new mechanism by which they may look into a living organism. Dramatic improvements in image resolution and the biophysics engineering varying imaging mechanisms, such as CT, SPECT, fMRI, DTI and PET have granted the medical community the unprecedented ability to view structural and functional anatomical features of the human body in precise and exquisite detail. A specific area of medicine has been most dramatically impacted by imaging innovations is neuropsychiatric illness and other brain disorders. Recently, technological growth has allowed various functional imaging techniques assess in vivo of human brain function. Positron emission tomography (PET), single photon emission computed tomography (SPECT) and diffuse weighted and tensor imaging offer temporal and spatial information which can be of use to specify regional brain activity throughout the latent stage or accurate controlled cognitive conditions.

Our progressed comprehension of the human brain function and the pathosphysiology of different neurological disorders is due to these techniques. Our ability to both treat and diagnose a plethora of neurological disorders has been highly augmented by the exquisite abilities of neuroimaging modalities. Molecular neuroimaging studies permit the examination of chemical changes in the brain related to different neuropsychiatric brain disorders, as well as other neurological disorders. For example, PET and SPECT have advanced molecular neuropharmacology and allowed for in vivo assessment in humans of the level of receptor availability in schizophrenia, and for the level of receptor occupancy by antipsychotic medications at doses leading to clinical efficacy and treatment side effects.

Basic Mechanisms of Neuroimaging Modalities

The intricate biophysics engineering of these various neuroimaging modalities is responsible for the vast spectrum of both the advantages and disadvantages per technique, as well as each modality's specific repertoire of capabilities. It is thus essential to grasp the differing mechanics behind the most utilized innovative neuroimaging instrumentation in the detection and categorization of neuropsychiatric illness and various other brain disorders.

Positron Emission Tomography (PET)

Fluorine18 (18F) labeled glucose is the radioligand most commonly used in clinical brain PET. Glucose is radiolabeled with 18F by substituting the hydroxyl group with 18F to create the radioligand 2 deoxy 2(18F)fluoro D glucose (18FDG). 18FDG is taken up by brain cells in the same way as unlabeled glucose, but after phosphorylation to 18FDG6 phosphate it cannot continue glycolysis and becomes trapped in the brain cell. The PET scanner detects the amount of labeled glucose taken up by the brain [1]. PET isotopes undergo radioactive decay via a process known as positron emission or positive beta decay. During this decay a positron and a neutrino are emitted from the radiotracer. The emitted positron travels through the tissue, until it collides with a random

electron and both are annihilated. Positron emitters contain proton rich nuclei and attempt to stabilize themselves by gaining neutrons and ridding themselves of excess protons. This can be accomplished in one of two isobaric decay processes: positron emission or electron capture (EC); the mass number in both the parent and daughter nuclei remains the same in either process. A PET scanner detects annihilation photons in coincidence, which results in a PET image. The resulting image is a map of the distribution of annihilation points within the organ being analyzed. The map illustrates the particular tissues in which the tracer has become concentrated. A nuclear medicine physician can then analyze these results in the context of the patient's diagnosis and treatment plan [2]. FDGPET is a universally accepted clinical test in the diagnosis and follow up of malignancy, myocardial viability, epilepsy, and degenerative brain disease [3-5]. Positron Emission Tomography, alongside the array of radiotracers, studies the various pathologic and psychologic states throughout the body. The functions used to explore the brain in research, have discovered essential findings. Thus, when PET studies specific psychiatric disorders, it can affect the management of patients including attention deficit disorder, mood and anxiety disorder, schizophrenia, and obsessive compulsive disorder (OCD) [6].

Single Photon Emission Computed Tomography (SPECT)

A nuclear medicine tomographic technique using gamma rays, SPECT is able to provide a 3D image of patient's functional information. The basic technique requires injection of a gamma emitting radioisotope into the bloodstream of the patient. Most of the time in SPECT, a marker radioisotope, which is of interest only for its radioactive properties, has been attached to a specific radioligand, which is of interest for its chemical binding properties to certain types of tissues. This marriage allows the combination of ligand and radioisotope to be carried and attached to the specific area of interest in the target organ. Subsequently, due to the gamma emission of the isotope, the ligand concentration is visualized by a gamma camera.

