The usefulness of PET and MRI in depression research

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The present narrative review paper explores the differences between magnetic resonance imaging (MRI) and positron emission tomography (PET) based on their applications to research depression. Multiple papers are used to illustrate how PET and MRI scans have previously been used by other researchers in the process of diagnosing depression and treating it. Both scans provide a wealth of information but are useful for very different reasons. While MRI scans were better for analyzing structural differences between the healthy control and the depressed subject, PET scans were better for analysing cellular changes in the brain. The advantages and disadvantages of PET and MRI are explained throughout the paper. This analysis aimsto determine which one should be used to further depression research and ultimately improve diagnosis and treatment. Improving the way doctors diagnose and treat depression is vital for the well-being of the patient. This is because the diagnosis of depression is quite difficult and often leads to patients being diagnosed with the wrong disorder. As a result treatment methods and therapies are not as effective and could even lead to the patient's symptoms getting worse. Limitations of, and future directions for, this analysis is also discussed.

Keywords: Depression, Magnetic resonance imaging (MRI), Postiron emission tomography (PET), Psychiatry, Clinical neuroscience

Introduction

Depression has been around for thousands of years, with the first case of depression appearing in the second century B.C.[1] Even since then, there has always been a stigma around the disorder and how to treat it. Still to this day, diagnosing depression is a challenge that doctors face regularly. The most common method has been clinical interviews, essentially verbal conversations with patients to assess their situation and determine if they meet diagnostic thresholds. This is a long process and is far from perfect. Even in thorough assessments, receiving a misdiagnosis is not uncommon. More than half of the patients diagnosed with major depressive disorder are not diagnosed correctly, with a 54.7%[2] misdiagnosis rate. This can cause patients to recieve incorrect treatment for prolonged periods of time, which may worsen their symptoms.

What if there was a better way? Doctors have tried many methods to improve their diagnostic accuracy. Brain scans present a potential solution to this issue of depression misdiagnosis. Research in clinical neuroscience has tried to use brain scanning to identify brain structures and brain processes that are associated with specific diagnoses. Inspecting the brain at a molecular level may reveal important information and clues that might provide more objective evidence in the diagnostic process. Particular brain scanning modalities, like Positron Emission Tomography (PET), which can analyze the brain on the molecular level, and Magnetic Resonance Imaging (MRI), which can show the brain's structure and function, are popular in depression research.[3,4] These methods are useful for different reasons and have advantages and disadvantages. Advancing these modalities could help maximize the advantages and cut down on the disadvantages. Even though many papers discuss the utilization of scanning modalities in depression diagnosis, very few directly compare two modalities against each other.This paper offers a brief background on depression, then reviews these technologies and their uses in depression research to help further future discovery.

Results

Depression

Depression is the most common mental health disorder in the United States, affecting 10% of the population.[5] This percentage has only increased in recent years and is not unlikely to decrease anytime soon. Depression affects all age demographics, from kids to adults. Depression is characterized by feelings of sadness, emptiness, and loss of interest in most activities, as well as a number of other physical symptoms, such as weight fluctuations and sleep disturbance.[6] There are different levels of severity in depressive disorders depending on the number of symptoms and degree of impairment caused by those symptoms.

There are many theories regarding why depression may

arise. For example, in many patients that experience depression, insufficient dopamine transmission in the brain causes disruption to pleasure and reward circuits, thereby negatively impacting a person's mood.[5] Like many mental health conditions, it is hard for doctors to pinpoint whether a patient should be diagnosed with a depressive disorder. This is because many disorders share similar symptoms with depression, such as helplessness, irritability, and difficulty concentrating, which are also found in patients with anxiety or attention-deficit/hyperactivity disorder.[6]

In addition to complex diagnosis, the treatment of depression is notoriously challenging. The treatment for depression usually combines psychotherapy and antidepressant medications, the latter of which is more common and accessible.[7] Just because these treatments are popular does not mean they are understood. For example, a standard class of antidepressant medications is selective serotonin reuptake inhibitors (SSRIs). SSRIs work by raising serotonin levels in the brain, which is thought to reduce depressive symptoms.[8] However, other recent research has debated the link between serotonin and depression, with studies suggesting the correlation should be regared with caution.[9] This demonstrates that there are lots of misconceptions about understanding and dealing with depression. Furthermore, it reinforces the need for advanced biological methods, including neuroimaging techniques like MRI and PET, to improve our knowledge of how depression occurs and how to identify and treat it correctly.

