Review

Forty years of structural imaging in psychosis: promises and truth

Fusar-Poli P, Meyer-Lindenberg A. Forty years of structural imaging in psychosis: promises and truth.

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 patients with psychosis published between 1976 and 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 article 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: Eighty 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.

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, as 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 through 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 through holes drilled in the skull of the patient. Pneumoencephalography became 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 were that the signal-to-noise ratio was poor, and as 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, while 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 et al. published the first brain computerized tomography study in patients with psychosis (Fig. 1) (9).

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

![Fig. 1. First modern computerized tomography of the brain in patients with psychosis (1976). Patients affected with psychosis showed enlarged ventricular size as compared to healthy controls. White dots indicate leucotomized patients with psychosis. From (9). [This figure is historical. Author append the original manuscript and have permission to reprint it].](image-url)
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 \(n = 5638\); Fig. 2), with about 200 structural imaging studies published per year over the recent 3 years. Structural neuroimaging has therefore promised much both to psychosis research and to clinical psychiatry.

The ultimate promise for MRI was to deliver reliable biomarkers to impact the clinical practice for patients with psychosis, 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 patients with psychosis by their likelihood for response to antipsychotics (15) or cognitive enhancement therapy (16)], pharmacodynamic [showing that a gray matter alterations have occurred in patients with psychosis after having received antipsychotics (17)], and surrogate (intended to substitute for another clinical efficacy endpoint). 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).

i) The principal aim of the current review was 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 patients with psychosis published between 1976 and 2015 in critically selected journals of relevance for the field.

ii) The second aim was to assess the included studies with a biomarker rating system based on quality of evidence and effect size.

iii) The third aim was 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...
Fusar-Poli et al.

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, and Brain. Literature search was conducted in Web of ScienceSM, MEDLINE®, and Scopus®. The search was extended until 23 September, 2015, and included abstracts in English language only. The electronic research adopted combinations of the above journal names with the following keywords: ‘psychosis’, ‘mri’ and ‘schizophrenia’. Journal selection and literature search were not intended to fulfill 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, and 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 patients with psychosis, and sample size of controls. Additionally, we qualitatively described the main structural findings of each article 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):

i) 0 for uncontrolled studies;

ii) 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, and type of psychotic diagnosis;

iii) 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, cutoff, and direction of effect of biomarker and response;

iv) 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;

v) 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):

i) 0 with estimates from studies with quality of evidence ≤1

ii) 1 with marginal effect (Cohen’s d < 0.2)

iii) 2 with small effect size (Cohen’s d ≤ from 0.2 to 0.5)

iv) 3 with medium effect size (Cohen’s d from 0.5 to 0.8)

v) 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 are 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 visualization of’ brain structures, all of subsequent studies employed MRI. Most of them investigated gray matter volumes in patients with psychosis as compared to healthy controls. Consequently, gray matter volume studies were the most frequent ones and were characterized by significant advancements in analytical methods and data processing techniques over time. For example, the first gray matter volume study (25) covered in our database focused on medial temporal lobe and ventricle 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 patients with psychosis (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), and 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 of 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 of psychosis (57, 58). The list of all included studies and the main structural ﬁndings are detailed in Table 1.

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 1. 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 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 aging, 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 vs. 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 aging, and disease stage signiﬁcantly moderated neuroanatomical diagnosis. In their validation study, the trained biomarker assigned 74% of the patients with bipolar disorder to the major depression group, while 83% of the patients with ﬁrst-episode psychosis and 77% of the individuals with a 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 (101).

Discussion

Forty years of structural brain imaging in psychosis: the truth

Despite the enduring efforts and the impressive number of MRI studies published in patients with schizophrenia (more than 5000; see Fig. 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 patients with psychosis as compared to healthy controls [for a detailed review on the main ﬁndings, see (102, 103)]. 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) is still valid. As recently conﬁrmed by positional statements by leading authors, imaging research has yielded no clinical advancement for patients with psychosis (see Table 2).

