40 YEARS OF STRUCTURAL IMAGING IN PSYCHOSIS (1976-2016): PROMISES AND TRUTH

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Review paper

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ABSTRACT

Objective

Since the first study published in the Lancet in 1976, structural neuroimaging has been used in psychosis with the promise of imminent clinical utility. The actual impact of structural neuroimaging in psychosis is still unclear.

Method

We present here a critical review of studies involving structural magnetic resonance imaging techniques in psychotic patients published between the 1976-2015 in selected journals of relevance for the field. For each study we extracted summary descriptive variables. Additionally we qualitatively described the main structural findings of each articles in summary notes and we employed a biomarker rating system based on quality of evidence (scored 1-4) and effect size (scored 1-4).

Results

80 studies meeting the inclusion criteria were retrieved. The number of studies increased over time, reflecting an increased structural imaging research in psychosis. However, quality of evidence was generally impaired by small samples and unclear biomarker definitions. In particular, there was little attempt of replication of previous findings. The effect sizes ranged from small to modest. No diagnostic or prognostic biomarker for clinical use was identified.

Conclusions

Structural neuroimaging in psychosis research has not yet delivered on the clinical applications that were envisioned.

Keywords psychosis, schizophrenia, MRI, CT, neuroimaging

Summations

Over the past four decades, structural neuroimaging has been used in psychosis with the promise of imminent clinical utility

However, no diagnostic or prognostic biomarker for clinical use is available

The lack of clinical utility of neuroimaging in psychosis is due to small samples, unclear biomarker definitions, and lack of replication.

Considerations

The current manuscript is not a systematic review of the literature and it may be affected by selection biases.

INTRODUCTION

At the dawn of in vivo brain imaging in psychiatry

The desire to visualize the structure of the body has characterized medicine since its origins. Psychiatry and the brain are not different. The history of structural brain imaging began with radiographic techniques. However, since the brain is composed of soft tissue that is not radio-opaque, it remained essentially invisible to plain x-ray investigations. The first attempt to visualize the brain traces back to 1918, when the neurosurgeon Walter Dandy(1), whose work on experimental hydrocephalus and cerebrospinal fluid circulation led to the development of pneumoencephalography(2). Most of cerebrospinal fluid was temporarily replaced trough a lumbar puncture with a contrast agent such as air, oxygen or helium, to improve brain contrast when imaging it with X rays. It was derived from ventriculography, an earlier method where the air was injected trough holes drilled in the skull of the patient. Pneumoencephalography become a common medical procedure mostly used to evaluate the size of the brain ventricles until the late 1970s. In 1927 Egas Moniz, neurologist and winner of the Nobel Prize in Physiology or Medicine (1949) for the discovery of leucotomy(3), introduced cerebral angiography, which allowed visualizing with great accuracy blood vessels in and around the brain(4). Drawbacks of these early methods was that that the signal to noise ratio was poor and since they were invasive techniques, the risk and discomfort for the patients were significantly high.

Non-invasive mapping of the human brain structure

The first non-invasive structural brain imaging method was computerized tomography (CT), developed in the late 1970s, when minicomputers and transverse axial scanning method became available. Transverse axial scanning was largely due to the work of Godfrey Hounsfield and Allan McLeod Cormack(5), who won the 1979 Nobel Prize for Physiology or Medicine for their work(6). With the CT available, better quality anatomical images of the brain became accessible to clinicians and researchers. About a decade later, in the early 1980s, a second non-invasive structural brain imaging method, Magnetic Resonance Imaging

(MRI), was introduced clinically. It was developed thanks to the work of several researchers who build its theoretical bases (for a detailed review see(7)), including Peter Mansfield and Paul Lauterbur. These researchers independently published in 1974 the technique that later became known as MRI, and were awarded the Nobel Prize for Physiology or Medicine in 2003(8). With regard to patient safety, MRI is superior to CT scan because CT scan is using ionizing radiation, whilst MRI uses harmless radio waves. Consequently, over the following years it has become the gold standard method to visualize non-invasively human brain structure, with a veritable explosion of technical refinements and diagnostic MR applications.

1976: The birth of structural brain imaging in psychosis

Modern structural brain imaging in psychosis started in 1976, when Eve Johnstone and colleagues published the first brain computerized tomography study in psychotic patients (Figure 1)(9).

*** Figure 1 ***

The authors aimed at elucidating the relationship between brain structural change and deterioration of intellectual function in 17 chronic institutionalized patients affected with schizophrenia (aged 42-70) as compared to 8 age-matched healthy controls. Two brain images at comparable levels were selected for each patient: one showed the body of the lateral ventricles and the other showed the anterior and posterior horns of the lateral ventricles, together with the third ventricle. The area of the ventricles was then measured with a "planimeter" (9). The authors found that patients with schizophrenia performed significantly poorer than the control group on cognitive functioning. They also found a significant correlation between ventricular size and cognitive functioning, mostly relating to memory domains, within a subset of 13 patients. After excluding the patients who were leucotomized –a procedure that may cause an increase in ventricular size-, a significant ventricular enlargement was still observed, as compared to controls. The authors concluded that among

patients with schizophrenia, “there is a group in which the disease is associated with increased ventricular size and impaired cognitive capacity” (9). It was therefore questioned whether “increased ventricular size is a consequence of the pathological process or whether increased ventricular size may in some way predispose to a severe and cognitively incapacitating form of the disease” (9). Further investigations “at different stages of the disease” (9) were recommended accordingly, to address these hypotheses.

Forty years of structural brain imaging in psychosis: the promises

Since the 1976 seminal study there has been an explosion of MRI or CT studies in psychiatry. Most of them were conducted in patients affected with psychosis(10). Structural neuroimaging has been embraced by investigators from different disciplines as a “window to the mind” to ultimately examine brain structure associated with psychotic disorders. A qualitative PubMed search uncovered an exponential increase of publications since 1976 (n=5638, Figure 2), with about 200 structural imaging studies published per year over the recent three years. Structural neuroimaging has therefore promised much both to psychosis research and to clinical psychiatry.

*** Figure 2 ***

The ultimate promise for MRI was to deliver reliable biomarkers to impact the clinical practice for psychotic patients, defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention”(11). Biomarkers promised by MRI in psychosis were diagnostic (e.g. characterizing patients vs controls(12) or affective psychoses vs schizophrenic psychoses(13)), prognostic (e.g categorizing clinical high risk patients by degree of probability of psychosis onset(14)), predictive (categorizing psychotic patients by their likelihood for response to antipsychotics(15) or cognitive enhancement therapy(16)), pharmacodynamic (showing that a gray matter alterations have occurred in psychotic patients

after having received antipsychotics(17)), surrogate (intended to substitute for another clinical efficacy end point). The ultimate promise of MRI was to "bring neuroscience into clinical practice"(18), by playing "a major role for a biological foundation of psychiatric diagnoses"(19) or by informing "tailored intervention strategies" (20) and leading "to more rational and efficacious treatment strategies than are available today"(21).

- The principal aim of the current review is to critically assess to what extent these promises have been maintained or not. We present here a critical review of studies involving structural magnetic resonance imaging techniques in psychotic patients published between the 1976-2015 in critically selected journals of relevance for the field.
- The second aim is to assess the included studies with a biomarker rating system based on quality of evidence and effect size.
- The third aim is to integrate the results and to suggest possible directions for future research.

METHODS

Type of review

We performed a critical review of the literature to address the impact of structural imaging in psychosis.

