Forty years of structural brain imaging in mental disorders: is it clinically useful or not?

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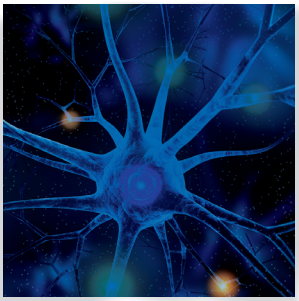

Structural brain imaging was introduced into routine clinical practice more than 40 years ago with the hope that it would support the diagnosis and treatment of mental disorders. It is now widely used to exclude organic brain disease (eg, brain tumors, cardiovascular, and inflammatory processes) in mental disorders. However, questions have been raised about whether structural brain imaging is still needed today and whether it could also be clinically useful to apply new biostatistical methods, such as machine learning. Therefore, the current paper not only reviews structural findings in Alzheimer disease, depression, bipolar disorder, and schizophrenia but also discusses the role of structural imaging in supporting diagnostic, prognostic, and therapeutic processes in mental disorders. Thus, it attempts to answer the questions whether, after four decades of use, structural brain imaging is clinically useful in mental disorders or whether it will become so in the future.

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Introduction

Brain imaging was more broadly introduced into neuroscience and the field of mental disorders in 1976, when ventricular enlargement was described in patients with multi-episode schizophrenia compared with controls.[1] Subsequently, a wide range of structural and functional brain imaging studies were performed that provided a plethora of findings in different brain disorders. To provide a manageable review of this data, this paper focuses on structural imaging in patients with Alzheimer disease, bipolar disorder, major depressive disorder (MDD), and schizophrenia; it thereby goes beyond the use of these data to exclude underlying brain diseases such as tumors and vascular and inflammatory conditions and discusses other applications.

The first successes in the attempts to identify structural imaging markers to support diagnostic, prognostic, and therapeutic processes are likely to be in Alzheimer disease because it is a classical neurodegenerative disorder with an established neuropathological basis. The search for such markers in so-called affective and nonaffective psychoses, namely bipolar disorder, MDD, and

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schizophrenia, is likely to take longer because these disorders lack an established neuropathological basis. It appears that a much greater number of brain imaging studies will be needed in these disorders to identify a common neurobiological basis in each of them.
The first section summarizes the state of the art of structural imaging findings in the above mentioned mental disorders and the second section outlines the future role of structural brain imaging in predicting diagnosis, outcome, and therapy.

State of the art of the clinical usefulness of brain imaging in mental disorders

Alzheimer disease

Alzheimer disease has been known for over one hundred years to be a progressive neurodegenerative disorder with a defined neuropathological basis. Large-scale epidemiological studies have convincingly shown that the disease process starts decades before the clinical manifestation of the disorder. This fact has fuelled many brain imaging studies to identify patients at risk of developing dementia.

Although medial temporal lobe volume loss seen in magnetic resonance imaging (MRI) is not specific for Alzheimer disease, the differential pattern of brain-wide atrophy separates patients with pathologically confirmed Alzheimer disease from healthy controls (sensitivity 97%, specificity 94%)[2,3] and from patients with dementias with other underlying pathological changes, such as frontotemporal lobe degeneration and Lewy body disease (sensitivity 91%, specificity 84%).[4,5]

Stephan et al[6] performed a large population-based cohort study to try to predict dementia in individuals aged older than 65. Brain MRI scans were performed a mean of 4.2 months after the baseline examination with a 1.5 Tesla Magnetom. Interestingly, the study found no significant differences in the discrimination performance of white matter lesion volume, brain volume, hippocampal volume, or all three variables combined. However, the inclusion of hippocampal volume alone or all three MRI variables in a conventional risk model that included cognitive, lifestyle, and genetic predictors, among others, significantly improved reclassification of risk and showed increased benefits in the decision curve analysis (a measure of the value of the prediction model).[6] A combination of functional imaging (positron emission tomography, PET) and structural imaging (MRI) best predicted conversion when PET signals were increased in posterior medial and lateral cortical regions, ^{18}F-fluordesoxyglucose (FDG) PET signals were increased in medial temporal and temporal basal regions and gray matter volume was decreased in medial basal and lateral temporal regions.[3] This finding indicates the benefit of including PET studies in diagnostic assessments. However, a Cochrane review on nine studies on ^{11}C-Pittsburgh compound B PET (^{11}C-PIB-PET, a compound that makes amyloid depositions visible in the living human brain) could not demonstrate the usefulness of this type of PET.[7] The review included 274 participants with any accepted definition of mild cognitive impairment (MCI) at baseline and found that 112 participants subsequently developed Alzheimer disease, equating to a conversion rate of 35%. For every hundred ^{11}C-PIB-PET scans, one person with a negative scan progressed to Alzheimer disease, whereas 28 people with a positive scan actually showed no progression. The authors concluded that "we cannot recommend ^{11}C-BIP-PETs for routine use in clinical practice."[7]