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 randomized clinical trials (of this biomarker vs standard care)
| Study ID       | Method                        | Psychosis group | Patients (n) | Controls (n) | Main structural finding                                                                                                                   | Biomarker Quality of evidence | Effect size |
|---------------|-------------------------------|-----------------|--------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------|
| Chung 2015    | Cortical Thickness            | CHR             | 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           |
| Koutsourelis 2015 | Machine Learning Validation | FEP, ChP       | 158          | 104          | 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     | Cortical Thickness + fMRI     | FEP, CHR        | 45           | 37           | Short-term treatment with antipsychotics associated with increased prefrontal functional activity, better cognitive control but prefrontal cortical thinning | 2                             | 3           |
| van Erp 2015  | Meta-analysis of gray matter volume | ChP            | 3028         | 2540         | 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                             | 2           |
| Crossley 2014 | Meta-analysis of connectome   | ChP             | 1925         | 2133         | Schizophrenia had significantly hub-concentrated lesion distributions, with lesions were concentrated in both fronto and temporal cortical hubs | 0                             | 0           |
| Hoptman 2014  | Cortical Thickness + fMRI     | ChP             | 33           | 31           | Impulsivity correlated with reduced cortical thickness in the right frontal pole, the medial and lateral orbitofrontal gyri and inferior frontal gyr, and the rostral anterior cingulate cortex | 1                             | 0           |
| Mathew 2014   | Hippocampal volume            | ChP             | 508          | 337          | Hippocampal volume reductions in patients with schizophrenia, schizoaffective and psychotic bipolar disorders, alterations in entorhinal cortex and parahippocampal regions in schizophrenia and schizoaffective only | 1                             | 0           |
| van Lutterveld 2014 | Cortical thickness          | ChP             | 100          | 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          |
| Meva 2013     | VBM                           | ChP, GHR        | 720          | 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 | Cortical gyrification       | FEP            | 80           | 46           | Reduction in gyrification across multiple brain regions. Non-responders to antipsychotics showed prominent hypogryria at bilateral insular, left frontal and right temporal regions when compared with responders | 1                             | 0           |
| Arango 2012   | 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      | VBM + genetic                 | ChP             | 118          | 244          | 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  | Gray matter volume + genetic  | ChP             | 305          | 198          | The results did not substantiate previously reported effects of rs1344706 on cerebral cortical GM volume. Two closely linked variants within the Prader–Willi and Angelman syndrome on chromosome 15q12 showed a genomewide significant association with average cortical thickness among patients with schizophrenia | 1                             | 0           |
| Balken 2011   | Cortical Thickness + genetic  | ChP             | 94           | 181          | The results did not substantiate previously reported effects of rs1344706 on cerebral cortical GM volume. Two closely linked variants within the Prader–Willi and Angelman syndrome on chromosome 15q12 showed a genomewide significant association with average cortical thickness among patients with schizophrenia | 1                             | 0           |
| Ho 2011       | 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 | VBM                           | CHR            | 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           |
| Study ID | Method | Psychosis group | Patients (n) | Controls (n) | Main structural finding |
|---------|--------|-----------------|--------------|--------------|-------------------------|
| Prasad 2011 (63) | VBM | FEP | 18 (12) | 24 (12) | HSV1 exposure associated with longitudinal GM loss in the posterior cingulate gyri and decline in executive functions in schizophrenia |
| Eack 2010 (16) | VBM | ChP | 30 (13) | 23 (13) | Within patients, cognitive enhancement therapy associated with GM preservation in the left hippocampus, parahippocampal gyrus, fusiform gyrus and significantly GM increase in the left amygdala |
| Gilmore 2010 (55) | VBM | GHR | 26 (14) | 26 (14) | Offspring of mothers with schizophrenia did not differ in prenatal lateral ventricle width. Male neonates at genetic risk of schizophrenia had several larger than normal brain volumes |
| Goldman 2009 (37) | Cortical Thickness | ChP | 187 (19) | 196 (19) | Widespread cortical thickness reductions in schizophrenia and widespread evidence for heritability for cortical thickness reduction throughout the brain |
| Koutsouleris 2009 (57) | Machine learning validation | CHR | 45 (15) | 33 (16) | Whole-brain neuroanatomical abnormalities classified by machine learning algorithms may serve as valuable biomarkers to distinguishing between CHS and control and from CHS developing psychosis or not (accuracy 86–96%) |
| Takahashi 2009 (64) | Gray matter volume | CHR, FEP | 58 (17) | 22 (17) | Progressive GM loss in volumes of the superior temporal subregions is associated with the onset of psychosis |
| Brans 2008 (65) | Gray matter volume | ChP, GHR | 38 (18) | 54 (18) | Significant additive genetic influences on the correlations between schizophrenia liability and progressive GM decrease in the left amygdala |
| Keller 2008 (66) | Gray matter volume | ChP | 23 (12) | 22 (12) | Depressed patients with psychosis had smaller amygdala volume relative to depressed patients without psychosis and healthy controls. Right and left hippocampus volumes were significantly smaller in psychosis patients compared with controls. |
| Koo 2008 (67) | Gray matter volume | FEP | 80 (40) | 40 (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 were observed. |
| Addington 2007 (46) | Gray matter volume | COP | 59 (19) | 165 (19) | In patients with COP, 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 |
| Kuroki 2006 (68) | Gray matter volume | FEP | 40 (23) | 23 (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 temporal GM volumes in schizophrenia but not in affective psychosis. |
| McDonald 2006 (54) | Gray matter volume | ChP, GHR | 189 (19) | 54 (19) | Schizophrenia and psychotic bipolar disorder are characterized by morphometric distinctions in ventricular and hippocampal regions. Lateral ventricular enlargement as morphometric endophenotype for schizophrenia |
| Velakoulis 2006 (56) | Gray matter volume | ChP, FEP, CHR | 386 (20) | 87 (20) | Chronic schizophrenia associated with bilateral hippocampal volume reduction. FEP schizophrenia associated with left hippocampal volume reduction. CHS subjects had normal baseline hippocampal illness. |
| Study ID           | Method       | Psychosis group | Patients (n) | Controls (n) | Main structural finding                                                                 | Biomarker Quality of evidence | Effect size |
|-------------------|--------------|-----------------|--------------|--------------|-----------------------------------------------------------------------------------------|-------------------------------|-------------|
| Lieberman 2005 (71) | 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 (72) | Gray matter volume | FEP             | 14           | 14           | Patients with new-onset schizophrenia showed smaller left angular gyrus volume than normal subjects | 0                             | 0           |
| Suzuki 2005 (73) | Gray matter volume | CHP             | 78_{26}      | 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           | Patients with schizophrenia showed less left-greater-than-right asymmetry in cortical complexity than the comparison subjects | 1                             | 0           |
| Dazzan 2004 (30) | VBM          | FEP             | 34_{26}      | 39_{26}      | In patients with FEP, higher rates of soft neurological signs are associated with a reduction of GM volume of subcortical structures | 1                             | 0           |
| Robinson 2004 (74) | Gray matter volume | FEP             | 107_{60}     | -            | In patients with FEP, more cerebral asymmetry was associated with full recovery and adequate social/vocational functioning | 0                             | 0           |
| Ettinger 2004 (75) | 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 (76) | Gray matter volume | COP             | 42_{26}      | 38           | Patients with COP 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_{30}     | -            | Genetic risk for schizophrenia was specifically associated with distributed GM volume deficits in the bilateral fronto-striato-thalamic and left lateral temporal regions | -                             | 0           |
| Prasad 2004 (77) | 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 (78)     | Gray matter volume | FEP             | 102          | -            | Within patients with FEP, untreated initial psychosis has no direct impact on GM volume and toxic neural effects | 0                             | 0           |
| Kasai 2003a (79) | 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 temporal-limbic regions are important factors in the differential and common manifestations of affective and schizophrenic psychoses | 1                             | 0           |
| Kasai 2003c (80) | 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 (81) | 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_{26}      | 52_{26}      | 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 did not develop psychosis | 2                             | n.a         |
| Szessko 2003 (82) | 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_{26}     | 54           | Fetal hypoxia predicted reduced GM trough the cortex in the patients and siblings | 1                             | 0           |
| Lee 2002 (83)    | Gray matter volume | FEP             | 42           | 24           | Schizophrenia associated with smaller fusiform gyrus GM volume compared with controls and patients with affective psychosis | 1                             | 0           |
| Study ID          | Method                        | Psychosis group | Patients (n) | Controls (n) | Main structural finding                                                                                                                                                                                                 | Biomarker Quality of evidence | Effect size |
|-------------------|-------------------------------|-----------------|--------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------|
| 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±28        | 48           | Relatives, compared to controls, had significantly smaller left hippocampi, reflecting core genetic liability to schizophrenia                                                                                     | 2                             | 2           |
| Sumich 2002 (84)   | 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±15      | 53           | Patients had smaller hippocampal 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 (85) | Gray matter volume            | FEP             | 38           | 23           | Thalamic volumes were smaller in patients                                                                                                                                                                                 | 1                             | 0           |
| Hulshoff Pol 2001 (86) | 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 (87) | 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 controls                                                                                   | 1                             | 0           |
| Shihabuddin 2001 (43) | Gray matter volume + PET      | ChP             | 58±15        | 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±20        | 12±20        | Gyrification index on the right side was significantly higher in siblings with schizophrenia or schizo-affective disorder than in unaffected siblings                                                                 | 0                             | 0           |
| Fannon 2000 (88)   | 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 (89) | 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 (90)     | 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           |
| Kumia 2000 (12)    | Gray matter volume            | COP, ChP        | 71±18        | 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 midcaudal, posterior cingulate, caudate and thalamic abnormalities                                                                 | 1                             | 0           |
| Hirayasu 1999 (91) | 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           |
| Rapoort 1999 (92)  | 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 (93) | Gray matter volume            | FEP             | 95           | -            | MRI measures were not significantly predicting time to relapse                                                                                                                                                             | 0                             | 0           |
| Velakoulis 1999 (94) | Gray matter volume           | ChP, FEP        | 78           | 140          | Chronic schizophrenia and FEP had significantly bilaterally smaller hippocampal volumes as compared with controls                                                                                                                                                       | 1                             | 0           |
| Cannon 1998 (47)   | Gray matter volume            | ChP, GHR        | 135±15       | 56           | Structural alteration of the cerebral cortex (frontal e temporal lobes) are present in patients with schizophrenia and in some of the siblings without schizophrenia, ventricular enlargement is unique to the clinical phenotype | 2                             | 2           |
| Hirayasu 1998 (95) | 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           |
Table 1. (Continued)