In the preceding years SPECT has shaped and developed new hardware technology and image processing algorithms. Specifically the improvements have been in scintillators and photon transducers and it has also made a greater accessibility of semiconductor technology. These products allow for the manufacture of smaller and more compressed systems to be modified for certain applications [7]. Conventional nuclear medicine images compress the 3 dimensional (3D) distributions of radiotracers into a 2 dimensional image. Therefore, the outcome concerning the areas of importance and the territory surrounding it is often drastically reduced. This reduction limits the diagnostic information that is available in the study. In addition, the exact location of an abnormality can be difficult to determine. Tomographic images remove these difficulties but at the price of longer acquisition times, poorer spatial resolution, and the susceptibility to artifacts. Recent advances in SPECT instrumentation and processing have made marked improvements in each of these areas. Most clinical SPECT systems used to perform patient studies still use scintillation cameras with NaI(Tl) used as the detector. These systems consist of one or more scintillation camera heads attached to a gantry that revolves around the patient to collect projection views. The most common configuration has 2 scintillation cameras that are either fixed at 90 or 180 degrees, or have the capability to be positioned at selected orientations. The projection information required for SPECT is acquired by gamma ray detectors, and much of the quality of the projection depends on the properties of these detectors. We desire detectors with high intrinsic efficiency, good energy resolution, and good intrinsic spatial resolution. Materials with high atomic numbers and high density are important for detector efficiency. Both energy resolution and spatial resolution depend on the size of the signal generated with each detected event.

Diffuse Tensor and Weighted Imaging

As a respected imaging modality, DTI/DWI, is a vital component of routine diagnostic protocols in many hospital settings. The basis of this imaging technique is its ability to demonstrate the diffusivity of water molecules [8-10]. DWI is a useful technique aimed at detecting timely signs of ischemia [11,12], but it also has been gradually useful for the recognition of various brain diseases like multiple sclerosis [13-15], trauma [16,17], brain tumors [18,19], and hypertensive encephalopathy [20,21]. Development in the imaging of water diffusion is a result of the progress of the more multifaceted diffusion tensor imaging (DTI). DTI permits examination, in vivo, of some properties of tissue microstructure; it produces enumerative measures reflecting the integrity of white matter fiber tracts, by taking advantage of the intrinsic directionality of water diffusion in human brain.

Neuroradiology of Brain Disorders

The introduction of brain imaging techniques to enhance our treatment of brain disorders has entered a new stage of efficacy unseen hitherto. Amen et al. [22] show how brain SPECT imaging introduces pragmatic and essential data for diagnosis and treatment well beyond conventional assessment tools in intricate psychiatric cases. Charts of 109 evaluated outpatients from four psychiatrics clinics that routinely utilize SPECT imaging for complex cases were analyzed in two stages. In stage one, psychiatrists reviewed detailed clinical histories, mental status exams, and the structured clinical interview for DSMIV, but not the results of SPECT studies, assigned a diagnosis based on DSMIV criteria, and then developed a thorough treatment plan. In stage two, evaluators were given access to the SPECT studies for each patient. The addition of SPECT modified the diagnosis or treatment plan in 78.9% (n=86; rated level 2 or 3 change) of cases. The most clinically significant changes were undetected brain trauma (22.9%), toxicity patterns (22.9%) and the need for a structural imaging study (9.2%). Specific functional abnormalities were seen as follows that potentially could impact treatment: temporal lobe dysfunction (66.1%) and prefrontal hypoperfusion (47.7%) [8]. SPECT, and other advanced neuroimaging modalities, has the potential to add clinically meaningful information to enhance patient care beyond current assessment tools in complex or treatment resistant cases [22].

Schizophrenia

Characterized as a brain disorder, the etiology of schizophrenia remains elusive. Nevertheless, neuroimaging modalities have advanced the understanding of the neuroscientific community in regard to the structural and functional abnormalities inherent in the brains of schizophrenics. Neurochemical and molecular strategies are beginning to form a subtle consensus in the biomedical community as to the specificities of the disease on an organic level. Developing our understanding of the micro abnormalities present in this disorder will allow the medical community to advance our neuropharmological approach to treating, curing, and perhaps preventing the onset of this disabling psychiatric disease. Positive Symptoms are usually categorized as: auditory, tactile, visual, or olfactory hallucinations; persecutory, grandiose, or religious delusions; aggressiveness; bizarre appearance; abnormal sexual behavior; disordered thoughts. Negative schizophrenic symptoms are categorized as: poor eye contact, speech, or hygiene; inappropriate affect; blocking; apathy;