Literature search

Given MRI has become the gold standard method to investigate in vivo structural alterations we have selectively restricted our search to MRI studies conducted in patients affected with psychosis. Furthermore, we have restricted our search to a critical selection of journals of significant relevance in the field of psychiatric neuroimaging: The Lancet, Archives of General Psychiatry/JAMA Psychiatry, Molecular Psychiatry, American Journal of Psychiatry,

Brain. Literature search was conducted in Web of Science[SM], MEDLINE® and Scopus®. The search was extended until September 23rd 2015, and included abstracts in English language only. The electronic research adopted combinations of the above journal names with the following keywords: "psychosis", "mri", "schizophrenia". Journal selection and literature search were not intended to fulfil the requirements for a systematic and comprehensive review of all MRI studies in psychosis.

Inclusion and exclusion criteria

We included original English studies using MRI methods in patients with psychosis published in any of the journals listed above here**.** We used a broad spectrum definition of psychosis also including patients with a genetic or clinical risk for the illness. We excluded abstracts or studies employing other structural, functional, neurochemical imaging methods such as Diffusion Tensor Imaging (DTI), functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), and Magnetic Resonance Spectroscopy (MRS).

Data extraction and analysis

For each study we extracted study ID, MRI method, illness stage, sample size of psychotic patients, sample size of controls. Additionally we qualitatively described the main structural findings of each articles in summary notes.

Biomarker assessment

To assess the clinical applicability of MRI findings in psychosis we adapted a biomarker rating system proposed by Lassere(22) and previously used in early psychosis populations(23). The scale is based on quality of evidence (scored 1-4) and effect size (scored 1-4). To assess quality of evidence we extracted a number of moderator factors that were considered in each study. We then qualitatively rated the level of evidence for a potential biomarker(23):

- 0 for uncontrolled studies;

- 1 in a study controlled for relevant extraneous variables, that is, matched, restricted or adjusted for at least four of the followings: illness stage, antipsychotic exposure, age, gender, IQ, socioeconomic status, ethnicity, type of psychotic diagnosis;
- 2 in a study as above (grade 1) but with an explicit a priori intent to discover a precisely defined biomarker for psychosis, that is, within a given measure or modality, cut-off and direction of effect of biomarker and response;
- 3 in studies as above (grade 2), but designed with adequate power informed by previous positive studies of the same biomarker, that is, replication in an independent cohort;
- 4 in at least two studies as above (grade 3).

Effect size was estimated for the main finding of each study with Cohen's d and then rated as follows(23):

- 0 with estimates from studies with quality of evidence ≤ 1
- 1 with marginal effect (Cohen's d <0.2)
- 2 with small effect size (Cohen's d ≤from 0.2 to 0.5)
- 3 with medium effect size (Cohen's d from 0.5-0.8)
- 4 with a large effect size (Cohen's d > 0.8)

The sum of the two scores was then used to assess the clinical applicability of a biomarker, using the cutoff of >6 previously indicated(23). Results were summarized with descriptive statistics and qualitatively described.

RESULTS

Database

A total of 80 studies published over the past four decades were included in our database, for a total of over than 11,000 patients with a psychotic spectrum disorder.

Descriptive summary of findings

After the first qualitative study(24) indicating that "MRI showed superiority to CT in visualisation of" brain structures, all of subsequent studies employed MRI. Most of them investigated grey matter volumes in psychotic patients as compared to healthy controls. Consequently, grey matter volume studies were the most frequent ones and were characterised by significant advancements in analytical methods and data processing techniques over time. For example, the first grey matter volume study(25) covered in our database focused on medial temporal lobe and ventricles abnormalities in a small sample of 66 first episode patients, while a recent multisite meta-analysis has investigated about 2028 patients and 2540 controls on different brain regions, uncovering smaller hippocampus, amygdala, thalamus, accumbens, and intracranial volumes and larger pallidum and lateral ventricle volumes in patients(26). As soon as voxel based morphometry methods were introduced in cognitive neurosciences, in 2000(27) (for an example of one of the first studies see(28)), such analytical approaches were immediately adopted in psychosis research(29), and were then followed by other studies(16, 30-33). Following emerging interest in more derived measures of anatomy such as cortical complexity, gyrification, symmetry and thickness(34), a few studies have addressed these alterations in psychotic patients(15, 35-42). Multimodal studies involved the use of MRI, eye tracking and markers of dopamine activity(25), MRI and PET(43), MRI and EEG measures(44), MRI and fMRI(40, 41), MRI and genetics(32, 38, 45, 46). Most studies focused on first-episode samples, with several MRI studies investigating the psychotic spectrum by including samples at genetic risk(28, 33, 37, 47-55) and a few studies that have investigated subjects at clinical risk for psychosis(14, 31, 56-58). One meta-analysis has investigated the human connectome in healthy brains as well as in psychotic disorders(59). Two recent studies adopted machine learning methods in patients with early psychosis or at clinical high risk for psychosis(57, 58). The list of all included studies and the main structural findings are detailed in Table I.

*** Table I ***

Clinical applicability of MRI-based biomarkers for psychosis

The ratings for the level of evidence of potential biomarkers and for the effect size of each included studies are detailed in Table I. None of the 80 studies but one(58) met the a-priori cutoff criteria for a potential clinical applicability in psychosis described above. This study used study used structural MRI-based multivariate pattern classification to identify and cross-validate a differential diagnostic signature separating patients with first-episode and recurrent stages of schizophrenia (n = 158) from patients with major depression (n = 104) and to quantify the impact of major clinical variables, including disease stage, age of disease onset and accelerated brain ageing on the classification performance. The diagnostic MRI signature was then externally validated in an independent patient cohort to test its generalizability to individuals with bipolar disorder (n = 35), first-episode psychosis (n = 23) and clinically defined at-risk mental states for psychosis (n = 89). The authors found that their neuroanatomical diagnosis was correct in 80% and 72% of patients with major depression and schizophrenia, respectively, and involved a pattern of prefronto-temporo-limbic volume reductions and premotor, somatosensory and subcortical increments in schizophrenia versus major depression. Furthermore, they found that diagnostic performance was not influenced by the presence of depressive symptoms in schizophrenia or psychotic symptoms in major depression, while earlier disease onset, accelerated brain ageing and disease stage significantly moderated neuroanatomical diagnosis. In their validation study, the trained biomarker assigned 74% of the bipolar patients to the major depression group, while 83% of the first-episode psychosis patients and 77% of the individuals with an clinical high risk state, respectively, were labeled with schizophrenia. Replication studies were scarce, although this may have been influenced by our critical literature search that was restricted to high impact factor journals(60).

DISCUSSION

Forty years of structural brain imaging in psychosis: the truth

Despite the enduring efforts and the impressive number of MRI studies published in

schizophrenia patients (more than 5,000, see Figure 2), there are no clinical biomarkers for structural MRI in psychosis. Recent systematic reviews and meta-analyses of the available evidence have identified specific cortical and subcortical alterations in psychotic patients as compared to healthy controls (for a detailed review on the main findings see(61, 62)). Yet, after four decades of research, the conclusion of the first 1988 study included in our database "none of the findings from CT or MRI explained clinical observation or led to a change in treatment"(24) are still valid. As recently confirmed by positional statements by leading authors, imaging research has yielded no clinical advancement for psychotic patients (see Table II).