| Study ID | Method | Psychosis group | Patients (n) | Controls (n) | Main structural finding | Biomarker Quality of evidence | Effect size |
|----------|--------|-----------------|--------------|--------------|-------------------------|-------------------------------|-------------|
| Keshavan 1998 (96) | 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 (97) | 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 (98) | Gray matter volume | COP | 21 | 33 | Brain anatomical abnormalities in childhood-onset schizophrenia are similar to those reported for adult population | 1 | 0 |
| Frazier 1996b (99) | 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 (100) | 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 | 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 23; (12) at 52 weeks, FEP patients with herpesvirus 1 12, without herpesvirus 1 7, without herpesvirus 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 patients with schizophrenia 57, patients with affective psychoses 38, GHR of patients with affective psychoses 52; (20) FEP 89, FEP 162, CHR-T 48, CHR-NT 23; (21) COP 12, 9 weeks of untreated psychosis less than 13 weeks 57 vs duration of untreated psychosis more than 13 weeks 48; (22) 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 patients with schizophrenia 36, patients with affective psychoses 37, GHR of patients with affective psychoses 50; (27) FEP 64, GHR 46, (28) CHR-T 23 vs CHR-NT 52; (29) FEP 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.
Clinical utility of structural imaging 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 (98, 99). 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 a risk of psychosis in antipsychotic-naïve participants with no impact of illness chronicity or medication (103). Structural imaging studies in subjects at clinical high risk of 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 (103). Furthermore, gray matter alterations in the temporal regions directly related to severity of psychotic symptoms (103). 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 of psychosis is not heterogeneous as it includes different clinical subgroups (111, 112).

