Journal of Neuroradiology 000 (2023) 1–6

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Advanced imaging in first episode psychosis: a systematic review

Marjorie Matéos[a,*], Lotfi Hacein-Bey[b], Riyad Hanafi[a,c], Luc Mathys[a], Ali Amad[c,d], Jean-Pierre Pruvo[a,c], Sidney Krystal[a,e,f]

[a] Lille University Hospital Center, Department of Neuroradiology, Lille, France
[b] Neuroradiology, Radiology Department, University of California Davis School of Medicine, Sacramento, CA, 95817, USA
[c] Univ. Lille, Inserm, CHU Lille, U1172 - LilNCog - Lille Neuroscience & Cognition, F-59000 Lille, France
[d] Department of neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[e] Radiology Department, A. de Rothschild Foundation Hospital, Paris, France
[f] Neurospin, CEA, Université Paris-Saclay, Gif-Sur-Yvette, Paris, France

ARTICLE INFO

Article History:
Available online xxx

Keywords:
Psychiatric disorders
First episode psychosis
MRI
Advanced imaging

SUMMARY

First-episode psychosis (FEP) is defined as the first occurrence of delusions, hallucinations, or psychic disorganization of significant magnitude, lasting more than 7 days. Evolution is difficult to predict since the first episode remains isolated in one third of cases, while recurrence occurs in another third, and the last third progresses to a schizo-affective disorder. It has been suggested that the longer psychosis goes unnoticed and untreated, the more severe the probability of relapse and recovery. MRI has become the gold standard for imaging psychiatric disorders, especially first episode psychosis. Besides ruling out some neurological conditions that may have psychiatric manifestations, advanced imaging techniques allow for identifying imaging biomarkers of psychiatric disorders. We performed a systematic review of the literature to determine how advanced imaging in FEP may have high diagnostic specificity and predictive value regarding the evolution of disease.

Introduction

First-episode psychosis (FEP) is defined as the first occurrence of delusions, hallucinations, or psychic disorganization of significant intensity, and duration of more than 7 days.[1]The incidence of FEP varies from 10 to 47 per 100,000 population per year depending on the study.[2,3] Its evolution is variable and difficult to predict. FEP can remain isolated, recur, or evolve secondarily to a schizo-affective disorder.[4–6] Early treatment of FEP is one of the major factors that impacts long-term prognosis.[7–10] Better understanding of FEP pathophysiology, proper patient selection for optimal treatment, and adequate prognostication of disease evolution are real challenges for current research.

The optimal diagnostic strategy for patients with psychiatric disorders, including patients with FEP, has not yet been clearly established. A recent study investigating the cost-effectiveness of various neuroimaging techniques, including positron emission tomography (PET), single-photon emission computerized tomography (SPECT), structural magnetic resonance imaging (MRI) and resting-state functional MRI in the management of psychiatric disorders found that MRI and PET were the most suitable, with the lowest cost and highest diagnostic accuracy.[11] MRI has now become the gold standard for imaging psychiatric disorders, showing structural abnormalities in 1 to 60% of patients, resulting in a change in the initial diagnosis in 1 to 20% of cases.[12,13]

In addition to allowing to rule out numerous neurological conditions that may have psychiatric manifestations, advanced imaging techniques play a role in identifying imaging biomarkers of psychiatric disorders, selecting patients for optimal treatment, and tracking treatment effects.[14,15] Given the specific problems posed by FEP, the contribution of advanced imaging to management is a particularly important issue. There are several advanced MRI techniques for imaging of brain structure and function. For example, new quantitative MRI techniques coming from T1-weighted sequences allow to evaluate anatomy with more and more details. At the same time, some sequences allow the evaluation of physiological or molecular parameters, such as functional MRI which evaluates neuronal activation indirectly by measuring the differences in deoxyhemoglobin concentration in the veins of the active brain regions, or spectroscopy which evaluates the molecular profile of the voxels studied, or ASL which informs about the distribution of arterial protons previously activated by radiofrequency waves.