*** Table II ***

This is further confirmed by our empirical analysis, which uncovered only one study satisfying the basic requirement for some potential clinical applicability of biomarkers in psychosis(58). This study suggested that neuroanatomical classification could provide generalizable diagnostic tools distinguishing schizophrenia from mood disorders early in the course of psychosis. However, it is important to note that the assessment of the theoretical clinical applicability per se does not assure real-world clinical utility(23). Indeed, proper randomised clinical trials (of this biomarker vs standard care) should be carried out so that additional factors such as cost of administration, potential risks and side effects, inconvenience and delays associated with testing can be balanced and a decision on its real-world clinical utility can then be made(23). Because of this, the clinical utility of the biomarker described by this unique study is still in need of additional converging support. This is particularly relevant given that the brain areas implicated by this study are only partially consistent with the largest MRI analysis in schizophrenic patients(26). Similarly, structural imaging is not clinically recommended for the differential diagnosis of incidental organic psychoses due to underlying brain abnormalities. A recent review of 1379 MRI scans found that none of the neuropathological findings observed in the patients represented a

possible substrate for organic psychosis, concluding that MRI brain scans should not be an essential part of routine screening for psychotic patients(63). On the basis of these findings, the current NICE guidelines do not recommend the use of structural neuroimaging for routinely examine all patients who have suffered from a first episode of psychosis(64). We will address practical and conceptual issues underlying this clinical failure of structural imaging in psychosis in the following sections.

The role of confounders and the lack of valid biomarker in psychosis

It is possible that several external factors may have played a confounding role impacting the lack of reliable MRI biomarker in psychosis. Early MRI studies identified in our literature search have soon highlighted the confounding role played by illness chronicity and antipsychotic exposure(65, 66). Since then, most of MRI studies have controlled their results for these factors. The development of the clinical high-risk paradigm, as well as the study of identified risk factors such as genetic polymorphisms or environmental exposures in health individuals has further allowed researchers to investigate putative biomarkers of an risk of psychosis in antipsychotic-naïve participants with no impact of illness chronicity or medication(62). Structural imaging studies in subjects at clinical high risk for psychosis have been summarized by voxel based meta-analyses indicating that psychosis onset is characterized by gray matter decreases in temporal, anterior cingulate, cerebellar, and insular regions(62). Furthermore, gray matter alterations in the temporal regions directly related to severity of psychotic symptoms(62). However, despite these promising findings, no reliable biomarker of psychosis risk has been validated to clinically predict the onset of the disorder. This may be in part due to the fact that the group of subjects at clinical high risk for psychosis is not heterogeneous as it includes different clinical subgroups(67, 68).

Additional modulators of brain structure in psychosis may include age(69), gender(70), type of psychotic disorder (e.g. schizophrenia spectrum disorders vs affective psychotic disorders(71)), smoking(72), ethnicity(73), substance abuse(74), all of which have been shown to impact on the MRI signal. However, over the recent years authors have become

more aware of these caveats, controlling their MRI studies for these factors. It is thus unlikely that the confounding factors alone could be responsible for the global lack of clinical reliable biomarkers in psychosis research.

Small samples and reporting biases in structural imaging of psychosis

Conversely, recent empirical evaluations of the neuroimaging literature suggest that study publication bias, selective outcome reporting bias, and selective analysis reporting bias are prevalent across diverse domains of cognitive science(75). There is specific evidence that these biases may affect both region of interest(76) and voxel based morphometry (VBM) (77)) structural imaging studies of psychotic patients.

Reporting biases may specifically affect small structural imaging studies and even meta-analyses with few studies, inflating the number of significant findings(77). Consequently, there has been a trend towards larger structural imaging studies of psychotic patients over time. This trend is observed in our database with an average sample size of 53 psychotic patients for the MRI studies conducted before 2000, 57 patients for the studies conducted between 2000-2005, 97 patients for studies published between 2005-2010 and 179 patients for studies conducted over the 2015-2010, with two meta-analytical outliers conducted in about 2000 psychotic patients(41, 59). An independent review confirmed our findings by concluding that there is limited evidence supporting grey or white matter changes in schizophrenia, which has previously been obscured by a large volume of conflicting, lower quality evidence(78). However, reporting biases are by no means specific or confined to psychiatric conditions(77) and are thus unlikely to account for the overall lack of reliable biomarkers in psychosis research. Available statistical tests and approaches to prevent bias have been made available (75)) which could improve the quality of structural imaging reports in the future.

Machine learning methods: myth or promising avenue?

Since no simple regional or global neuroanatomical measure has been unequivocally associated with psychosis, researchers started investigating more complex patterns of brain alterations with advanced analytical methods. Indeed, the one study identified by our literature search meeting advanced criteria for biomarker detection was based on machine learning methods, and delivered a neuroanatomical-based biomarker to differentiate schizophrenia from mood disorders early in the course of psychosis(58). Machine learning methods are one of today's most rapidly growing technical fields, lying at the intersection of computer science and statistics, and at the core of artificial intelligence and data science (for a review of machine learning methods in modern sciences see(79)). Machine learning methods may ultimately address the complexity of psychotic disorders capitalizing on the abilities of machines to tease out subtle statistical regularities from massive data sets(79). Because of this, machine learning methods are fast becoming the mainstream analytical avenue for modern neuroimaging studies of psychiatric disorders (see Figure 3 for a summary of its method).

*** Figure 3 ***

Authors hope that in the near future these methods applied in psychosis "might help clinicians in reliable and early detection of affected patients, potentially becoming a crucial tool for the real world of psychiatric practice"(80). However, "nowadays we are far away from using automatic image-based classification techniques to make a diagnosis" (80), and the limitations of these methods are often underreported. For example, the majority of studies have tried to discriminate patients with a particular DSM/ICD diagnosis (e.g. schizophrenia) from healthy controls, or to disambiguate between patients from different DSM/ICD-defined disease states. Therefore, machine-learning approaches which use diagnostic labels from DSM/ICD for training a classifier applied to neuroimaging data are using a sophisticated procedure(81) to replicate a diagnostic classification that may in itself be biologically problematic. An additional, more generic risk of machine learning is that these approaches tend to deliver what are effectively 'black-box' classifiers, which are statistically powerful

but may provide very limited insights into disease mechanisms(81). This is a fundamental limitation, since without mechanistic interpretability a diagnostic procedure will be ill placed to promote a change in disease concepts or guide the development of future therapies(81).

Structural neuroimaging in other neuropsychiatric disorders

Contrary to clinical psychiatry, structural imaging is already in use as clinical diagnostic criterion for other complex neuropsychiatric disorders, for example for the most prevalent non-Alzheimer Dementias (AD): vascular dementia, frontotemporal degeneration, dementia with Lewy bodies, and Creutzfeldt–Jakob disease(82). With respect to AD, the recent guidelines of the Alzheimer's Association and the National Institute on Aging (NIA) have detailed the differential diagnostic impact of structural neuroimaging for the three phases of the disorder: dementia due to Alzheimer's (probable AD dementia, possible AD dementia, probable/possible AD dementia with evidence of the AD pathophysiological process)(83), mild cognitive impairment (MCI) due to Alzheimer's(84) and preclinical (presymptomatic) Alzheimer's(85). For established AD dementia (possible or probable) "the use of AD biomarker tests for routine diagnostic purposes at the present time" is not advocated neither required for the diagnosis(83). However, the field is more advanced as compared to psychosis since in persons who meet the core clinical criteria for probable AD dementia, biomarker evidence "may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process"(83). These biomarkers are well defined and include structural measures such as atrophy on structural MRI in media, basal, and lateral temporal lobe and medial parietal cortex(83). Similarly to the prodromal phase of psychosis, the high risk MCI diagnosis can be formulated "without access to advanced imaging techniques" (84). However, a separate set of research criteria is already available, which include a number of biomarkers(86) reflecting signs of neuronal injury(84). Of relevance, the guidelines outline a probabilistic framework for the way in which biomarkers may be used to provide increasing levels of certainty that AD pathology is the cause of an individual's clinical symptoms (cognitive decline) (84). This is a significant advancement as compared to psychosis research

where no clear guidelines are put forward. For example, cortical thinning/gray matter loss in a specific anatomic distribution (i.e., lateral and medial parietal, posterior cingulate, and lateral temporal cortices) and/or hippocampal atrophy on volumetric MRI are clearly indicated as leading biomarkers for the diagnosis of preclinical AD(85).