Additional modulators of brain structure in psychosis may include age (113), gender (114), type of psychotic disorder [e.g., schizophrenia spectrum disorders vs affective psychotic disorders (115)], smoking (116), ethnicity (117), and substance abuse (118), 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 (119). There is specific evidence that these biases may affect both region-of-interest (120) and voxel-based morphometry (VBM) (121) structural imaging studies of patients with psychosis.

Reporting biases may specifically affect small structural imaging studies and even meta-analyses.
Fusar-Poli et al.

...with few studies, inflating the number of significant findings (121). Consequently, there has been a trend toward larger structural imaging studies of patients with psychosis over time. This trend is observed in our database with an average sample size of 53 patients with psychosis for the MRI studies conducted before 2000, 57 patients for the studies conducted between 2000 and 2005, 97 patients for studies published between 2005 and 2010, and 179 patients for studies conducted over the 2015–2010 period, with two meta-analytical outliers conducted in about 2000 patients with psychosis (41, 59). An independent review confirmed our findings by concluding that there is limited evidence supporting gray or white matter changes in schizophrenia, which has previously been obscured by a large volume of conflicting, lower quality evidence (122). However, reporting biases are by no means specific or confined to psychiatric conditions (121) 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 (119), which could improve the quality of structural imaging reports in the future.

Machine learning methods: myth or promising avenue?

As 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 (123)]. Machine learning methods may ultimately address the complexity of psychiatric disorders capitalizing on the abilities of machines to tease out subtle statistical regularities from massive datasets (123). Because of this, machine learning methods are fast becoming the mainstream analytical avenue for modern neuroimaging studies of psychiatric disorders (see Fig. 3 for a summary of its method).

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’ (125). However, ‘nowadays we are far away from using automatic image-based classification techniques to make a diagnosis’ (125), 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 (126) 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 (126). This is a fundamental limitation, as without mechanistic interpretability a diagnostic procedure will be ill-placed to promote a change in disease concepts or guide the development of future therapies (126).

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 Creutzfeld–Jakob disease (127). 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/predictive AD dementia with evidence of the AD pathophysiological process) (128), mild cognitive impairment (MCI) due to Alzheimer’s (129), and preclinical (presymptomatic) Alzheimer’s (130). 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 (128). However, the field is more advanced as compared to psychosis because 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’ (128). These
biomarkers are well defined and include structural measures such as atrophy on structural MRI in medial, basal, and lateral temporal lobe and medial parietal cortex (128). Similarly to the prodromal phase of psychosis, the high-risk MCI diagnosis can be formulated ‘without access to advanced imaging techniques’ (129). However, a separate set of research criteria is already available, which includes a number of biomarkers (131) reflecting signs of neuronal injury (129). 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) (129). 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 anatomical 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 (130).

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’ (106). 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 (132). 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 seeking MRI biomarkers that can

Fig. 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 (124).
‘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 (105). However, this approach may be ‘over-promising about the future blithely ignored the sobering lessons of the past (104)’ 40 years of imaging research. The claim that this approach is substantially different from those endorsed in the past decades, which were unable to produce significant biomarkers, is not supported by preliminary findings (108). On the other hand, it stands to reason that mapping data such as structural neuroimaging onto criteria or scales closer to the underlying pathologies 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 (133). 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 (134, 135). Recent work by the psychiatric GWAS consortium and the ENIGMA consortium further supports this by indicating that polygenic 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 (136). 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 (e.g., 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.