social inattentiveness. A regular finding done by studying molecular imaging in schizophrenia is that dopamine abnormalities is a fundamental pathophysiological feature of the disorder. These studies show that schizophrenia is connected to increased presynaptic striatal dopamine synthesis and storage and increased striatal release of dopamine following amphetamine administration. In addition to dopamine abnormalities, theories of schizophrenia indicate other neurotransmitters which may be aberrantly affected. Abi-Dargham et al. [23] have reported that when healthy individuals take uncompetitive antagonists for the NMDA (NmethylDasparate) receptor (such as PCP (phencyclidine) or ketamine) they develop transient positive and negative psychotic symptoms and cognitive impairments that resemble those of schizophrenia. This is significant because NMDA receptor blockade on GABAergic interneurons can lead to a disinhibition of glutamatergic projection neurons and similar mechanisms could occur in schizophrenia, through dysfunction of NMDA receptors or the GABAergic interneurons upon which they are expressed. Elevated glutatame as a potential pathophysiological mechanism in schizophrenics is useful as it has a potential to reduce the grey matter volume that is seen in the MRI studies of schizophrenics.

Numerous PET studies were performed to decide whether left hemispheric dysfunction is also associated with schizophrenia. And some have found that indeed, at a resting state, patients with schizophrenia have a proliferation and increased metabolism in the left hemispheric cerebral cortex in comparison to the right [24]. Therefore, these studies intend that the gravity of the symptoms discovered in schizophrenic patients is associated with the amount of hyperactivation of the left hemisphere, and specifically not with the amount of hypofrontality. Sheppard et al. reports a finding which agrees with this, in that the augmentation in blood flow to the left hemisphere was found using 15O H$_2$O PET. In further studies, Early et al. [25] found increased cerebral blood flow in the left globus pallidus in patients with schizophrenics. In supporting the concept of disrupted brain lateralization in schizophrenics, Laasko et al. conducted a study which illustrated that patients do lack asymmetry in caudate dopamine transporter binding compared to controls [26]. The utilization of PET studies in schizophrenics is not exclusive to metabolic and blood flow studies. PET imaging of the dopmaninergic system in patients has been vital since the dopaminergic system which has been demonstrated to be involved in the pathophysiology of this disorder is also the site of action for neuroleptic drugs. These drugs are key therapeautic modality in these patients. Although primary studies have stated no changes in dopamine receptor density or affinity in the basal striatum between schizophrenics and controls [25,26], additional studies have discovered an increased density of dopamine receptors in both neuroleptic naïve and previously treated, but currently drug free schizophrenic patients [27]. Kessler et al. [28] report that when using subjects demonstrated an increase in dopamine D2 receptor levels in the substantia nigra and an important association concerning symptoms of confused thought processes and nonparanoid delusions with binding in the right temporal cortex [29,30]. Howes and Kapur [31] report a study that elevated striatal dopamine uptake is found in patients with prodromal symptoms of schizophrenia as well as those with frank schizophrenia. This study suggests that striatal dopamine overactivity actually can predate the onset of schizophrenia [29]. Hypofrontality is the most common illustration on a SPECT image of the brain suffering from schizophrenia. Further detected abnormalities detected by SPECT under these diseased conditions include, but are not limited to: perfusional changes in the basal ganglia, hypoperfusion in the temporal lobe, usually located on the left side and mostly hypothesized to be

associated with ipsilateral frontal lobe hypoperfusion [30]. At the time of visual or auditory hallucinations, patients injected with perfusion agents demonstrate hyperperfusion of the primary visual or auditory cortex [31]. Certain studies have demonstrated that striatal D2 or D3 receptor blockade by neuroleptic drugs was found to simulate negative symptoms [32]. In variance to these results, other investigators [33] have suggested that the increase of the negative symptoms might be associated to increased availability of D2 receptors. It is hypothesized that this is because of the lessening in endogenous dopamine. Studies done before and after challenge with intravenous amphetamine showed that D2 receptor density was regular in the baseline study but decreased after an amphetamine challenge, and this finding was associated with positive symptoms [34]. Quantitative analysis of these images might be useful in assisting the prognosis and outcome of patients. For example, the ratio of the basal ganglia to the frontal cortex decreased with therapy in good responders and increased in poor responders. Although brain imaging studies utilizing both structural and functional techniques have discovered varied brain aberrations in schizophrenia, no private brain area has been evidently or dependably recognized as the precise region of this disorder. It is hypothesized that disturbances of interconnections between brain structures in schizophrenia, as opposed to exclusive anatomical brain regions, will provide a better and more thorough explanation as to the source of this disease [35]. Novel imaging techniques can be utilized to view these neurocircuits in the brain and how altering their connections may manifest in diseased type patients. For example, diffusion anisotropy imaging may be used to study the commisural white matter pathways. The method is sensitive to disruptions of commisural bundles or tracts. It can be used to study regional axonal connectivity, myelin packing and fiber orientation. In a study measuring fractional anisotropy and the mean diffusion coefficient in the cerebral volume of 20 schizophrenic and 24 healthy subjects, men and women, using diffusion tensor imaging, Agartz et al. [36] reported that the mean diffusion was increased in the total white and grey matter volume of the schizophrenic patients compared with the healthy subjects [37]. This report also showed that fractional anisotropy was reduced in the splenium of the corpus callosum and adjacent regions in the occipital white matter bilaterally. This finding supports the view that global and regional white matter abnormalities occur in chronic schizophrenia. Lim et al., found that schizophrenic patients exhibited widespread lower FA in the white matter, extending from frontal to occipital regions, despite an absence of a white matter volume deficit compared with age matched controls [38].