In a more recent systematic review based on 29 papers on amyloid imaging, 23 papers on FDG-PET and 8 papers on both techniques, both amyloid and FDG-PET qualified as suitable biomarkers for the diagnosis of Alzheimer disease.[8] Although the authors concluded that both techniques detect Alzheimer disease with high sensitivity and specificity compared with other neurodegenerative processes and cognitively normal, aged-matched individuals, they recommended further studies with standardized conditions and a lengthier longitudinal follow-up. Furthermore, to establish these two techniques as state-of-the-art biomarkers for clinical practice they recommended studies to validate the link between these imaging techniques and the neuropathological diagnosis, rather than just the clinical diagnosis. The authors noted that biomarkers such as these are urgently needed to identify subgroups of patients with Alzheimer disease in whom disease-modifying drugs can be tested and later used successfully. This approach is based on the assumption that in the near future the underlying pathophysiological mechanisms of such subgroups will be better understood, leading to the development of targeted treatment options.

In summary, hippocampal volume as determined from structural MRI is an established parameter to support the diagnosis of Alzheimer disease and its at-risk

states. FDG-PET and amyloid PET are on their way to qualifying as biomarkers to identify persons at an increased risk to develop Alzheimer disease and thus require specific treatment.

Bipolar disorders

Bipolar disorders, in particular bipolar I disorder, are clinically characterized by manic and depressive phases. The prevailing hypothesis is that dysfunctional catecholaminergic systems and inflammatory processes play a role in the pathophysiology, at least in a subgroup of patients. Furthermore, there is increasing evidence from basic science that glial and microglial processes are involved.[9]

Considering that only about 35% of patients with bipolar I disorder,[10,11] it is interesting that there are only a few consistent brain imaging findings in this disorder. A meta-analysis of individuals with bipolar I disorder (n=321) only found an increase in the volume of the left temporal lobe, right putamen, and right lateral ventricle compared with healthy individuals (n=442).[12] It found no significant differences between bipolar patients and healthy controls in any other brain regions. These findings are supported by a recent MRI analysis by the ENIGMA bipolar working group.[13] Taking the influence of lithium treatment into account, the group found that patients with bipolar disorder treated with lithium had a larger mean total, left and right hippocampal volumes and total, left, and right amygdala volumes than patients not treated with lithium and healthy individuals. Global cerebral volume also differed significantly between the groups in that patients with bipolar disorder not taking lithium had a smaller mean volume than both healthy individuals and patients with bipolar disorder taking lithium. All bipolar patients, regardless of lithium use, had larger total and left temporal lobe volumes than the healthy individuals, although after correction for multiple testing only the findings for the left temporal lobe remained significant. With regard to the current discussion on the influence of antipsychotic treatment on brain structure, it is interesting to note that this study found no difference in any regional brain volume between those patients taking antipsychotic medication and those not taking such medication.[12]