To conclude, 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, and 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 talking to the patients, use observation, description and classification, test explanatory hypotheses, and formulate clinical decisions in the absence of such structural biomarkers.

Financial support
None.

Declaration of interest
None.

References
1. Kilgore EJ, Elster AD. Walter Dandy and the history of ventriculography. Radiology 1995;194:657–660.
Clinical utility of structural imaging in psychosis

and a proposal for a criterion-based, quantitative, multi-dimensional hierarchical levels of evidence schema for evaluating the status of biomarkers as surrogate endpoints. Stat Methods Med Res 2008;17:303–340.

22. Michelli A, Prata D, Kieford C, Kapur S. Predicting clinical response in people at ultra-high risk of psychosis: a systematic and quantitative review. Drug Discovery Today 2015;20:924–927.

24. Cohen BM, Buonanno F, Keck PE Jr, Pinkleton SP, Benjamin FM. Comparison of MRI and CT scans in a group of psychiatric patients. Am J Psychiatry 1988;145:1084–1088.

25. Lieberman JA, Judd D, Alvir JM et al. Brain morphology, dopamine, and eye-tracking abnormalities in first-episode schizophrenia. Prevalence and clinical correlates. Arch Gen Psychiatry 1993;50:357–368.

26. van Erp TGM, Hbar DP, Rasmussen JM et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry 2016;21:585. doi:10.1038/mp.2015.118.

27. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. NeuroImage 2000;11:805–821.

28. Maguire EA, Gadman DG, Johnsrude IS et al. Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci USA 2000;97:4398–4403.

29. Sowell ER, Levitt J, Thompson PM et al. Brain abnormalities in early-onset schizophrenia spectrum disorder observed with statistical parametric mapping of structural magnetic resonance images. Am J Psychiatry 2000;157:1475–1484.

30. Dazzan P, Morgan K, Orr K et al. The structural brain correlates of neurocognitive soft signs in AESOP first-episode psychoses study. Brain 2004;127:143–153.

31. Michelli A, Reicher-Rossler A, Meisenzahl EM et al. Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study. Arch Gen Psychiatry 2011;68:489–495.

32. Tan HY, Chen AG, Chen Q et al. Epistatic interactions of AKT1 on human medial temporal lobe biology and pharmacogenetic implications. Mol Psychiatry 2012;17:1007–1016.

33. Ileva EI, Bidesh AS, Keshavan MS et al. Gray matter volume as an intermediate phenotype for psychosis: hippoco-limbic-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry 2013;170:1285–1296.

34. Monuki ES, Walsh CA. Mechanisms of cerebral cortical patterning in mice and humans. Nat Neurosci 2001;4 (Suppl):1199–1206.

35. Wiberg LA, Warren SK, Levitt J et al. An in vivo MRI study of prefrontal cortical complexity in first-episode psychosis. Am J Psychiatry 2005;162:65–70.

36. Vidal CN, Raspport JL, Hayashi KM et al. Dynamically spreading frontal and cingulate deficits mapped in adolescents with schizophrenia. Arch Gen Psychiatry 2006;63:25–34.

37. Goldman AL, Pezawas L, Mattay VS et al. Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch Gen Psychiatry 2009;66:467–477.

38. Barks TE, Blois CS, Rodd JC et al. Association of genetic variants on 1Sq12 with cortical thickness and cognition in schizophrenia. Arch Gen Psychiatry 2011;68:781–790.