The lack of gold standard and the exceptionalism of the human being

A core difference between psychosis and other complex neuropsychiatric disorders such as AD is that, unlike AD, there is no objective neuropathological gold standard for psychotic diagnoses. Unlike our definitions of other medical conditions such as ischemic heart disease, lymphoma, or AIDS, the psychotic "diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure"(87). Indeed a recent meta-analysis of structural studies across several psychiatric disorders such as schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety found converging gray matter loss in the same brain areas with a few diagnosis-specific effects(88). Because of these nosographic limitations, the NIMH has launched the Research Domain Criteria (RDoC) project to transform psychiatric diagnoses by the mean of genetics, imaging, cognitive science, and other levels of information to lay the foundation for a new classification system based on neurobiology. Rather than seek MRI biomarkers that can 'diagnose' clinically defined disorders, RDoC will help future MRI studies focusing on identifying biologically homogenous subtypes that potentially cut across phenotypic diagnosis—thereby sidestepping the issue of a gold standard(89). However, this approach may be "over-promising about the future blithely ignored the sobering lessons of the past(90)" 40 years of imaging research. The claim that this approach is substantially different from those endorsed in the past decades, that were unable to produce significant biomarkers, is not supported by preliminary findings(91). On the other hand, it stands to reason that mapping data such as structural neuroimaging onto criteria or scales closer to the underlying pathologie(s) of the clinical states of interest is more informative, especially if multivariate techniques are employed whose output may be intrinsically harder to interpret mechanistically.

The future of structural neuroimaging in psychosis

Although the spatial resolution of modern MRI protocols is very high, 1 mm^3 of cortical gray matter can contain up to 60,000 neurons, up to four times as many glial cells per neuron, as well as neuronal processes, blood vessels, intracortical myelin and dendritic spines. Therefore, alterations found at a cellular/synaptic/microstructural level, may not be visualized with current MRI techniques(92). However, it may be time to consider the alternative possibility that brain structure, while certainly altered in the majority of patients with psychosis, may never be – in isolation - a useful biomarker for psychosis just as high blood pressure, while certainly altered in the majority of patients with type II diabetes, is not a useful biomarker for this condition. In other words, if structural brain alterations are too far downstream or only distantly related to causal pathology of psychotic illness, they may not index informative biology related to the clinical critical parameters of differential diagnosis and prediction of course and therapeutic stratification. Some evidence for this assumption comes from imaging genetics, which studies the arguably biologically best defined risk factors for the highly heritable disease of schizophrenia in the absence of many confounds discussed above. Here, the experience is that structural neuroimaging measures underperform functional neuroimaging measures when the effects of common genetic variants are mapped(93, 94). Recent work by the psychiatric GWAS consortium and the ENIGMA consortium further supports this by indicating that polygenetic risk scores for schizophrenia fail to explain meaningful variance in even very large neuroimaging datasets. A recent study integrating common variant studies of schizophrenia (33,636 cases, 43,008 controls) and volumes of several (mainly subcortical) brain structures (11,840 subjects) found no evidence of genetic overlap between schizophrenia risk and brain volume measures either at the level of common variant genetic architecture or for single genetic markers(95). There are several potential neurobiological reasons that might underlie such an absence, notably the fact that schizophrenia is a neurodevelopmental process where several neural longitudinal changes may map in opposite fashion onto regional volumes (for example, cortical pruning as a

mechanism of maturation in adolescence and pathology-induced neuronal loss both may lead to cortical thinning; antipsychotic treatment and neural plasticity may both lead to same-direction volume changes in the striatum). By the same token, the usefulness of structural imaging biomarkers may potentially be much enhanced if information from other sources, some of which – functional neuroimaging, for example of the resting state – can be measured in the same sitting, is included. This might extend to genetic and clinical information, for example. Machine learning, with all the problems inherent in its interpretation discussed above, lends itself to that approach, as well.

CONCLUSIONS

The current critical review suggests that structural neuroimaging in psychosis research has not (yet) delivered on the clinical applications that were envisioned. Several reasons for this as yet disappointing outcome have been discussed. Better nosological criteria, biomarker studies at a higher methodological standard, biomarkers including complementary information (such as functional and clinical data) may yet resolve that impasse. Until then, after four decades of promises, in their everyday practice, psychiatrists continue talk to the patients, use observation, description and classification, test explanatory hypotheses, and formulate clinical decisions in the absence of such structural biomarkers.

FIGURES

Figure 1. First modern computerized tomography of the brain in psychotic patients (1976). Patients affected with psychosis showed enlarged ventricular size as compared to healthy controls. White dots indicate leucotomised psychotic patients. From(9)