Structural MRI machine-learning paradigms seem to be helpful when attempting to distinguish patients with bipolar I disorder from patients with schizophrenia. One study used the gray matter density images of 66 schizophrenia patients, 66 patients with bipolar I disorder, and 66 healthy individuals to train three support vector machines to separate patients with schizophrenia from both healthy individuals and patients with bipolar disorder and patients with bipolar disorder from healthy individuals.[14] The predictive power of the models was tested by cross-validation and in an independent validation set of 46 patients with schizophrenia, 47 patients with bipolar disorder, and 43 healthy individuals scanned on a 3T MRI scanner. The patients with schizophrenia could be separated from the healthy individuals with an average accuracy of 90% and from the patients with bipolar disorder with an average accuracy of 88%.[14] The model was less accurate for the patients with bipolar disorder and correctly classified 67% of the healthy individuals and only 53% of the patients with bipolar disorder. All in all, these results show that gray matter pathology shows a unique pattern in schizophrenia and bipolar disorder and can thus help to reliably differentiate between these disease groups by using machine-learning paradigms. In another study that assessed structural and resting-state functional MRI data from 21 patients with bipolar disorder, 25 patients with unipolar depression, and 23 healthy controls, a linear support vector machine with a forward-backward search strategy classification of bipolar and unipolar depression achieved an accuracy of 92%.[15]

In summary, patients with bipolar I disorder show a specific pattern of brain abnormalities in structural imaging in the temporal lobe, basal ganglia, and ventricular system. In addition, cortical abnormalities are prominent enough to allow bipolar disorder to be distinguished from schizophrenia with the help of machine learning.

Major depressive disorder

Depressive illness is characterised by phases of significantly depressed mood and lack of drive, lasting at least 2 weeks. Besides these two main symptoms, other symptoms include sleep disturbances, cognitive dysfunction, weight problems, and other features. The most common hypothesis for the pathophysiology of Major Depressive Disorder (MDD) suggests disturbed serotonergic and noradrenergic subsystems caused by a dysbalance of neuroplastic processes related to the stress axis.[16] In short, MDD is a stress-related disorder that is sensitive to acute stressors, especially environmental ones.

Gray matter volume deficits reported in voxel-based morphometry (VBM) studies in MDD have been found in frontotemporal regions, the anterior cingulate cortex, and the occipital gyrus, among others.[17] After antidepressant treatment in this study, patients still had gray matter volume reductions in the dorsal anterior insula, cingulate cortex, and superior frontal gyrus.

In the quest to identify prognostic subgroups of patients with depression, one interesting line of evidence is based on structural brain imaging in late-life depression (LLD) and its treatment-resistant variant. LLD has been associated with global cerebral atrophy, decreased myelin integrity, and lesions in frontostriatal-limbic regions. In particular the association with cerebral lesions in frontostriatal-limbic areas helps to explain the "depression-executive dysfunction syndrome" observed in LLD and supports cerebrovascular burden as a pathogenic mechanism.[18] In a similar line, in LLD regional atrophy is associated with treatment outcome; in particular, hippocampal volume reduction is found in patients showing an unfavorable outcome. An increased number of white-matter hyperintensities (WMH load) and diminished white-matter functional anisotropy are also associated with poor therapeutic outcome in LLD. In summary, the vascular burden as defined by regional volume reduction, WMH load, and disturbed white-matter integrity seems to represent the common ground for an increased risk of LLD and an unfavorable treatment outcome in this subgroup of patients. Brain imaging and especially structural methods clearly help to distinguish this prognostic subgroup of depression. Novel treatment options are needed to target this subgroup of "vascular depression" and the "executive dysfunction-depressive syndrome."[18]

By targeting treatment-refractory depression in general, one study was able to use gray matter volume in structural MRI to predict individuals with treatment-resistant depression compared with healthy controls with 85% accuracy. By using an automated feature selection method the authors found that the major brain regions supporting this significant classification were the caudate, insula, habenula, and periventricular gray matter.[19]

Finally, a learning method called alternating decision trees provided the most accurate prediction models for diagnosis of LLD (87% accuracy) and treatment response (89% accuracy).[20] The authors suggested that combining multi-modal imaging with non-imaging measures may help to better predict LLD diagnosis and treatment response.

In summary, imaging can be used as a kind of biomarker in attempts to define the usefulness of structural brain imaging in MDD and in particular non-response in LLD. The subgroup of patients with LLD can be defined on the basis of structural brain imaging because of their common pathophysiology, described as increased vascular load. Identifying the key vascular mechanisms for the development of LLD might pave the way to unravelling the pathophysiology of this subgroup of patients and identifying new treatment approaches.