39. van Lutterveld R, van den Heuvel MP, Diederik KM et al. Cortical thickness in individuals with non-clinical
and clinical psychotic symptoms. Brain 2014;137:2664–2669.
40. HOFFMAN MJ, ANTONIU S D, MAURO CJ, PARKER EM, JAVITT DC. Combined training, functional connectivity, and mood-related impulsivity in schizophrenia: relationship to aggressive attitudes and behavior. Am J Psychiatry 2014;171:939–948.
41. LESH TA, TANASE C, GEIN BR et al. A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. JAMA Psychiatry 2015;72:226–234.
42. CHUNG Y, JACOBSON A, Ht G et al. Prodromal symptom severity predicts accelerated gray matter reduction and third ventricle expansion among clinically high risk youth developing psychotic disorders. Mol Neuropsychiatry 2015;1:13–22.
43. SHIHABUDDIN L, BUSCHBAUM MS, HAZLETT EA et al. Striatal size and relative glucose metabolic rate in schizotypal personality disorder and schizophrenia. Arch Gen Psychiatry 2001;58:877–884.
44. McCARLEY RW, SALISBURY DF, HIRAYASU Y et al. Association between smaller left posterior superior temporal gyrus volume on magnetic resonance imaging and smaller left temporal P300 amplitude in first-episode schizophrenia. Arch Gen Psychiatry 2002;59:321–331.
45. WASSINK TH, EPFING EA, RUDD D et al. Influence of ZNF804a on brain structure volumes and symptom severity in individuals with schizophrenia. Arch Gen Psychiatry 2012;69:885–892.
46. ADDINGTON AM, GORMICK MC, SHAW P et al. Neuregulin 1 (8p12) and childhood-onset schizophrenia: susceptibility haplotypes for diagnosis and brain developmental trajectories. Mol Psychiatry 2007;12:195–205.
47. CANNON TD, van ERP TG, HUTTUNEN M et al. Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry 1998;55:1084–1091.
48. VOGELEY K, TEPEST R, PFEIFFER U et al. Right frontal hypergria differentiation in affected and unaffected siblings from families multiply affected with schizophrenia: a morphometric mri study. Am J Psychiatry 2001;158:494–496.
49. van ERP TG, SALEH PA, ROSSO IM et al. Contributions of genetic risk and fetal hypoxia to hippocampal volume in patients with schizophrenia or schizoaffective disorder, their unaffected siblings, and healthy unrelated volunteers. Am J Psychiatry 2002;159:1514–1520.
50. SEDMAN LJ, FARAOINE SV, GOLDSTEIN JM et al. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. Arch Gen Psychiatry 2002;59:839–849.
51. CANNON TD, van ERP TG, ROSSO IM et al. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry 2002;59:35–41.
52. van ERP TG, SALEH PA, HUTTUNEN M et al. Hippocampal volumes in schizophrenic twins. Arch Gen Psychiatry 2004;61:346–353.
53. MCDONALD C, BULLMORE ET, SHAM PC et al. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. Arch Gen Psychiatry 2004;61:974–984.
54. MCDONALD C, MARSHALL N, SHAM PC et al. Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives. Am J Psychiatry 2006;163:478–487.
55. GILMORE JH, KANG C, EVANS DD et al. Prenatal and neonatal brain structure and white matter maturation in children at high risk for schizophrenia. Am J Psychiatry 2010;167:1083–1091.
56. VELAKULIL D, WOOD SJ, WONG MT et al. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Arch Gen Psychiatry 2006;63:139–149.
57. KOUTSOULIRES N, MEISENZAHL EM, DAVATZIKOS C et al. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. Arch Gen Psychiatry 2009;66:700–712.
58. KOUTSOULIRES N, MEISENZAHL EM, BOREWARDT S et al. Individualized differential diagnosis of schizophrenia and mood disorders using neuroanatomical biomarkers. Brain 2015;138:2059–2073.
59. CROSSTLE NA, MICHIELLA A, SCOTT J et al. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain 2015;137:2382–2395.
60. MATHIE1 I, GARDIN T, TANDON N et al. Temporal lobe structures and hippocampal subfields in psychotic disorders: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. JAMA Psychiatry 2014;71:769–777.
61. ARANGO C, RAFADO-CASTRO M, REIG S et al. Progressive brain changes in children and adolescents with first-episode psychosis. Arch Gen Psychiatry 2012;69:16–26.
62. HO BC, ANDREASEN NC, ZIEBEL S, PIERSON R, MAGGOTTA V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 2011;68:128–137.
63. PRASAD KM, EACK SM, GORADA D et al. Progressive gray matter loss and changes in cognitive functioning associated with exposure to herpes simplex virus 1 in schizophrenia: a longitudinal study. Am J Psychiatry 2011;168:822–830.
64. TAKAHSI T, WOOD SJ, YUNG AR et al. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch Gen Psychiatry 2009;66:366–376.
65. BRANS RG, van HAREN NE, van BAAL GC, SCHNACK HG, KAM RS, HULSBROCH POLHE. Heritability of changes in brain volume over time in twin pairs discordant for schizophrenia. Arch Gen Psychiatry 2008;65:1259–1268.
66. KELLER J, SHEN L, GOMEZ RG et al. Hippocampal and amygdalar volumes in psychotic and nonpsychotic unipolar depression. Am J Psychiatry 2008;165:872–880.
67. KOO MS, LEVITT JJ, SALISBURY DF, NAKAMURA M, SHENTON ME, McCARLEY RW. A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. Arch Gen Psychiatry 2008;65:746–760.
68. KURORI N, SHENTON ME, SALISBURY DF et al. Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. Am J Psychiatry 2006;163:2103–2110.
69. CORYELL W, NORDHEUS D, DREVETS W, WILSON T, ANDREASEN NC. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. Am J Psychiatry 2005;162:1706–1712.
70. HO BC, ALCATEA D, MOLA C, ANDREASEN NC. Hippocampus volume and treatment delays in first-episode schizophrenia. Am J Psychiatry 2005;162:1527–1529.
Clinical utility of structural imaging in psychosis

71. Lieberman JA, Tolleson GD, Charles C et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 2005;62:361–370.

72. Neubert JD, Salisbury DF, Leventhal JY, David EA, McCarley RW, Shenton ME. Reduced left angular gyrus volume in first-episode schizophrenia. Am J Psychiatry 2005;162:1539–1541.

73. Suzuki M, Zhou SY, Takahashi T et al. Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. Brain 2005;128:2109–2122.

74. Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry 2004;161:473–479.