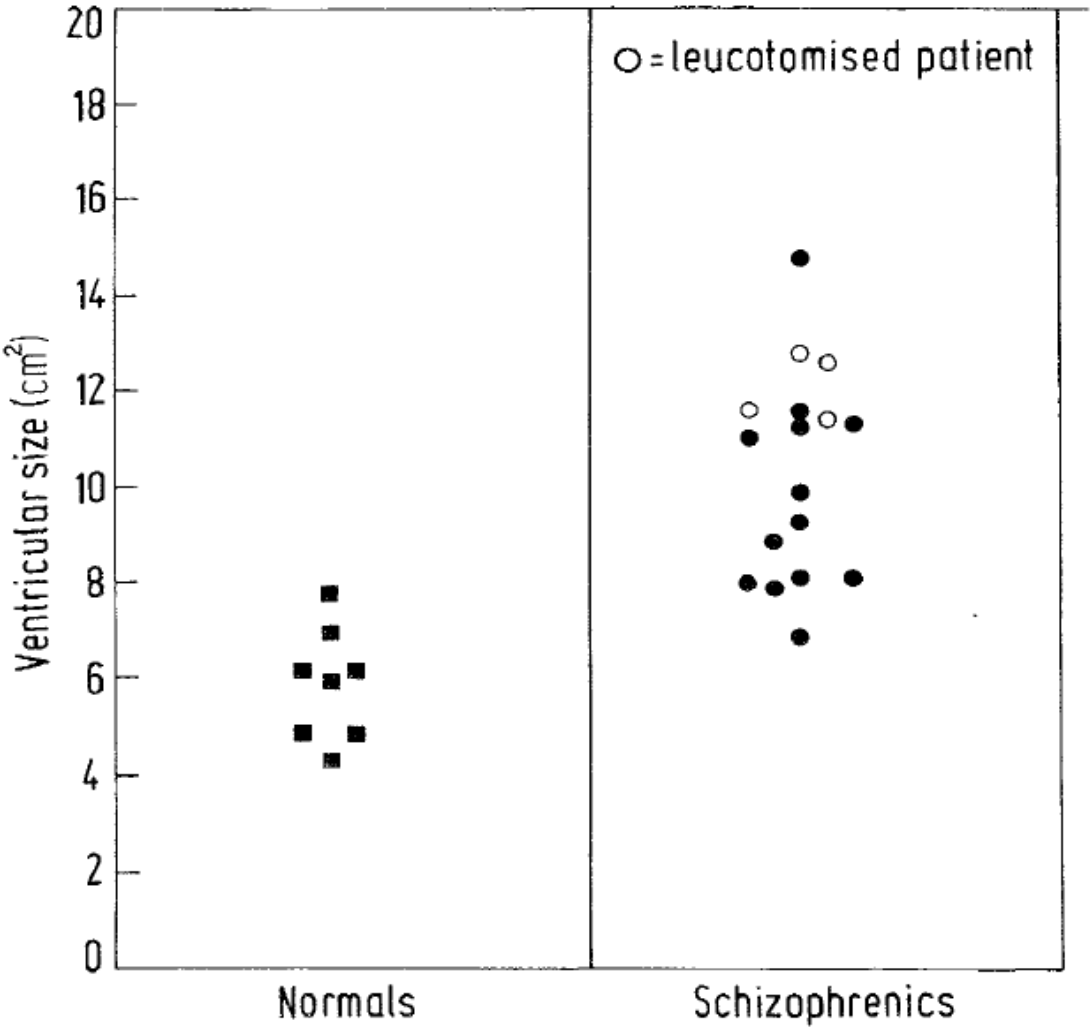


Figure 2. Number of PubMed studies employing MRI or CT in schizophrenia over the past four decades, up to 2015 (keywords "mri", "schizophrenia", search date 28rd May 2016, number of records=5638).

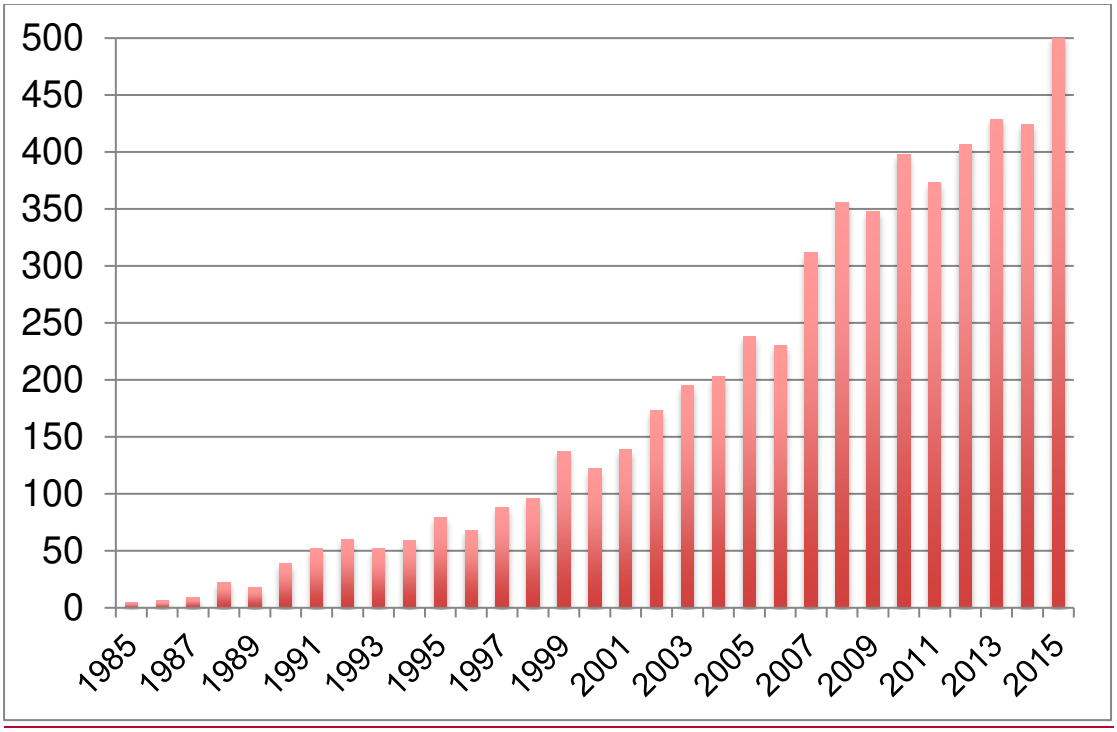


Table 1 Study ID	Method	Psychosis group	Patients (n)	Controls (n)	Main structural finding	Biomarker Quality of evidence	Effect size
Chung 2015(42)	Cortical Thickness	CHR (1)	274	135	Among CHR-T, higher levels of baseline unusual thought content related to steeper rate of GM loss in the bilateral prefrontal cortex and with third ventricle expansion.	2	2
Koutsouleris 2015(58)	Machine Learning Validaton	FEP, ChP FEP, CHR	158 112(3)	104(2) 35(4)	Neuroanatomical diagnosis based on a biomarker involving a pattern of prefronto-temporo-limbic volume reductions and premotor, somatosensory and subcortical increments correctly identified 83% of patients with first episode psychosis and 77% of CHR subjects.	3	4
Lesh 2015(41)	Cortical Thickness + fMRI	FEP	45(5)	37	Short-term treatment with antipsychotics associated with increased prefrontal functional activity, better cognitive control but prefrontal cortical thinning.	2	3
van Erp 2015(26)	Meta-analysis of grey matter volume	ChP	2028	2540	Compared with healthy controls, patients with schizophrenia had smaller hippocampus, amygdala, thalamus, accumbens, and intracranial volumes and larger pallidum and lateral ventricle volumes.	3	2
Crossley 2014(59)	Meta-analysis of connectome	ChP	1925	2133	Schizophrenia had significantly hub-concentrated lesion distributions, with lesions were concentrated in both frontal and temporal cortical hubs.	0	0
Hoptman 2014(40)	Cortical Thickness + fMRI	ChP	33	31	Impulsivity correlated with reduced cortical thickness in the right frontal pole, the medial and lateral orbitofrontal gyrus and inferior frontal gyri, and the rostral anterior cingulate cortex.	1	0
Mathew 2014(96)	Hippocalmpal volume	ChP	508(6)	337	Hippocampal volume reductions in schizophrenia, schizoaffective and psychotic bipolar patients, alterations in entorhinal cortex and parahippocampal regions in schizophrenia and schizoaffective only.	1	0
van Lutterveld 2014(39)	Cortical thickness	ChP	100(7)	50	Individuals with non-clinical psychotic symptoms show a similar but less pronounced pattern of cortical thinning as patients with a psychotic disorder.	2	na

Ivleva 2013(33)	VBM	ChP, GHR	720(8)	200	Extensive neocortical GM reductions in psychosis probands and relatives with psychosis spectrum disorders. Partially divergent GM phenotypes for probands with schizophrenia of schizoaffective disorder relative to those with psychotic bipolar disorder.	2	1
Palaniyappan 2013(15)	Cortical gyrification	FEP(9)	80	46	Reduction in gyrification across multiple brain regions. Non-responders to antipsychotics showed prominent hypogyria at bilateral insular, left frontal and right temporal regions when compared with responders.	1	0
Arango 2012(97)	Gray matter volume	COP	61	70	Patients with schizophrenia or other psychoses showed greater loss of GM matter volume and increase of CSF in the frontal lobe relative to controls.	2	2
Tan 2012(32)	VBM+genetic	ChP	118(10)	20(10)	Patients with the AKT1-A-allele who were also on mood stabilizer had larger GM volume in the medial temporal lobe and prefrontal cortex than patients not receiving mood stabilizers.	1	0
Wassink 2012(45)	Gray matter volume+genetic	ChP	335	198	The results did not substantiate previously reported effects of rs1344706 on cerebral cortical GM volume.	1	0
Bakken 2011(38)	Cortical Thickness + genetic	ChP	94	181	Two closely linked variants within the Prader-Willi and Angelman syndrome on chromosome 15q12 showed a genome-wide significant association with average cortical thickness among patients with schizophrenia.	1	0
Ho 2011(98)	Gray matter volume	ChP	211	-	Greater intensity of antipsychotic treatment was associated with indicators of generalized and specific brain tissue reduction. Illness severity had relatively modest correlations with tissue volume reduction.	0	0
Mechelli 2011(31)	VBM	CHR(11)	182	167	The UHR group had less prefrontal GM volume than controls in the frontal regions bilaterally. GM reductions in the left parahippocampal were associated with psychosis onset.	1	0
Prasad 2011(99)	VBM	FEP	18(12)	24(12)	HSV1 exposure associated with longitudinal GM loss in the posterior cingulate gyrus and decline in executive functions in schizophrenia.	1	0
Eack 2010(16)	VBM	ChP	30(13)	23(13)	Within patients, cognitive enhancement therapy associated with GM preservation in the left hyppocampus, parhyppocampal gyrus, fusiform gyrus and significantly GM increase in left amygdala.	2	3