We performed a systematic review of the literature to determine how advanced imaging in FEP can allow for increasing diagnostic specificity and predicting disease's evolution.

* Corresponding author.
E-mail address: marjorie.mateos@orange.fr (M. Matéos).

https://doi.org/10.1016/j.neurad.2023.04.001
0150-9861/© 2023 Published by Elsevier Masson SAS.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed searches were conducted on December 9, 2022, using combinations of the following predetermined search terms: “first episode psychosis” and “advanced imaging” or “functional MRI”, or “resting state MRI” or “spectroscopy” or “ASL” or “DTI” or “diffusion imaging”, with filters Clinical Trial, Meta-Analysis and Randomized Controlled Trial. Manual review of the citations was performed.

Studies were included if they were articles describing structural and/or functional imaging in patients with a diagnosis of FEP. Studies were excluded insofar as the aim of the study was related to treatments or in case there were based on machine learning. Studies were extracted by a single author, and classified according to the imaging methods used.

Results

The study selection process is shown in Fig. 1.

Quantitative MRI coming from T1-weighted sequences

To date, brain imaging studies have shown grey matter deficits, ventricular enlargement and reduced overall brain volume in FEP,[16] Advanced techniques may allow for better structural analysis than the eye of the radiologist alone as done in routine clinical practice. Morphology is commonly assessed using T1-weighted volumetric MRI with automated computerized methods. Quantitative MRI coming from T1-weighted sequences allow a fine-tuned measurement of brain structure which examines the whole brain and can detect small regional differences in grey or white matter concentration and volume[17].

Patients presenting a FEP show a thinning of certain cortical regions notably involved in emotional processing and higher executive functions. A meta-analysis of 965 patients with FEP found a decrease in grey matter volume in the insula, the operculum and the superior temporal gyrus, as well as the medial frontal and anterior cingulate cortices compared to a healthy population.[18] Zhao et al (2022) observed from a large cohort of 2765 subjects a cortical thinning in the right lateral superior temporal cortex, the right anterior cingulate cortex and the right insula in patients with FEP compared to healthy controls.[19] Prasad et al. (2004) examined the parahippocampal gyrus morphology in neuroleptic-naive subjects with FEP, and showed that patients with delusions had relatively smaller parahippocampal gyrus compared to nondelusional subjects.[20]

These morphological changes seem to increase over time after FEP in patients who develop chronic psychosis secondarily, which could indicate progressive grey matter alterations. Greater cortical thinning in right insula, right inferior frontal cortex, left lateral temporal cortex, and right temporal pole was found in patients with long-term schizophrenia compared to individuals with FEP.[19] Accelerated age-related cortical thickness reductions were quantified in bilateral middle temporal cortex and right pars orbitalis cortex, suggesting a progressive gray matter reduction during transition to psychosis. These findings were in agreement with those of another large study by Takahashi et al (2009) that analyzed volumes of superior temporal subregions at baseline and follow-up (mean, 1.8 years) in 70 patients: 25 ultrahigh-risk individuals (of whom 12 later developed psychosis [UHRP] and 23 did not [UHRNP]), 23 patients with FEP and 22 control subjects. Only the FEP group had significantly smaller planum temporale and caudal superior temporal gyrus than other groups at baseline. In longitudinal comparison, UHRP and FEP patients showed significant gray matter reduction (between 2% to 6% per year) in the planum polare, planum temporale, and caudal region compared with controls and/or UHRNP subjects.[21]

On the other hand, if the loss of cortical volume seems to be a marker of psychotic disorder, it does not seem to point to a specific