75. Ettinger U, Kumari V, Chitnis XA, et al. Volumetric neuroanatomical correlates of antiscadace eye movements in first-episode psychosis. Am J Psychiatry 2004;161:1918–1921.

76. Gogtay N, Sporn A, Claesen LS et al. Comparison of progressive cortical gray matter loss in children-onset schizophrenia with that in childhood-onset atypical psychoses. Arch Gen Psychiatry 2004;61:17–22.

77. Prasad KM, Patel AR, Mehdiasan S, Sweeney J, Keshtavan MS. The entorhinal cortex in first-episode psychotic disorders: a structural magnetic resonance imaging study. Am J Psychiatry 2004;161:1612–1619.

78. Ho BC, Alicata D, Ward J et al. Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. Am J Psychiatry 2003;160:142–148.

79. Kasai K, Shenton ME, Salisbury DF et al. Progressive decrease of left temporal lobe MRI volumes in patients with first-episode schizophrenia. Am J Psychiatry 2003;160:156–164.

80. Kasai K, Shenton ME, Salisbury DF et al. Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 2003;60:766–775.

81. Keshtavan MS, Sanders RD, Sweeney JA et al. Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. Am J Psychiatry 2003;160:1298–1304.

82. Szaszko PR, Goldberg E, Gunduz-Bruce H et al. Smaller anterior hippocampal formation volume in antipsychotic-naive patients with first-episode schizophrenia. Am J Psychiatry 2003;160:2190–2197.

83. Lee CU, Shenton ME, Salisbury DF et al. Fusiform gyrus volume reduction in first-episode schizophrenia: a magnetic resonance imaging study. Arch Gen Psychiatry 2002;59:775–781.

84. Sumich A, Chitnis XA, Fannon DG et al. Temporal lobe abnormalities in first-episode psychosis. Am J Psychiatry 2002;159:1232–1235.

85. Ettinger U, Chitnis XA, Kumari V, et al. Magnetic resonance imaging of the thalami in first-episode psychosis. Am J Psychiatry 2001;158:116–118.

86. Hulshoff PW, H., Schonke HG, Mandl RC et al. Focal gray matter density changes in schizophrenia. Arch Gen Psychiatry 2001;58:1118–1125.

87. Matsuzato H, Simons A, Williams S et al. Superior temporal gyrus abnormalities in early-onset schizophrenia: similarities and differences with adult-onset schizophrenia. Am J Psychiatry 2001;158:1299–1304.

88. Fannon D, Chitnis X, Doku V et al. Features of structural brain abnormality detected in first-episode psychosis. Am J Psychiatry 2000;157:1829–1834.

89. Hiraayas Y, McCarley RW, Salisbury DF et al. Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. Arch Gen Psychiatry 2000;57:692–699.

90. Hoff AL, Sakuma M, Razi K, Heyderbrand G, Csernansky JG, Delisi LE. Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. Am J Psychiatry 2000;157:1824–1828.

91. Hiraayas Y, Shenton ME, Salisbury DF et al. Subgenual cingulate cortex volume in first-episode psychosis. Am J Psychiatry 1999;156:1091–1093.

92. Rapoport JL, Greed JN, Blumenthal J et al. Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 1999;56:649–654.

93. Robinson D, Woerner MG, Alvir JM et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999;56:241–247.

94. Velakoulis D, Pantesco C, McGorry PD et al. Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. Arch Gen Psychiatry 1999;56:133–141.

95. Hiraayas Y, Shenton ME, Salisbury DF et al. Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. Am J Psychiatry 1998;155:1384–1391.

96. Keshtavan MS, Rosenberg D, Sweeney JA, Pettegree JW. Decreased caudate volume in neuroleptic-naive psychotic patients. Am J Psychiatry 1998;155:774–779.

97. Zipursky RB, Lambe EK, Kapur S, McKiels DJ. Cerebral gray matter volume deficits in first episode psychosis. Arch Gen Psychiatry 1998;55:540–546.

98. Frazier JA, Greed JN, Hamberger SD et al. Brain anatomical magnetic resonance imaging in childhood-onset schizophrenia. Arch Gen Psychiatry 1996;53:617–624.

99. Frazier JA, Greed JN, Kayser D et al. Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. Am J Psychiatry 1996;153:564–566.

100. Bilder RM, Wu H, Bogerts B et al. Absence of regional hemispheric volume asymmetries in first-episode schizophrenia. Am J Psychiatry 1994;151:1437–1447.

101. Menafro MR, Stothart G, Flint J. Bias in genetic association studies and impact factor. Mol Psychiatry 2009;14:119–120.

102. Haaima SV, Van Haren N, Cahn W, Koolschijn PC, Hollshoff PW, HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull 2013;39:1129–1138.

103. Fusar-Poli P, Radeva J, McGuire P, Borgwardt S. Neuroanatomical maps of psychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies. Schizophr Bull 2012;38:1297–1307.

104. Frances A. RDoC is necessary, but very oversold. World Psychiatry 2014;13:47–49.

105. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol Psychiatry 2012;17:1174–1179.