Gilmore 2010(55)	Gray matter volume	GHR	26(14)	26(14)	Offspring of mothers with schizophrenia did not differ in prenatal lateral ventricle width. Male neonates at genetic risk for schizophrenia had several larger than normal brain volumes.	2	3
Goldman 2009(37)	Cortical Thickness	ChP, GHR	307	196	Widespread cortical thickness reductions in schizophrenia and widespread evidence for heritability for cortical thickness reduction throughout the brain.	2	na
Koutsouleris 2009(57)	Machine learning Validation	CHR	45(15) 33(16)	25 17	Whole-brain neuroanatomical abnormalities classified by machine learning algorithms may serve as valuable biomarker to distinguishing between CHR and control and from CHR developing psychosis or not (accuracy 86%-96%).	3	2
Takahashi 2009(100)	Gray matter volume	CHR, FEP	58(17)	22	Progressive GM loss in volumes of the superior temporal subregions are associated with the onset of psychosis.	2	3
Brans 2008(101)	Gray matter volume	ChP, GHR	38(18)	54	Significant additive genetic influences on the correlations between schizophrenia liability and progressive whole brain, frontal lobe, and temporal lobe volume change.	1	0
Keller 2008(102)	Gray matter volume	ChP	23	22	Depressed patients with psychosis had a smaller amygdala volume relative to depressed patient without psychosis and healthy comparisons.	1	0
Koo 2008(103)	Gray matter volume	FEP	80	40	In schizophrenia, significantly smaller left subgenual, left and right affective subregion, right cognitive, and right posterior cingulate gyrus GM compared with controls and progressive GM decreases in the cingulate subregions at follow-up.	2	3
Addington 2007(46)	Gray matter volume+genetic	COP	59	165	In COP patients, neuregulin risk allele 0 at 420M9-1395 carriers had greater total GM and white matter volume in childhood and a steeper rate of subsequent decline in volume into adolescence.	1	0
Kuroki 2006(104)	Gray matter volume	FEP	40	23	Smaller GM volumes in left and right middle temporal gyri and left superior temporal gyrus in schizophrenia but not in affective psychosis. Smaller bilateral posterior inferior temporal gyrus GM volume in both schizophrenia and affective psychosis.	1	0
McDonald 2006(54)	Gray matter volume	ChP, GHR	189(19)	54	Schizophrenia and psychotic bipolar disorder are characterized by morphometric distinctions in ventricular and hippocampal regions. Lateral ventricular enlargment as morphometric endophenotype for schizophrenia.	2	4

Velakoulis 2006(56)	Gray matter volume	ChP, FEP, CHR	386[20]	87	Chronic schizophrenia associated with bilateral hippocampal volume reduction. FEP schizophrenia associated with left hippocampal volume reduction. CHR subjects had normal baseline hippocampal and amygdala volume whether or not they subsequently developed a psychotic illness.	2	3
Vidal 2006(36)	Cortical pattern	COP, FEP	21[21]	12	Selective, frontal GM loss occurred bilaterally in a dorsal-to-ventral pattern across the medial hemispheric surfaces in schizophrenia.	2	na
Coryell 2005(105)	Gray matter volume	ChP	20	10	Posterior subgenual prefrontal cortex is smallest for psychotic major depressive disorders patients as compared to controls or patients with schizophrenia.	2	3
Ho 2005(106)	Gray matter volume	FEP	57[22]	48[22]	No significant associations between hippocampal volumes and duration of untreated initial psychosis.	1	0
Lieberman 2005(107)	Gray matter volume	FEP	161	58	Haloperidol-treated patients exhibited significant decrease in GM volume, whereas olanzapine-treated patients did not.	2	2
Nierenberg 2005(108)	Gray matter volume	FEP	14	14	Patients with new-onset schizophrenia showed smaller left angular gyrus volume than normal subjects	0	0
Suzuki 2005(109)	Gray matter volume	ChP	78[23]	59	Volume reductions in the amygdala and hippocampus are the common morphological substrates for the schizophrenia spectrum.	2	3
Wiegand 2005(35)	Cortical complexity	FEP	34	17	Schizophrenia patients showed less left-greater-than-right asymmetry in cortical complexity thant the comparison subjects.	1	0
Dazzan 2004(30)	VBM	FEP	34[24]	39[24]	In FEP patients a higher rates of soft neurological signs are associated with a reduction of GM volume of subcortical structures.	1	0
Robinson 2004(110)	Gray matter volume	FEP	107[6]	-	In FEP patients, more cerebral asymmetry was associated with full recovery and adequate social/vocational functioning	0	0
Ettinger 2004(111)	Gray matter volume+antisaccades	FEP	20	18	FEP significantly differed from controls in terms of antisaccade error rate and amplitude gain but not brain region volumes.	1	0
Gogtay 2004(112)	Gray matter volume	COP	42[25]	38	COP patients had significantly greater total, frontal and temporal and parietal GM loss as compared to controls and psychosis not otherwise specified.	2	3

McDonald 2004(53)	Gray matter volume	ChP, GHR	148[26]	-	Genetic risk for schizophrenia was specifically associated with distributed GM volume deficits in the bilateral fronto-striato-thalamic and left lateral temporal regions.	0	0
Prasad 2004(113)	Gray matter volume	FEP	44	43	Patients with schizophrenia and non schizophrenic psychoses had smaller left entorhinal cortex volume than healthy subjects.	2	2
van Erp 2004(52)	Gray matter volume	ChP, GHR	110[27]	109	Probands had smaller hippocampal volumes than did their full siblings, who in turn had smaller hippocampal volumes than did the healthy comparison subjects.	2	4
Ho 2003(114)	Gray matter volume	FEP	102	-	Within FEP patients, untreated initial psychosis has no direct impact on GM volume and toxic neural effects.	0	0
Kasai 2003a(115)	Gray matter volume	FEP	28	14	Progressive volume reduction of the left superior temporal gyrus GM in patients with schizophrenia as compared to affective psychosis or controls.	1	0
Kasai 2003b(13)	Gray matter volume	FEP	53	29	Partially different and partially similar structural abnormalities in olfactocentric paralimbic and temporolimbic regions are important factors in the differential and common manifestations of affective and schizophrenic psychoses.	1	0
Kasai 2003c(116)	Gray matter volume	FEP	28	22	FEP schizophrenia showed significant decreases in GM volume over time in the left Heschl gyrus and left planum temporale vs patients with FEP affective psychosis and controls.	1	0
Keshavan 2003(117)	Gray matter volume	FEP	26	18	In schizophrenia, higher score for the cognitive/perceptual abnormalities factor correlated with smaller volumes of the left heteromodal association cortex.	1	0
Pantelis 2003(14)	Gray matter volume	CHR	23[28]	52[28]	CHR patients who did develop psychosis had less GM in the right medial temporal, lateral temporal, and inferior frontal cortex, and the cingulate cortex bilaterally, compared with CHR who didn't develop psychosis.	2	na
Szeszko 2003(118)	Gray matter volume	FEP	46	34	Patients had reduced anterior hippocampal volume relative to control subjects.	2	2
Cannon 2002(51)	Gray matter volume	Chronic, GHR	115[29]	54	Fetal hypoxia predicted reduced GM trough the cortex in the patients and siblings.	1	0
Lee 2002(119)	Gray matter volume	FEP	42	24	Schizophrenia associated with smaller fusiform gyrus GM volume compared with controls and patients with affective psychosis.	1	0