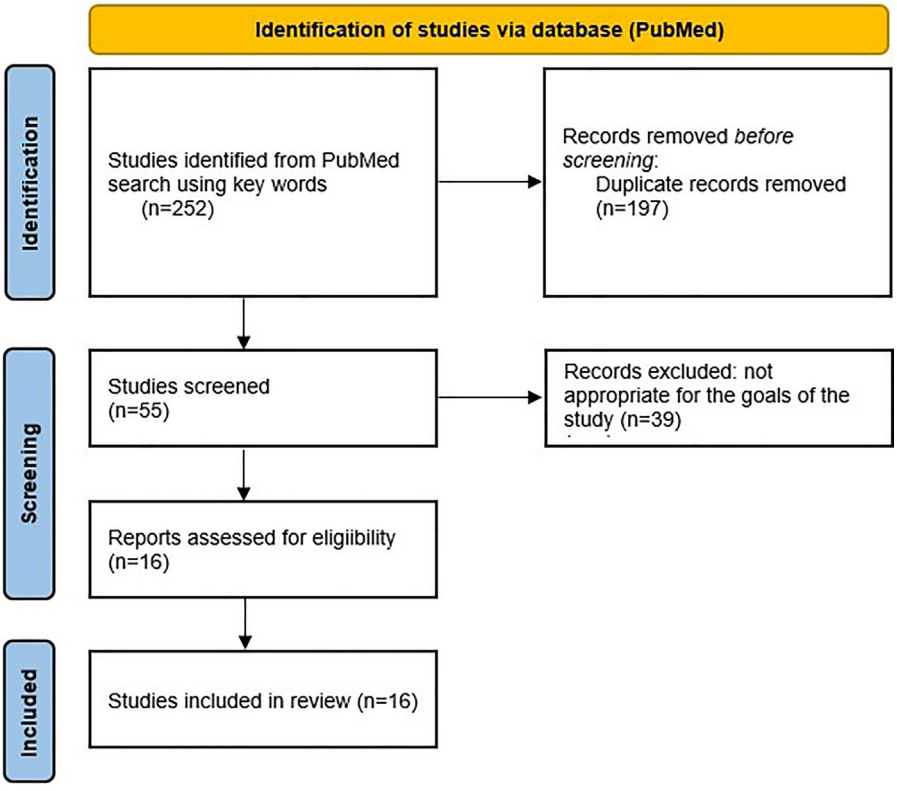

Fig. 1. Chart illustrating the study selection process for this review.

etiology. Palaniyappan et al (2016) conducted a quantitative MRI coming from T1-weighted sequences accuracy review to determine whether it could help to differentiate schizophrenia from other types of psychosis in participants who have received a clinical diagnosis of FEP. After including four studies with a total of 275 participants with FEP, they did not find evidence to support diagnosing schizophrenia as opposed to other psychotic disorders using quantitative MRI coming from T1-weighted sequences.[22]

The findings from structural studies are summarized in Table 1.

Functional MRI

Functional MRI (fMRI) is based on the BOLD (Blood Oxygen Level Dependent) contrast, which uses the paramagnetic properties of deoxygenated hemoglobin, during task-activation or resting-state paradigms. Neuronal activity is associated with changes in oxygen consumption and thus in deoxyhemoglobin concentration. Correlations between BOLD signal time series of distant brain regions reflect their functional interactions, allowing for the identification of different functional resting state networks (RSNs).

One of the main RSNs activated at rest, i.e. in the absence of any specific action, is the Default-Mode Network (DMN). Under physiological conditions, the DMN is deactivated when performing goal-directed tasks. The Central Executive Network (CEN) and the DMN are therefore negatively correlated.[23,24] The Salience Network (SN) is theorized to mediate switching between them.[25] In FEP, functional imaging alterations have been described, such as dysconnectivity within the DMN, SN and CEN, to different degrees. The most noteworthy disturbances were hypoconnectivity within the DMN, and between the SN and the DMN.[26]