Schizophrenia

Schizophrenia is a severe mental disorder characterized by illness episodes with positive symptoms, such as delusions and acoustic hallucinations, and/or negative symptoms, such as lack of drive and cognitive disturbances. Because of the success of treatment with dopamine blocking agents, schizophrenia is regarded as a disorder of disturbed dopaminergic transmission. If one looks further downstream in the neurobiological cascade, this group of illnesses can be regarded as a disturbance of the regenerative capacities of the human brain[21] and to a lesser extent, a disturbance of inflammatory processes. For quite some time, however, schizophrenia was regarded as a consequence of a classical degenerative process that resulted in an unfavorable long-term functional outcome in the majority of cases. Thus, the interest in unravelling the neurobiological basis of schizophrenia has a long and distinctive history that is rooted in neuropathology and is accompanied by a plethora of structural brain imaging literature, starting in 1976 with the first computer tomography (CT) study in schizophrenia.[1] Meanwhile, large-scale studies have been performed, such as those by the ENIGMA consortium that assessed 2018 patients with schizophrenia and 2540 healthy controls at 15 centers worldwide and used a meta-analytic approach.[22] Compared with healthy controls, patients with schizophrenia had smaller hippocampus, amygdala, thalamus, nucleus accumbens, and intracranial volumes and larger pallidum and lateral ventricle volumes. The putamen and pallidum volume enlargements were positively associated with illness duration (length of treatment) and hippocampal volume deficits were more severe in those samples that had a higher proportion of unmedicated patients.[22]

Another meta-analysis and critical review of studies involving structural MRI techniques in patients with psychosis selected 80 studies published between 1976 and 2015 and searched for biomarkers for schizophrenia.[23] The authors concluded that, despite having data from structural brain imaging studies on psychosis from over 40 years, they could not identify a diagnostic or prognostic biomarker for clinical use. According to the authors, this lack of clinical usefulness of neuroimaging on psychosis was due to small samples, unclear biomarker definitions, and a lack of replications. In their literature search, the authors did identify one study, however, that meets advanced criteria for biomarker detection. The study used machine-learning methods and neuroanatomical-based biomarkers and was able to differentiate schizophrenia from mood disorders early in the course of the illness.[24] Therefore, the currently unsuccessful search for simple regional or global neuroanatomical measures that are unequivocally associated with psychosis might turn into progress with the help of more advanced analytical methods, such as machine learning. For example, these methods have helped to develop neuroanatomical biomarkers to predict progression from prodromal psychosis to first-episode schizophrenia[25,26] and the response to treatment[27] and to predict symptomatic outcome or functional outcome.[28,29] However, the very promising predictive results, ie, for the short- and long-term outcome in first-episode psychosis,[30] need to be replicated in independent samples. A reliable prediction of 80% or more might not be achieved when the same predictive biomarkers are used in an independent replication sample.

In conclusion, in the past 40 years a substantial number of structural brain imaging studies have been published on schizophrenia. They have helped to identify a pattern of structural abnormalities (in particular in hippocampus, amygdala, thalamus, nucleus accumbens, intracranial, pallidum, and lateral ventricle volumes) that differ from Alzheimer disease and other psychotic illnesses such as MDD and bipolar disorder. However, because no regional or global neuroanatomical measure has been unequivocally associated with psychosis, new analytical methods need to be implemented to progress the field. Machine learning might be one such method that can support the development of biomarkers to aid diagnosis, prognosis, and treatment outcome.[31]

Future directions: biomarkers for prediction

Diagnosis

Since the introduction of structural brain imaging methods into clinical practice, researchers have been promising that these methods will aid diagnosis, outcome, and therapy. In daily clinical practice, structural imaging does help to identify organic disorders such as tumors, infarction, or inflammatory processes that cause or exacerbate the symptomatology in mental disorders. This is certainly helpful because it allows a small subgroup of patients to be identified and treated, eg, by the neurosurgical removal of a tumor, who otherwise may not have been diagnosed correctly; in such cases, a thorough psychiatric and neurological workout may not indicate an underlying organic cause and, consequently, the use of structural imaging might be life-saving. A study in 656 patients with schizophrenia and 722 healthy controls, however, found clinically relevant pathology in only 11.1% of the patients and 11.8% of the controls.[32] None of the neuropathological findings observed in the patients was interpreted as a possible substrate for organic psychosis. This study suggested that MRI scans do not need to be an essential part of routine screening in psychotic patients. This conclusion was accepted by the National Institute of Health and Care Excellence (NICE) and included in the current version of their guidelines on schizophrenia.[33]