McCarley 2002(44)	Gray matter volume+P300	FEP	33	18	Schizophrenia showed smaller GM volumes of left posterior superior temporal gyrus related to control and affective psychosis. These alterations were correlated with P300 abnormalities.	1	0
Seidman 2002(50)	Gray matter volume	ChP, GHR	63[29]	48	Relatives, compared to controls, had significantly smaller left hippocampi, reflecting core genetic liability to schizophrenia.	2	2
Sumich 2002(120)	Gray matter volume	FEP	25	16	Patients had smaller bilateral hippocampal and planum temporale volumes than the comparison subjects.	2	4
van Herp 2002(49)	Gray matter volume	ChP, GHR	130[30]	53	Patients had smaller hipocampal volumes than did their full siblings, who in turn had smaller hippocampal volumes than did the healthy comparison subjects. Smaller hippocampal volumes in fetal hypoxia patients.	2	2
Ettinger 2001(121)	Gray matter volume	FEP	38	29	Thalamic volumes were smaller in patients.	1	0
Hulshoff Pol 2001(122)	Gray matter density	ChP	159	158	GM density is decreased in several distinct focal areas in ChP, with an age effect in left amygdala.	1	0
Matsumoto 2001(123)	Gray matter volume	COP	40	40	GM volume of the right superior temporal gyrus was significantly lower in patients with early onset-schizophrenia than in the controls.	1	0
Shihabuddin 2001(43)	Gray matter volume+PET	ChP	58[31]	47	Smaller size of putamen in schizophrenia as compared to controls. Glucose metabolism reduced in schizophrenia.	2	2
Vogeley 2001(48)	Cortical gyrification	ChP, GHR	12[32]	12[32]	Gyrification index on the right side was significantly higher in siblings with schizophrenia or schizoaffective disorder than in unaffected siblings.	0	0
Fannon 2000(124)	Gray matter volume	FEP	37	25	Patients had deficits in cortical GM, temporal lobe GMr, and whole brain volume and enlargement of the lateral and third ventricles.	1	0
Hirayasu 2000(125)	Gray matter volume	FEP	44	22	Patients with schizophrenia have GM reductions in the left planum temporale and bilateral Heschl gyrus GM volume reduction.	1	0
Hoff 2000(126)	Gray matter volume	FEP	50	20	No significant correlations were observed between measures of untreated illness and the severity of structural brain deficit at the baseline.	0	0
Kumra 2000(12)	Gray matter volume	COP, ChP	71[33]	106	Patients had a smaller total cerebral volume and larger lateral ventricles than healthy comparison subjects.	1	0

Sowell 2000(29)	VBM	COP	9	10	Early-onset schizophrenia had larger ventricles, predominantly in the posterior horn of the lateral ventricles, and midcallosal, posterior cingulate, caudate and thalamic abnormalities.	1	0
Hirayasu 1999(127)	Gray matter volume	FEP	41	20	Schizophrenia did not differ from comparison group in left subgenual cingulate volume. Left subgenual cingulate abnormalities are present in psychotic affective disorder and in patients with family history of affective disorder.	2	3
Rapoport 1999(128)	Gray matter volume	COP	15	34	Childhood onset schizophrenia had a distinctive disease specific GM volume decrease mostly affecting frontal and temporal regions.	1	0
Robinson 1999(129)	Gray matter volume	FEP	95	-	MRI measures were not significantly predicting time to releapse	0	0
Velakoulis 1999(130)	Gray matter volume	ChP, FEP	78	140	Chronic schizophrenic and FEP had significantly bilaterally smaller hippocampal volumes as compared with controls.	1	0
Cannon 1998(47)	Gray matter volume	ChP, GHR	135(34)	56	Structural alteration of the cerebral cortex (frontal e temporal lobes) are present in patients with schizophrenia and in some of their siblings without schizophrenia, ventricular enlargement is unique to the clinical phenotype.	2	2
Hirayasu 1998(131)	Gray matter volume	FEP	33	18	Temporal lobe abnormalities are present in schizophrenia. Low GM volume of the left posterior superior temporal gyrus is specific for schizophrenia compared with affective disorder.	2	4
Keshavan 1998(132)	Gray matter volume	FEP	25	17	Both patient groups had bilaterally reduced caudate, but not putamen, volumes, compared to the healthy subjects.	1	0
Zipursky 1998(133)	Gray matter volume	FEP	77	61	Patients had significantly smaller GM volume than normal controls. Within patients, GM volumes were positively correlated with IQ.	1	0
Frazier 1996a(65)	Gray matter volume	COP	21	33	Brain anatomic abnormalities in childhood onset schizophrenia are similar to those reported for adult population.	1	0
Frazier 1996b(66)	Gray matter volume	ChP	8	8	Caudate enlargement in patients with schizophrenia who are taking typical neuroleptics appears to be secondary to medication exposure.	0	0
Bilder 1994(134)	Gray matter volume	FEP	70	51	No volumetric differences but abnormal hemispheric asymmetry.	0	0