Autism

Social cognition inability is a trademark indicator of autism. This severe developing disorder can also manifest itself by deficits in interaction and limited patterns of behavior. Adolphs et al. [39] accounts that the facility to participate in social relations involves various cognitive and perceptual capabilities and is assumed to need the integrated activity of numerous consistent brain regions [39]. An important qualitative cognition skill for social interaction is the capability to attribute mental conditions to self and others. This is generally called "Theory of Mind" [39]. Several studies utilizing functional MRI techniques have demonstrated that theory of mind tasks involve activation of the amygdala, the medial prefrontal cortex, cingulate cortex, the extrastriate cortex, and the temporoparietal junction [40]. Baron-Cohen et al. that compared to control subjects, autistic patients performing theory of mind tasks show irregular activation in the prefrontal cortex, anterior cingulate cortex, the temporoparietal junction, and the temporal poles adjacent to the

amygdale. Further, they fail to activate the amygadlya normally when processing emotional facial and eye expressions [41]. Therefore, researchers have theorized that the abnormal relation amid such regions involving a social cognition network can contribute to the social shortfalls perceived in autism [42]. To study structural integrity of white matter tracts in individuals with autism, Barnea-Goraly et al. [40], used DTI in 16 patients and presented that white matter structure is disturbed in individuals with autism. Particularly, they displayed less FA values nearby the brain regions that have been concerned with in social cognition. Further, this study illustrated areas of aberrant white matter found between the grey matter regions which are activated in theory of mind activities, such as the ventromedial prefrontal cortex, anterior cingulate, temporoparietal junction, superior temporal sulcus, and the amygdale [39]. In order to detect the metabolic abnormalities which may be present in the brains of autistic patients, Grady and Keightley [43] report a study in which FDGPET was used in patients with autism and illustrated greater metabolism in the right caudate nucleus, as well as lower glucose metabolism in the ventral caudate, putamen and thalamus [42]. These outcomes imply that there is a deficiency in the anterior cingulate–ventral striatum–anterior thalamic pathway in autistic patients with autism spectrum disorders. A PET study with 15OH2O demonstrated decreased CBF in the superior temporal lobe in autistic patients that also correlated with the severity of disease [43]. SSRI treatment is common in autistic patients. An analysis on the results of SSRI usage in patients with autism displayed that metabolic rates were considerably greater in the right anterior cingulate gyrus subsequent fluoxetine treatment [44]. Further, patients demonstrating greater metabolic rates in the medial frontal region and anterior cingulate preceding the treatment were more expected to respond to fluoxetine.

Although the pathophysiology of autism remains to be fully elucidated, it is thought to be associated to the abnormalities in the serotoninergic and dopaminergic systems. Nakamura et al. [45] report that serotonin transporter binding is significantly lower in the brain of autistic individuals with controls [46]. This study also suggested that the decline in the cingulate cortex was associated with impairment of social cognition. Furthermore, there was found to be a suggestive relationship between recurring or obsessive behaviors and the decrease of serotonin transporter binding in the thalamus.

Alzheimer's Disease

Functional imaging methods, such as PET, can help in diagnosing AD patients. Further, structural imaging methods are limited in the capability of portraying the mechanisms underlying the disorder. However, the future of functional imaging of the brain might include novel methods which will allow us to elucidate the neuronal mechanisms causing AD. A crucial role in the utilization of PET imaging in AD is to aid in the accurate diagnosis of AD as early as possible in the course of the onset and progression of the disease. The Working Group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association defined the criteria for diagnosing AD as such: evidence of progressive, chronic cognitive deficits in middle aged and elderly patients with no identifiable cause. Patients with AD demonstrate different magnitudes of hypometabolism which correlate with the degree of severity of dementia symptoms [46]. Patients with early mild AD manifest with minimal decreases in the parietal lobes. Patients moderately affected by AD display significantly decreased metabolism in the left midfrontal lobes, bilateral parietal lobes, and the superior temporal regions. Severe AD patients present with these regions being significantly augmented in