Irrespective of the role of structural imaging in clinical routine the question arises whether structural imaging is useful in patients with mental disorders, beyond excluding organic brain disease. In Alzheimer disease, studies have convincingly shown that hippocampal volume reduction, as determined with structural MRI, helps to establish the diagnosis and independently identifies individuals at an increased risk of developing the disease. The hippocampus volumes assessed in structural images can be combined with other parameters from cerebral spinal fluid, neuropsychology, and functional imaging (FDG-PET, amyloid PET) to increase the predictive value. In this way, structural imaging complements the clinical diagnosis of Alzheimer disease with a number of biomarkers that allow a diagnostic certainty of up to 90% in cases later verified by neuropathological examinations.

In psychotic disorders such as MDD, bipolar disorder, and schizophrenia, the search for biomarkers to support the diagnostic process seem to be more difficult than in Alzheimer disease.[23] In MDD, structural imaging helps to define a distinctive subgroup, namely LLD, and more specifically its treatment-resistant variant. Moreover, taking hippocampal volume, the load of white matter intensities, and white matter integrity into account might help to define this relevant subgroup of MDD and thus to establish specific therapeutic possibilities for it.

The application of machine learning as a new analytical approach has allowed structural imaging to be reliably used in the early phases of psychosis to distinguish between patients with schizophrenia and those with MDD.[24] Beyond this, machine learning has allowed "converters" from prodromal to first-episode schizophrenia to be identified with an accuracy of more than 80%.[25,26] This rate was achieved not only at single study centres such as university hospitals in Munich, Germany, and Basel, Switzerland, but also at a network of several centres. Currently, the large PRONIA study (www.pronia.eu) is attempting to replicate these findings on a Europe-wide level. If successful, this study may show that structural imaging can help to identify people with prodromal psychosis who are in need of intensive care and treatment to prevent conversion.

Outcome

In addition to the need for biomarkers to aid diagnosis eg, for Alzheimer disease or psychosis, there is an even greater need for biomarkers to help identify relevant subgroups of patients with regard to their short- and long-term outcome. Much of the success in oncology stems from the development of biomarkers that identify subgroups of patients with a specific pathophysiology who can then be given targeted treatment. Along these lines, a study was able to use clinical data to predict functional outcome at 4 weeks and 1 year in patients with first-episode schizophrenia.[34] Retrospectively, machine learning enabled the identification of patients with a functional outcome above and below a Global Assessment of Functioning (GAF) score of 65.[30] If replicated in a prospective fashion (eg, in OPTiMiSE[28]), this finding would help to identify different prognostic subgroups of schizophrenia and improve pathophysiological understanding, ideally leading to more specific treatment options.

Therapy

Combining real-time functional MRI with neurofeedback can help to improve treatment in psychiatry. Besides functional MRI other metabolic neurofeedback instruments, such as near-infrared spectroscopy, have become potential therapeutic tools.[35-37] MRI neurofeedback has been shown to be effective in schizophrenia,[38] in both emotion regulation[39] and alcohol abuse.[40] In summary, the use of functional imaging to complement structural imaging in the development of "theranostic" biomarkers is a promising area.[37]

Conclusion

The current review examines the clinical usefulness of structural brain imaging in Alzheimer disease, MDD, bipolar disorder, and schizophrenia. Besides identifying underlying organic brain pathologies (eg, brain tumors and vascular or inflammatory processes), structural brain imaging can support diagnostic processes in Alzheimer disease. When used together with machine learning and related analytical methods, structural imaging allows patients with schizophrenia to be distinguished from patients with depression in the early phases of psychotic illness. Besides these diagnostic markers, biomarkers of short- and long-term outcome are needed to establish prognostic subgroups of mental disorders, as has been achieved in oncology, for example. Such biomarkers will help to identify subgroups of patients with a distinct pathophysiology and to develop more specific treatment options. The use of real-time functional MRI in neurofeedback has developed into a very useful "theranostic" biomarker to increase therapeutic success.