106. Insel T. Transforming Diagnosis. [Web] NIMH Director’s Blog: NIMH; 2013 [updated 2013; cited 2015 Oct 12]. Available from: http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml.
107. Excellence Nifhac. Structural neuroimaging in first-episode psychosis. 2008 Contract No.: Document Number.

108. Fava GA. Road to nowhere. World Psychiatry 2014;13:49–50.

109. Parnas J. The RDoC program: psychiatry without psyche? World Psychiatry 2014;13:46–47.

110. Sommer IE, de Kort GA, Meijering AL et al. How frequent are radiological abnormalities in patients with psychosis? A review of 1379 MRI scans. Schizophr Bull 2013;39:815–819.

111. Fusar-Poli P, Cappuccetti M, Borgwardt S et al. Heterogeneity of risk for psychosis within subjects at clinical high risk: meta-analytical stratification. JAMA Psychiatry 2016;73:113–120.

112. Fusar-Poli P, Cappuccetti M, Bosoldi I et al. A momentary lapse of reason: meta-analytical prognosis of brief psychotic episodes. JAMA Psychiatry 2016;73:211–220.

113. Pons-Camacho L, Del Rey-Velas A, Janssen J et al. Age at first episode modulates diagnosis-related structural brain abnormalities in psychosis. Schizophr Bull 2016;42:344–357.

114. Fricker JA, Hodge SM, Breeze JL et al. Diagnostic and sex effects on limbic volumes in early-onset bipolar disorder and schizophrenia. Schizophr Bull 2008;34:37–46.

115. de Peri L, Crescini A, Di Sante G, Fusar-Poli P, Sacchetto E, Vita A. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. Curr Pharm Des 2012;18:486–494.

116. Johrjessen KN, Sakzewski I, Mørch-Johnsen L et al. Cigarette smoking is associated with thinner cingulate and insular cortices in patients with severe mental illness. J Psychiatry Neurosci 2015;40:241–249.

117. Morgan KD, Dazzan P, Morgan C et al. Differing patterns of brain structural abnormalities between black and white patients with their first episode of psychosis. Psychol Med 2010;40:1137–1147.

118. Rapp C, Walter A, Studerius E et al. Cannabis use and brain structural alterations of the cingulate cortex in early psychosis. Psychiatry Res 2013;214:102–108.

119. Ioannidis JP, Munafò MR, Fusar-Poli P, Noruez BA, David SP. Publication and other reporting biases in cognitive sciences: detection, prevalence, and prevention. Trends in Cognitive Sciences. 2014;18:235–241.

120. Ioannidis JP. Excess significance bias in the literature on brain volume abnormalities. Arch Gen Psychiatry 2011;68:773–780.

121. Fusar-Poli P, Radua J, Frascaroli M et al. Evidence of reporting biases in voxel-based morphometry (VBM) studies of psychiatric and neurological disorders. Hum Brain Mapp 2014;35:3052–3065.

122. Shepherd AM, Laurens KR, Matheson SL, Carr VJ, Green MJ. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci Biobehav Rev 2012;36:1342–1356.

123. Jordan MJ, Mitchell TM. Machine learning: trends, perspectives, and prospects. Science 2015;349:255–260.

124. Gifford G, Crossley N, Fusar-Poli P et al. Using neuroimaging to help predict the onset of psychosis. Neuroimage 2016. doi:10.1016/j.neuroimage.2016.03.075. [Epub ahead of print].

125. Veronese E, Castellani U, Peruzzo D, Bellani M, Brambilla P. Machine learning approaches: from theory to application in schizophrenia. Comput Math Methods Med 2013;2013:867924.

126. Brodersen KH, Deserno L, Slagenaunha F et al. Dissecting psychiatric spectrum disorders by generative embedding. Neuroimage Clin 2014;4:98–111.

127. Frisoni GB, Fox NC, Jack CR Jr, Scheitens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nature reviews. Neurology 2010;6:67–77.

128. McKhann GM, Knopman DS, Chertkow H et al. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:263–269.

129. Albert MS, Dekosky ST, Dickson D et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:270–279.

130. Sperling RA, Aisen PS, Beckett LA et al. Toward defining the preclinical stages of Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:280–292.

131. Lang A, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA 2014;312:2551–2561.

132. Goodkind M, Eickhoff SB, Oathes DJ et al. Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 2015;72:305–315.

133. Miller KL, Tannen CK. Methods and considerations for longitudinal structural brain imaging analysis across development. Dev Cogn Neurosci 2014;9:172–190.

134. Munafò MR, Brown SM, Harriri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. Biol Psychiatry 2008;63:852–857.

135. Mier D, Kirsch P, Meyer-Lindenberg A. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. Mol Psychiatry 2010;15:918–927.

136. Franke B, Stein JL, Ripke S et al. Genetic influences on schizophrenia and subcortical brain volumes: large-scale proof of concept. Nat Neurosci 2016;19:420–431.