Overview of MRI

MRI is an imaging technique that uses magnetic fields and radio waves to take pictures of the body's internal structures (including the brain).[3] The strength of the magnets greatly affects image quality. There are three types of MRI machines: open, closed, and sitting/standing machines. Closed MRI machines have the strongest magnets, which is why they can produce higher-quality pictures compared to other MRI machines and are commonly used in research and medical settings.[3] MRI is usually painless and does not require much preparation from the patient prior to scanning. An MRI can take more than 90 minutes or as little as 15 minutes. Structural MRI allows doctors and researchers to analyze tissues in the brain, and functional MRI permits examination of brain activity via cerebral blood flow.[10] Usually, brain MRI is used in medical contexts to help assess traumatic brain damage or look for types of cancers. In recent years, MRI research has involved scanning the brain to study depression and how it affects brain structure and function.[3]

Advantages Of MRI

MRI is considered one of the safer brain scans a patient can choose even though there are some possible risks.[11] This is because an MRIrarely requires chemical injections.[12] This means patients will not have to worry about possible side effects, such as diarrhea, nausea, or allergic reactions.[13] MRI scans also do not transmit large amounts of radiation, unlike other scanning modalities. This is an important factor for patients to consider if the doctor plans on taking multiple scans. MRI can be used to observe still photos of the brain, which allows doctors to see through bone and capture specific tissues of interest, like white matter tracts. An MRI is able to do this through because the magnet and radiofrequency cause hydrogen atoms to move within the patient's body. The movement is then captured on a computer and analyzed by doctors.[14] MRI can also model brain activity over time, either while the brain is at rest or engaged in some cognitive or emotional task.[15,16] The ability to see deep into the body can help doctors to diagnose many health conditions, including but not subject to, heart diseases, tumours, and cancers. Furthermore, MRI utilizes a multiplanar imaging technique, meaning the doctor can take images of multiple planes within the human brain such as the sagittal, axial, and coronal planes. Because of this feature, MRI scans may be able to provide a more extensive analysis of the brain because the doctor will be able to evaluate the brain as a whole.[17]

Disadvantages of MRI

The large magnets used in MRI might be problematic for some, for example, people with pacemakers or metal devices inside of them, such as a metal joint pin or replacement.[18] If someone with implanted or embedded metal attempted to undergo an MRI, the magnetic attraction could rip the metal out of the patient, creating a potentially lethal situation. MRI is also extremely sensitive to motion. Even slight movements within an MRI machine can drastically change the results, and this is particularly true for head motion in neuroimaging studies. Research has shown that motion can cause similar data comparisons to yield different effect sizes and implicate different neuroanatomical substrates.[19] In other words, motion in MRI can lead researchers to make false conclusions about how the brain handles emotions and cognitive abilities differently in depressive disorders.

MRI also produces the most false results relative to other scans and can be very challenging for medical professionals to interpret correctly. The scans can be hard to interpret because of their low resolution and could ultimately lead to doctors being unable to decipher what a scan is showing them.[20] In one study, about 43% of the MRI scans produced incorrect results.[21] Another study estimated that even if the scan is performed correctly and the equipment is not faulty, there is still a 70% chance that the patient will not receive a valid report,[22] ultimately leading to a misdiagnosis. Receiving a false negative during diagnostic scanning can cause consider-

able setbacks for patients. Without an accurate diagnosis, a patient can not receive the treatment they need. Without appropriate treatment, their condition may worsen and become a bigger problem than before.

Applications of MRI in Depression Research

In the past few decades, it has become apparent that MRI scans could help expand our understanding of the causes and mechanisms of depression in the brain. Despite hundreds and thousands of MRI research papers being published about depression, with many studies attempting to pinpoint specific areas of the brain that are affected when a patient has depression, the answer remains unclear.