As a final point, one must note that despite the frequent use of the term "biomarker" in this paper, the development of clinically useful biomarkers for mental disorders is a tedious process that follows a defined pathway and requires large samples for replication and verification.[41,42]

In conclusion, a number of mostly uncontrolled studies have shown that structural brain imaging is needed to exclude organic brain disorder after the initial clinical diagnosis in Alzheimer disease, depression, bipolar disorder, and schizophrenia. This application is not completely undisputed, however, eg, in schizophrenia. A recent large-scale study comparing patients with

schizophrenia with healthy controls identified no excess of brain pathology in the patient group that would explain the psychotic symptomatology.[14] This finding was taken by NICE as a lack of evidence for including brain imaging methods in the diagnostic process and included as such in its recent schizophrenia guideline.[33] However, in our opinion it is premature to claim that brain imaging methods are not useful and at least one other prospective, well-controlled study is needed to draw such a conclusion.

Beyond this, studies with new biostatistical methods, such as machine learning, have provided evidence that structural imaging allows us to predict the risk for developing the illness, identify prognostic subgroups, and determine the efficacy of treatments in mental disorders, in particular schizophrenia. In schizophrenia, brain imaging parameters predict the risk to develop the illness with a good probability of 0.75 and above,[26] help to distinguish between affective and nonaffective psychoses,[24] and identify groups with a good or fair outcome.[30] Currently, well-controlled prospective studies are trying to replicate these initial findings. If they do so, there will be little doubt that structural brain imaging is clinically useful to exclude organic brain disorder and that it may serve as a biomarker for diagnosis, prognosis and treatment. ❑

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Cuarenta años de imágenes cerebrales estructurales en los trastornos mentales: son clínicamente útiles o no?

Las imágenes estructurales del cerebro se introdujeron en la práctica clínica de rutina hace más de 40 años con la esperanza que respaldarían el diagnóstico y el tratamiento de los trastornos mentales. En la actualidad se emplean ampliamente para excluir enfermedades cerebrales orgánicas (como tumores cerebrales, alteraciones cardiovasculares y procesos inflamatorios) en los trastornos mentales. Sin embargo, hoy en día han surgido dudas de si aún se requieren imágenes cerebrales estructurales y también de si podría ser útil clínicamente la aplicación de nuevos métodos bioestadísticos, como el aprendizaje de máquinas. Por lo tanto, en este artículo no solo se revisan los hallazgos estructurales en la Enfermedad de Alzheimer, la depresión, el trastorno bipolar y la esquizofrenia, sino que también se analiza el papel de las imágenes estructurales en el apoyo a los procesos diagnóstico, pronóstico y terapéutico en los trastornos mentales. Por consiguiente, se intenta responder a las preguntas sobre si, después de cuatro décadas de empleo, las imágenes cerebrales estructurales son clínicamente útiles en los trastornos mentales o si lo serán en el futuro.

L'utilité clinique de 40 ans d'imagerie cérébrale structurelle dans les troubles mentaux en question.

L'imagerie cérébrale structurelle a été introduite en pratique clinique de routine il y a plus de 40 ans avec l'espoir qu'elle aiderait au diagnostic et au traitement des troubles mentaux. Aujourd'hui elle est largement utilisée pour exclure une maladie cérébrale organique (par exemple, des tumeurs cérébrales, des processus cardiovasculaires et inflammatoires) dans les maladies mentales. Cependant, les questions suivantes se posent : l'imagerie cérébrale structurelle est-elle encore utile aujourd'hui ? De nouvelles méthodes biostatistiques comme l'apprentissage automatique ne seraient-elles pas cliniquement utiles ? Par conséquent, cet article ne s'attache pas seulement à analyser les résultats structuraux dans la maladie d'Alzheimer, la dépression, les troubles bipolaires et la schizophrénie mais discute aussi du rôle de l'imagerie structurelle dans l'aide au diagnostic, au pronostic et aux processus thérapeutiques dans les troubles mentaux. Il tente donc de répondre aux questions de l'utilité clinique de l'imagerie cérébrale structurelle dans les troubles mentaux après 40 ans d'utilisation et de son devenir.