Abnormal activations have been highlighted in particular in regions that are part of the limbic system, which is involved in our behavioural and emotional responses. A meta-analysis of 362 patients with FEP by Radua et al (2012) has shown during cognitive tasks an hypoactivation in the anterior part of the right insula, in the dorsal anterior cingulate cortices and in left precuneus.[18] These data were corroborated by Soldevila-Matias et al. (2022) who has found an hypoactivation in the left precuneus, insula and bilateral striatum during cognitive tasks,[27] and by Lukow et al. (2021) who has reviewed functional magnetic resonance studies using emotion processing task paradigms in FEP patients and has shown decreased neural responses to emotion in the amygdala and anterior cingulate cortex[28]. Another study by Radua et al (2015), has observed bilateral ventral striatal hypoactivation during reward anticipation and feedback in patients with psychosis.[29]

Conversely, some studies have shown a hyperactivation or a relative reduction in deactivation of certain brain areas in patients with FEP. Radua et al (2012) observed during cognitive tasks a greater activation in the right basal ganglia and thalamus extending to the posterior part of the insula and in the medial frontal cortex, in the right inferior frontal and left precentral gyri.[18] Shafritz et al. (2019) employed a simple response conflict task: patients were asked to press a response button on the same side or opposite side of a circle that appeared. This study has shown a reduction in deactivation in the anterior cingulate cortex and intraparietal sulcus in patients with FEP.[30]

Delusion is a frequent symptom of psychosis, occurring in the major part of first-episode psychosis patients. Raji et al (2018) has shown that patients with delusional experiences had a stronger activation of the ventral striatum in both hemispheres than patients with non-delusional experiences.[31]

The findings from functional studies are summarized in Table 2.

Other MRI-based advanced imaging sequences

Magnetic resonance spectroscopy sequences allow to differentiate various metabolites according to their resonance frequency and to assess their concentration. The latter may vary in psychiatric disorders. In particular, a decrease in N-acetyl-aspartate (NAA), the main neuro-axonal marker, was demonstrated within the frontal and temporal lobes, and the thalamus in patients with FEP.[32,33] Sydnor et al. (2020) and Nakahara et al. (2022) tried to measure glutamate (Glu), glutamine (Gln), glutamate+glutamine (Glx), gamma aminobutyric acid (GABA), and glutathione (GSH) in patients with psychosis, but these studies were not consistent.[34,35]

Other MRI-based advanced imaging sequences are now available. Cerebral perfusion can be assessed quantitatively without intravenous contrast with arterial spin labeling (ASL), which allows cerebral blood flow (CBF) measurement. Using this non-invasive MRI technique, Percie du Sert et al. (2022) has shown a decrease in CBF in the left superior, the middle frontal and the right middle occipital gyri, as well as an increased CBF in the left putamen in FEP patients compared to healthy controls.[36]

These findings are summarized in Table 3.

Table 1
Structural MRI

Study	Number of patients	Main results
Zhao et al. 2022	2675 (859 UHR, 671 FEP, 579 schizophrenia, 566 controls)	Cortical thinning in right lateral superior temporal cortex, right anterior cingulate cortex and right insula.
Takahashi et al. 2009	80 (35 UHR, 23 FEP and 22 controls)	Volumes of superior temporal subregions measured at baseline and follow-up (1.8 years) Only the FEP group had significantly smaller planum temporale and caudal superior temporal gyrus than other groups at baseline. In longitudinal comparison, UHRP and FEP patients showed significant gray matter reduction (approximately 2%-6% per year) in the planum polare, planum temporale, and caudal region compared with controls and/or UHRNP subjects.
Radua et al. 2012	2005 (965 FEP, 1040 controls)	Bilateral decreases of grey matter volume in the insula, operculum and the superior temporal gyrus, and in the medial frontal and anterior cingulate cortices Relatively greater grey matter volume than controls in the right lingual gyrus and left precentral gyrus.
Prasad et al. 2004	87 (44 FEP- 33 schizoaffective disorder and 11 nonschizophrenia psychotic disorders- 43 controls).	Patients with delusions had relatively smaller parahippocampal gyrus compared to nondelusional subjects.
Pariante et al. 2005	156 (78 FEP, 78 controls)	Larger pituitary volume
Palaniyappan et al. 2016	275 FEP	No evidence to support diagnosing schizophrenia (as opposed to other psychotic disorders) using the pattern of brain changes seen in voxel−based morphometry studies in patients with FEP