Using MRI, some researchers have found that the structures comprising key neuroanatomic circuits seem to differ in depressed patients. For example, the limbic – cortical – striatal – pallidal – thalamic (LCSPT) tract[23] is a major neurocircuit involving numerous reciprocal connections, including the prefrontal cortex, amygdala, and hippocampus.[24] These regions are most often associated with decision-making,[25] the handling of fear and emotions,[26] and memory[27], respectively. Patients with depression demonstrated significant volume loss, including both the shrinkage of neuronal and glial cells and reduction in cell counts. These cells are the foundation of the central nervous system, carrying out and supporting all of the system's lower- and higher-order functions. In particular, glial cells produce nutrients such as glucose, which provides fuel to neurons and allows them to communicate and coordinate, which is necessary to regulate emotions and physiological responses.[28] MRI can be used to model and quantify an individual's glial cells by examining their white matter tracts, which could allow for a deeper analysis of the interconnections among parts of the brain that affect how the patient experiences emotions and contributes to depression.

Researchers in 2013 also recognised that self-reporting measures and supervised classification modalities of major depressive disorder (MDD) are ineffective due to reasons previously stated, such as doctors misinterpreting a patient's symptoms or because of patient bias.[29] These researchers specifically wanted to test the ability of MRI scans to diagnose MDD via an unsupervised method. The unsupervised approach generally entails that a machine performs the analytical and classification tasks instead of a qualified individual.[30] They diagnosed and analysed their data from the MRI using maximum margin clustering (MMC) algorithms. They used this methodology while studying areas of interest, such as the sub-genual anterior cingulate cortex (sACC) and the pregenual anterior cingulate cortex (pACC). These areas were then examined by the MRI and MMC after healthy controls and clinically diagnosed depressed patients were exposed to emotional and cognitive stimuli. The MMC algorithm used on the sACC regions captured by the MRI scans produced the most accurate results, with clustering consistencies being 92.5%.[29] A similar study that also involved the examination of the sACC region was done a couple of years earlier in 2011. These researchers used MRI scans to see if the sACC had experienced a volume reduction. This volume reduction is a common factor in patients diagnosed with MDD. The results of this study were 2.5% less accurate than the 2013 study, with a 90% accuracy in diagnosis.[31]

Another study released around the same time in 2010 studied fourteen different brain regions previously known to be affected by depression. Some of these regions were the right and left middle temporal gyrus, right and left cingulate gyrus, right and left superior temporal gyrus, right thalamus, right and left inferior frontal gyrus, right parahippocampal gyrus, and the right and left middle frontal gyrus. Just like the previous study, patients were exposed to an emotional stimulus. After the stimulus was presented, the MRI scans were examined using statistical perimetric mapping (SPM2) software. The researchers were able to conclude that their experiment was feasible and allowed them to identify depression and see how the disorder progresses over time within the patient. Their approach provided a clearer and more accurate analysis of their patient, which could aid in treatment plans and recovery.[32]

Overview of PET

PET is a functional neuroimaging technique that uses radiochemicals to map out an organ or tissue's metabolic properties.[4] PET scans can either be two-dimensional or three-dimensional.[33] PET allows doctors to observe the distribution of space within the brain and the movements of radionuclide chemicals that are injected into the patient prior to the scan. These chemicals, or tracers, can be customized for specific purposes so that doctors can analyze specific regions of the brain. This customization is possible because the tracers mimic neurotransmitters, and can thus show how enzymes travel inside the brain.[33]

In neuroimaging, the radionuclide includes glucose, which flows through the blood and into the brain. The radionuclide is broken down to access glucose for metabolism, which causes the radioatom to be released.[4] Once the glucose is metabolized, it releases energy, which can then be used to perform important life functions, such as regulating emotions and cognition. PET scans can detect this energy creation by detecting the release of the radioatoms. Active neurons will metabolize more glucose and will appear as red regions on the scan, called hot spots. The more inactive neurons will not metabolize as much glucose and will appear as blue regions. The task given to the patient, as well as any existing differences in their brain's metabolic functions, will affect which areas of the brain become hot spots and which areas do not.[33] PET

scans are commonly used by medical professionals to check for heart disease and brain disorders.