their hypometabolic state [47]. An additional role which PET imaging may play in AD is its ability to measure changes in neurotransmitter systems that might be affected by the disease. Shinotoh et al. [48] showed a significant decreases in acetylcholinesterase activity in the neocortex, hippocampus, and amygdala of all patients with AD, suggesting a loss of cholinergic innervation in the basal forebrain. The temporal and parietal cortices were the most affected, although reductions were relatively uniform in the cerebral neocortex. PET can also play an important role in the evaluation of varying therapeautic interventions for the disease [49].

The development of different neuropharmacoological interventions for AD provides an important area for PET imaging. Patients treated with donepezil were found to have relatively similar cerebral metabolism at 24 weeks compared with the placebo group that was observed to have a 10% decline [48]. The pharmacologic mechanism by which these pharmaceutical therapies work by can also be elucidated by PET imaging. Kuhl et al. [50] report that patients struck with Alzheimer's disease show that Donepezil hydrochloride offers an almost thorough inhibition of cerebral cortical acetylcholinesterase activity [49]. Yet, this study confirmed an average of only 27% inhibition of acetylcholinesterase activity. Further current studies have said that the beneficial reaction to drugs, like donepezil and rivastigmine, is related with acetylcholinesterase activity mainly in the frontal lobes.

Alterations in anisoptropy have been hypothesized as been associated with the progression of AD in patients already diagnosed with an early stage of the disease. Through measuring diffusivity in the corpus callosum abnormalities in diffusion anisotropy have been illustrated in regions where axons are usually oriented transversely. Studies have demonstrated that anisotropy was lower in the splenium in patients with AD when compared with matched controls. This might be due to axonal loss or demyelineation in these specific areas [50]. Rose et al. [51] report the use of DTI in AD by detecting the integrity of axonal tracts in areas associated with cognitive function and tracts associated with motor function. Although the motor tracts were well preserved, axonal degeneration in the cognitive tracts was detected. Varying forms of cognitive impairments have been researched with DTI mechanisms, such as persons with reading difficulties [52] and the detection of degenerate fiber tracts in the disconnection syndrome [53]. Patients that are found to have a struggle in reading have shown decreased diffusion anisotropy in temporoparietal white matter. Additionally, white matter diffusion anisotropy in the left temporoparietal region had significant correlation with reading scores of impaired adults. These studies illustrate that white matter tracts which are abnormally affected may be responsible for cognitive impairments.

Usually brain SPECT of AD patients demonstrate bilateral hypoperfusion of the posterior and bilateral temporal lobes. The defects are often symmetric although don't essentially have the same degree of severity. Some authors consider hypoperfusion of the posterior association cortices as specific evidence for AD diagnosis [54]. According to Dewan and Gupta [55], the sensitivity and specificity of brain SPECT for the diagnosis of AD are 86% and 96%, respectively, with a diagnostic confidence of 98% [56]. Labeling of the amyloid and plaques for a more specific diagnosis of AD has been attempted. With monoclonal antibody for Ab protein 128 labeled with 99mTc [55] uptake of the tracer in AD patients could not be shown with brain SPECT. More recently, rhenium complexes, analogs of the potential imaging agent 99mTc, were shown to bind to amyloid fibrils in vitro and to stain amyloid plaques and vascular amyloid in postmortem brain sections of AD patients [57].

Conclusion

The clinical method in neurology is essential and irreplaceable in the approach to various diseases of both the central and peripheral nervous system. However in recent years modern radiological techniques and nuclear medicine modalities have become an essential complement to better define and characterize both the topographic diagnosis and sometimes the etiological causes of psychiatric illness. Radiological instrumentation has been widely used in the study of various central nervous system (CNS) disorders and has advanced our abilities to both treat and diagnose with accuracy various neurological disorders [58].

Neuroimaging technologies will continue to play a critical role in both clinical and research applications with regard to CNS disorders. These imaging methodologies are beneficial in the preliminary diagnosis of patients showing CNS symptoms and might assist clinicians decide the most beneficial way of therapy. Imaging studies likewise are favorable for learning the response to therapy. From the standpoint of research, the numerous neurotransmitter and other molecular tracers now obtainable or in process of development will offer significant knowledge concerning the pathophysiological processes in the brain. The novel introduction of these molecular tracers into the clinic will further augment the necessary utilization of brain imaging modalities in order to properly evaluate and manage different CNS disorders.

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