Table 2
Functional MRI

Study	Number of patients	Main results
Soldevila-Matias et al. 2022	1167 (598 FEP, 567 controls)	Hypoactivation in the left anterior insula, precuneus and bilateral striatum during cognitive tasks.
Shafritz et al. 2019	66 (33 FEP, 33 controls)	Greater activation in the anterior cingulate cortex and intraparietal sulcus.
Raij et al. 2018	13 FEP	Delusional experiences were related to stronger activation of the ventral striatum in both hemispheres
Radua et al 2012	765 (362 FEP, 403 controls)	Hypoactivation in the anterior part of the right insula, in the dorsal anterior cingulate cortices and in left precuneus. Relative reduction in deactivation in the right basal ganglia/thalamus extending to the posterior part of the insula and in the medial frontal cortex, in the right inferior frontal and left precentral gyri.
Radua et al. 2015	917	Bilateral ventral striatal hypoactivation during reward anticipation and feedback. Left ventral striatal abnormality was more severe in patients with high scores of negative symptoms during reward.
O'Neill et al. 2019	946 (420 FEP, 526 controls)	The Default Mode Network (DMN), Salience Network (SN) and Central Executive Network (CEN) were all found to display a combination of hyper- and hypoconnectivity, to different degrees, though the most noteworthy disturbances were hypoconnectivity within the DMN, and between the SN and the DMN.
Lukow et al. 2021	121 (48 FEP, 73 controls)	Decreased neural responses to emotion, particularly in the amygdala and anterior cingulate cortex.

Discussion

Structural analyses have found changes in grey matter volume and cortical thinning in patients with FEP, particularly in the insula, operculum, superior temporal gyrus and in the medial frontal and anterior cingulate cortices. Altered brain responses were observed in these same areas.

Some studies have shown a progressive volume reduction during transition to psychosis,[19,21] suggesting progressive neuroanatomic alterations following illness onset. Levels of NAA, a marker of neuronal metabolism, are reduced in the frontal cortex and thalamus in FEP and in many cortical and white matter areas in chronic schizophrenia.[33] These results suggest that schizophrenia is associated with lower neural metabolic activity affecting more brain areas as the disorder progresses. Those observations emphasize the importance of early intervention during or before the FEP.

Being able to predict the evolution of the FEP, which can remain isolated, recur or evolve towards a schizo-affective disorder would constitute a major advance. One study tried to differentiate schizophrenia from other types of psychosis in first-episode psychosis, but did not find evidence to support the diagnosis of schizophrenia using the pattern of brain changes seen in voxel–based morphometry studies in 275 patients with FEP.[16] Advanced MRI techniques, especially functional imaging may allow improved diagnostic specificity, and play a predictive role, in particular in the assessment of response to treatment. Although the purpose of this review does not include a discussion of treatment, some of the studied references evaluated treatment response as a second objective. For example, Shafritz et al (2019) observed that among patients, greater baseline anterior cingulate cortex, temporal-parietal junction, and superior temporal cortex activation were predictive of greater symptom reduction and therapeutic response following treatment.[30] Using spectroscopy, Nakahara et al. (2022) observed that treatment-resistant schizophrenia patient had elevated Glx and Glu levels in the midcingulate cortex.[34]

Other MRI-based advanced imaging sequences not discussed in this review exist and may play a useful future role. Structural connectivity can be assessed by tractography, using diffusion tensor imaging (DTI) or High Angular Resolution Diffusion Imaging (HARDI). Nevertheless, such evaluation currently remains poorly characterized in case of FEP.