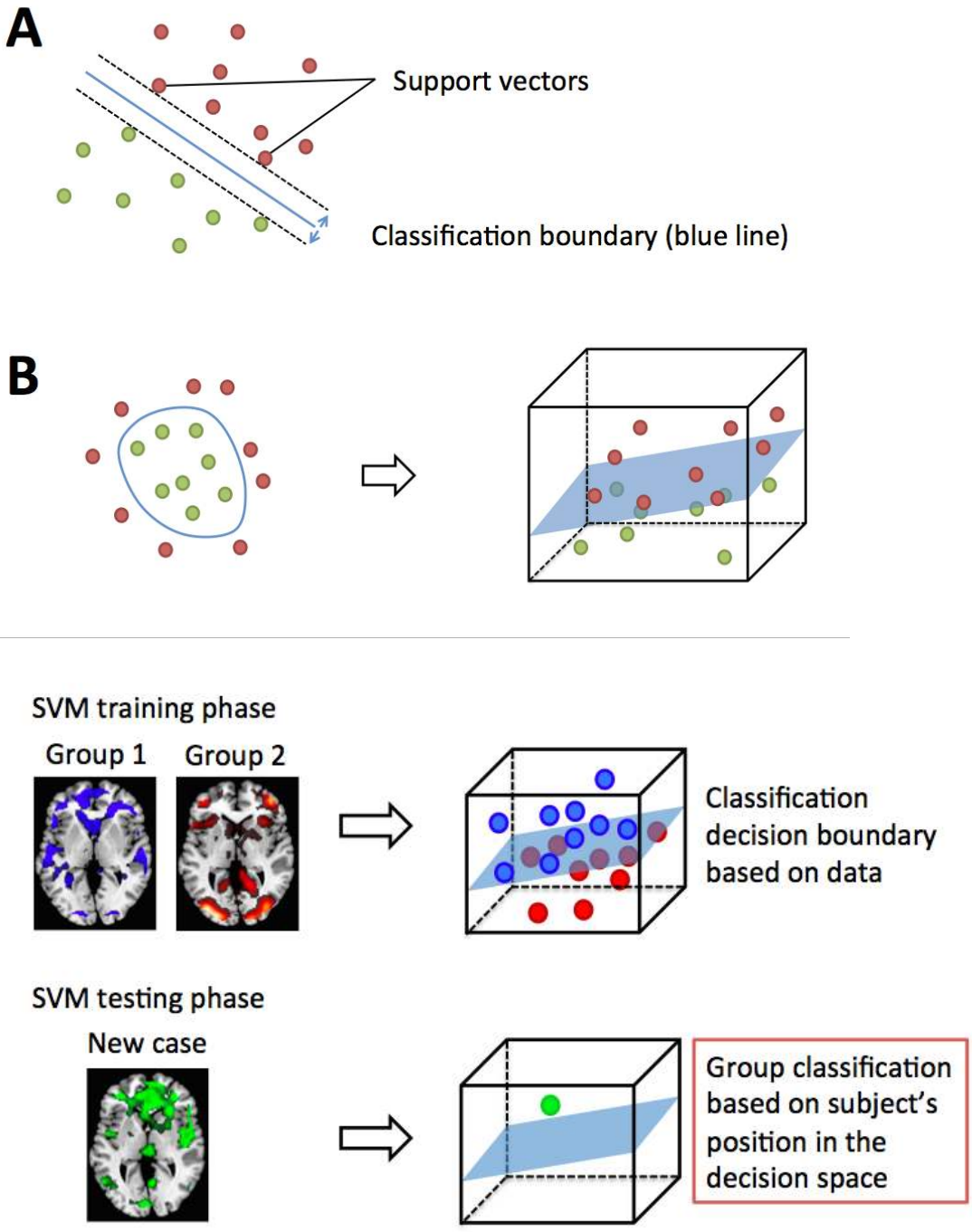
Lieberman 1993a(17)	Gray matter volume	FEP	66	-	Frontal and parietal cortex, lateral ventricle, third ventricle, medial temporal lobe structures brain pathomorphology significantly predicted time to remission.	0	0
Lieberman 1993b(25)	Gray matter volume + eye tracking + dopamine activity	FEP	66	42	Decreased GH response to apomorphine related to third ventricle enlargement. Morphologic abnormalities of the medial temporal lobe and third ventricle were associated with normal eye tracking.	1	0
Cohen 1988(24)	Qualitative reading of CT and MRI	Chronic	16	-	MRI showed superiority to CT in visualization of midline structure. None of the findings from CT or MRI explained clinical observation or led to a change in treatment.	0	0

FEP, first episode psychosis; ChP: Chronic psychosis; CHR, Clinical High Risk; CHR-T, Clinical High Risk with subsequent Transition to psychosis; CHR-NT, Clinical High Risk without subsequent transition to psychosis; GHR, Genetic High Risk; COP: Childhood-Onset Psychosis; VBM: Voxel-Based Morphometry; GM: Gray Matter; WM: White Matter; (1) CHR-T 35, CHR-NT 239; (2) patients with Major Depressive Disorder; (3) CHR 89, FEP 23; (4) patients with Bipolar Disorder; (5) patients treated with antipsychotics 23, patients untreated 22; (6) some patients from the initial sample discharged because of imaging artifacts; (7) patients with non clinical auditory verbal hallucinations 50, patients with ChP and auditory verbal hallucinations 50; (8) ChP 351, GHR, 369; (9) FEP responders 40, FEP non responders 40; (10) patients not receiving mood stabilizers 118 vs patients receiving mood stabilizers 20; (11) CHR-T 48, CHR-NT 134; (12) at 52 weeks, FEP patients with herpes virus 1 12, without herpes virus 1 6, healthy controls with herpes virus 1 7, without herpes virus 1 17; (13) patients receiving Cognitive Enhancement Therapy 30 vs patients receiving Enriched Supportive Therapy 23; (14) GHR males 12, GHR females 14, healthy controls males 12 healthy controls females 14; (15) CHR early phase 20, CHR late phase 25; (16) CHR-T 15, CHR-NT 18; (17) CHR-T 12, CHR-NT 23, FEP 23; (18) 9 monozygotic and 10 dizygotic twin pairs discordant for schizophrenia; (19) patients with schizophrenia 42, GHR of schizophrenic patients 57, patients with affective psychoses 38, GHR of patients with affective psychoses 52; (20) Chp 89, FEP 162, CHR 135, CHR-T 39; (21) COP 12, FEP 9; (22) duration of untreated psychosis less than 13 weeks 57 vs duration of untreated psychosis more than 13 weeks 48; (23) 25 patients had Schizotypal Personality Disorder; (24) (6) psychotic patients with high 34 vs low 35 Neurological Soft Signs; (25) COP 23, psychosis not otherwise specified 19; (26) patients with schizophrenia 25, GHR of schizophrenic patients 36, patients with affective psychoses 37, GHR of patients with affective psychoses 50; (27) ChP 64, GHR 46; (28) CHR-T 23 vs CHR-NT 52; (29) ChP 64, GHR 51; (29) GHR 45, ChP 18; (30) ChP 72, GHR 58, Chp with fetal hypoxia 15, ChP without fetal hypoxia 52; (31) 16 patients had Schizotypal Personality Disorder; (32) affected vs unaffected siblings of patients with schizophrenia; (33) COP 44, psychosis not otherwise specified 27; (34) ChP 75, GHR 60.

Table II

Source	Positional statement addressing the clinical relevance of structural brain imaging in psychosis
Frances(90)	"None of the exciting scientific findings has had any impact whatever on the everyday practice of clinical psychiatry"
Kapur(89)	"Profusion of statistically significant, but minimally differentiating, biological findings"
Insel(87)	"Unlike our definitions of ischemic heart disease, lymphoma, or AIDS, the DSM diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure". "It became immediately clear that we cannot design a [diagnostic] system based on biomarkers".
NICE(64)	"Structural neuroimaging, using methods called magnetic resonance imaging (MRI) or computed axial tomography (CT) scanning, is not recommended for use routinely to examine all people who have had a first episode of psychosis"
Fava(91)	"Neurosciences have exported their conceptual framework into psychiatry much more than serving as an investigative tool for addressing the questions addressed by clinical practice"
Parnas(135)	"A psychiatrist treats a person and not a brain circuit. We will therefore continue to need a classification anchored in phenomenology, and into which the brain enters in so far that the neural pathology is diagnostically or therapeutically relevant to this suffering and not because the brain de jure is of principal interest for psychiatry"

Figure 3. A) classification boundary is created based on the maximum margin space between data points. Only data points near the margin (the support vectors) affect the classification boundary, thus facilitating a good generalization of the classification boundary. B) If it is not possible to create a linear 2D classification boundary, a kernel function can be used to transform the data into higher dimensional space where classes become linearly separable. Bottom figure) schematic of SVM training and testing with neuroimaging data. In training, information from the two groups is used to make a classification algorithm based on the predictive differences of the two groups. In testing, the algorithm is applied to data from a new subject to classify them as belonging to either group. From(136)



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