Advantages of PET

PET scans are very sensitive because of the radiochemicals injected into the patient before they are scanned. The injection of these chemicals is what differentiates PET from other scanning modalities. They allow doctors to observe how the brain works, down to the interactions of cells, with considerable accuracy. Because PET scans can work at the cellular level, they can also be used to analyse neurotransmission in the brain.[34] In terms of cancer, PET scans are able to differentiate between benign and malignant tumours, which is an important step in cancer diagnosis.[35] Not only can they differentiate between types of tumours, but they can reveal what stage the cancer is at by showing how far the tumour(s) have spread across the area of interest. Since PET scans assess the functionality of different tissues and organs (such as the brain) they are good candidates for diagnosing Parkinson's or Alzheimer's. For patients with Alzheimer's disease, doctors can see and evaluate the accumulation of unusual amyloid protein in the brain which is a major indicator of this neurodegenerative disease.[36] As for Parkinson's, PET scans can do in vivo estimations of glucose metabolism and see the binding of different neuroreceptors in the brain.[37] A patient's response to a medication can also be shown on PET scans. This can help doctors change treatment plans and decide what to prescribe to their patients. These changes can help increase the treatment's effectiveness so the doctor can adequately combat or eliminate the problem.

Disadvantages of PET

While PET scans are quite detailed, they are also considered a higher-risk neuroimaging technique. One of the main concerns with PET is the substantial amount of radiation that the patient receives. These scans emit approximately 950% more radiation than a standard X-ray.[38] This radiation level may cause cancer or other severe health issues.[39] This may lead to patients selecting a different scanning modality, such as an MRI or computed tomography (CT) scan.

An MRI or CT scan may be better for cancer patients who want to see the precise location of a tumour. While PET scans may help in other areas of cancer treatment and diagnosis, these scans are not suited to analyse anatomical changes. This means that a combination of scans could be used in this situation such as a PET/CT. This will give the doctor the information they need to properly analyse and treat their patient.[40]

PET scans are also very sensitive and can be heavily impacted by small factors, such as consuming food prior to the exam. This disrupts the results because the food can increase blood sugar levels in patients. This means the machine's ability to accurately examine glucose metabolism could be flawed.[41] PET scans are also very expensive. On average, the price of ranges from $3,000 to $6,000.[34] This high price range makes PET scans less accessible, especially for people without insurance.

Applications of PET in Depression Research

PET has become a major focus in depression diagnosis and research. In a study conducted by Small and colleagues,[42], retired NFL players were examined with PET to see if there was any correlation between their brain injuries and the depression they were suffering from. The researchers created their own radiotracer to measure metabolic function of brain regions that are associated with chronic brain injuries. They were able to find that the binding levels of the tracer was higher in the amygdala, thalamus, and the cerebral white matter in NFL players who had more concussions. These high levels of binding produced by the tracer impacted their depression scores.[42] This information suggests these sites play a role in depression, given that their damage was associated with symptoms.

Another study done by researchers at the University of California, Los Angeles also utilized their own radiotracer-FDNNP. This molecule was used because of its tendency to bind with amyloid plaques and neurofibrillary tangles. It is important to note that both depression and anxiety were tested in this experiment. They were able to find that the lateral temporal region of the brain was affected in the depression subjects while the posterior cingulate was affected by the anxiety subjects. Depression and anxiety are often very similar to diagnosis due to their shared symptoms. This makes it difficult for doctors to make an accurate assessment of their patients. The study discussed could help solve this problem by allowing doctors to have an easier and clearer way to interpret both of these disorders. It was also noted that the researchers found that the biomarkers and tau deposition in the brain fluctuated depending on the severity of the patient's cognitive impairment.[43]

PET has also revealed that depressed patients show abnormalities in their prefrontal and cingulate cortices.[44] These areas of the patient's brain showed an increase in activity when compared to the control group of non-depressed participants. There was also a lot of connectivity in the brain where the subgenual cingulate, the thalamus, the orbitofrontal cortex, and the precuneus were. These high levels of activity in these regions only happened in depressed patients, not in healthy patients,[44] suggesting it may be a specific mechanism related to depressed mood.