Neuromelanin, present in dopaminergic neurons of the substantia nigra and noradrenergic neurons of the locus coeruleus, is a pigment that has paramagnetic properties and appears hyperintense on T1-weighted MRI images. The development of sequences that are sensitive to neuromelanin may now allow an indirect non-invasive measurement of dopaminergic function, which could be notably modified in schizophrenia.[37,38] A MRI sequence was recently developed at ultra-high field (7T) to study cerebral distribution of lithium. This sequence appears to be of interest in the follow up of bipolar disorders, which current treatment relies on lithium-based medications, whose mechanism of action remains poorly understood.[39]

Difficulty in performing advanced imaging techniques during a first episode psychosis must also be acknowledged. The decision to image a patient should result from appropriate communication between the psychiatrist and the radiologist. The request for a MRI study should therefore include accurate and detailed clinical information in order to allow the neuroradiologist to optimize the imaging protocol. The patient must be proactively educated as to what to expect during the examination, and may be accompanied by a member of the psychiatric care team.

Our review has limitations, including considerable methodological heterogeneity in the included studies. Also, the delay between symptom onset and MRI is poorly described. Moreover, antipsychotic treatment was used in some patients only, such that the distinction between the effect of disease and that of treatment is not possible. Furthermore, the common limitations of reported structural and functional studies is that they all deal with group versus group comparison, which makes it impossible to explore a single subject.

Artificial intelligence (AI), via supervised and unsupervised machine learning, is currently under active investigation, with the expectations that it will aid diagnosis, and play a role in personalized and precision medicine. Research in AI is mainly done by supervised

Table 3
Other MRI-based advanced imaging

Study	Number of patients	Main results
Whitehurst et al. 2020	2339	NAA concentrations are lower in the frontal lobe and thalamus in patients with first episode psychosis compared to controls
Sydnor et al. 2020	548 (255 individuals with psychiatric disorders -121 FEP-, 93 controls)	Glutamate and Glutathione concentrations significantly lower No significant difference for Glutamine, Glutamate+Glutamine and gamma aminobutyric acid.
Nakahara et al. 2022	16737 (7993 UHR, FEP and schizophrenia, 8744 controls)	Glutamine+Glutamate elevated in the basal ganglia.GABA decreased in the midcingulate cortex
Percie du Sert et al. 2022	827 (426 FEP, 401 controls)	Hypoperfusion in the left superior and middle frontal gyri and right middle occipital gyrus. Hyperperfusion in the left putamen.

learning using the SVM (Support Vector Machine) method, which means that a software program is trained to classify subjects according to groups that have been predetermined by experts. This SVM method allows for quality classification for many neurological and psychiatric pathologies.[40] The value of machine learning in risk prediction at the individual level in a population at risk for developing a psychiatric pathology has been investigated. A study which used the SVM to predict the 6-year clinical course of FEP demonstrated a sensitivity of 71% and a specificity ranging from 61% to 68%.[41] More recently, the SVM has been used to predict therapeutic response. These models use imaging data collected before treatment initiation as baseline as part of the learning phase, while follow-up studies allow to differentiate responders from non-responders.[42]

Machine learning performance will most likely continue to improve through a combination of model improvements and the extended inclusion of additional biomarkers, i.e. molecular, genetic, transcriptomic and pharmacological.

Conclusion

In the routine management of a FEP, brain imaging is mainly used to rule out other conditions. In this indication, structural brain MRI is considered the standard examination. In the near future, advanced sequences, particularly functional imaging studies, may allow improved diagnostic specificity, and play a predictive role, in line with the increasing development of personalized medicine.

In addition to such clear benefits in daily clinical practice, research in psychiatric imaging will allow to develop new physiopathological models toward an improved understanding of mental illnesses. The merging of imaging with genetics, transcriptomics, neurobiology, molecular medicine and clinical pharmacological research will allow to close the gap between structural anatomical and functional findings, eventually leading to the demonstration that mental disorders are but genuine "organic" pathologies.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest to this work.

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