Other brain regions were studied later on in 2011. These brain regions included the right anterior cingulate, middle frontal gyrus, and inferior frontal gyrus. The researchers particularly noticed that their depressed subjects experienced de-

creased blood flow in these regions. However, the opposite was true in the bilateral posterior cingulate (Brodmann areas 23, 29, and 30), the right caudate and the left parahippocampal gyrus. The severity of the subject's depression further affected blood flow, meaning that as the severity of depression increased, blood flow decreased. However, this inverse relationship was only present in the left middle and inferior frontal gyri.[45]

While some PET studies focus on the diagnosis aspect of depression, others are more interested in the treatment process. Researchers in Austria decided to test the efficacy of electroconvulsive therapy (ECT) on clinically depressed patients. All of the subjects in this study had not responded to previous depression treatments and did not experience any changes in their symptoms. ECT was used to see its effect on the serotonin-1A receptor (5-HT1A). This serotonin receptor is crucial when it comes to formulating anti-depressant medications. The researchers found that the receptor binding of the 5-HT1A significantly decreased in the cortical and subcortical regions. The subcortical regions included the hippocampus and amygdala, mainly known to regulate emotions and make decisions. However, these brain regions only experienced these decreases after receiving ECT. While this treatment method was previously not recognized for its ability to treat depression, the PET scans allowed the researchers to see just how effective it is.[46]

Discussion

Differences ofMRI and PET

While MRI and PET have proven useful in depression research, with only a microscopic slice of their literatures reviewed here, few studies have directly compared these methodologies in terms of their utility. In 2015, researchers[47] compared PET and MRI scans and found that PET was best suited for analyzing the concentration of neurotransmitters within the brain. On the other hand, MRI could detect changes in the white and gray matter in the brain, which is something PET scans can not do. The authors did not reach a conclusion of which scan was better,[47] once again leaving doctors to once again ask: should I be using PET or MRI scans to detect depression in my patients?

MRI scans can help doctors understand how the structures in a depressed patient's brain differ from the same structures in a healthy patient's brain. These scans have also discovered the importance of glial cell function and how that impacts depression.[48] However, MRI scans present many problems because of how temperamental they can be, requiring extreme precision. Even if doctors could overcome these obstacles, they would still have to correctly interpret the scan. This can be extremely challenging because only 30% of MRI scans are examined without error.[21]

PET scans are more customizable, however, this also means that they transmit more radiation compared to other scanning modalities. However, the benefits far outweigh the risks. These scans have not only revealed structural abnormalities,[43] but also cellular abnormalities.[48] PET has also shown how medication affects the brain of a depressed patient.[49] This allows doctors to test different formulas and prototypes to see which ones are most effective and why. Lastly, PET has also demonstrated specificity in finding changes in the brain that are unique to depression, independent of medication-related effects.[43]

Limitations

One general limitation of research in clinical neuroscience is its translatability. Despite the wealth of research using PET and MRI to identify disorder markers, clinical neuroimaging is not advanced enough for doctors to make psychiatric diagnoses solely based on brain scans. Scans afford a deeper understanding of how the patient's brain looks and works under certain conditions, however, it is unlikely that scans will ever be the only data a doctor uses to make a psychiatric diagnosis. Even if these scans could give an exact diagnosis, they would come with a high price tag, with no guarantee that insurance would cover the cost.

In terms of the main debate of this paper, a major limitation is that there is likely not a single answer. MRI and PET scans are usually compared depending on which scan is more effective or useful in a specific scenario or experiment. Any final conclusion about which one is better would be biased by their performance in certain situations, not in general. This makes it difficult for other scientists or researchers to apply generalistic rules to decide which one to use. Researchers must decide which modality is best suited for their research aims and hypotheses.

And finally, this paper is limited by its scope. A Google Scholar search of "Depression MRI" returns over 1.5 million papers, and "Depression PET" returns roughly 800,000 more. This paper could not possibly review all of the research that might weigh into the debate about their usefulness in depression diagnosis and treatment. Though a lot of research could not be discussed, the information included aimed to take a fair and thorough approach.

Future Directions

In terms of clinical practice, this research could aid in diagnosis and treatment planning in psychiatry. Brain scans can be used by psychiatrists or psychologists in the planning process to determine the most effective treatment for depression, and even track its efficacy as it is administered. This precision is the ultimate goal of the personalized medicine movement. If

more resources are directed towards these scans, the integration of brain scanning into psychology and psychiatry visits may not be so far in the future

Conclusion

Ultimately, both PET and MRI scans could allow doctors to differentiate between psychological disorders in clinical practice, a central challenge in the field. Solving this problem could lead to fewer misdiagnosed patients, who can receive accurate treatment options. Investing more time and money into developing scanningtechnology could allow these modalities to become an effective way to diagnose depression in future patients. There is still much work to be done in terms of technological advancements, but brain scans show very promising results.

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