Neuroimaging of Schizophrenia and Other Primary Psychotic Disorders

Achievements and Perspectives

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Preface

The project of a book on the state of the art of neuroimaging in schizophrenia and other primary psychotic disorders matured within the activities of the Section on Neuroimaging in Psychiatry of the World Psychiatric Association.

Deciding the focus was not an easy task, in the light of the lively debate on the limitations of current diagnostic categories in psychiatry. Should we adopt a comprehensive approach (e.g., across all psychiatric disorders) or a specific focus (e.g., schizophrenia)? Should each chapter deal with diagnostic categories or psychopathological dimensions? Should we move from brain circuits and review their involvement in different disorders? Most of us agreed on the opportunity to focus on primary psychotic disorders in a transnosographic perspective (e.g., looking at psychopathological dimensions, reviewing data on at-risk mental states). We also agreed on the need to review both structural and functional, as well as neurochemical and multimodal, neuroimaging studies.

The nine chapters provide an in-depth coverage of current achievements and limitations of neuroimaging research in psychotic disorders. Throughout the book, the authors highlight that abnormalities of brain structure and function do not reflect boundaries of current diagnostic categories but are relevant to important clinical aspects, such as the severity of the clinical picture, the persistence of the symptoms over time, and the overall response to treatment.

The first chapter reviews data supporting the claim that we are close to identifying biomarkers for diagnosis, prediction of conversion from at-risk states to psychotic disorders, and prediction of treatment response, as well as of functional outcome or disease progression.

The second chapter reviews research aimed at mapping individual symptoms and psychopathological domains on specific neural systems. It summarizes the contribution provided by research findings to the understanding of pathophysiological underpinnings of psychopathological dimensions of psychotic disorders, highlights gaps in current knowledge, and proposes directions for future research efforts.

The third chapter covers research findings on neurotransmitter alterations and their relevance to cognitive dysfunctions and negative symptoms. It reviews PET and spectroscopy data on dopaminergic, gabaergic, and glutamatergic abnormalities and discusses models of dysfunctional network interactions in schizophrenia.

The fourth chapter reviews data relevant to the link between genetic and neuroimaging research and highlights recent progress in the field of "imaging genetics."

It discusses the potential contribution of the research approach to the identification of intermediate phenotypes and concludes with the hope that future use of these study designs will ultimately provide an important tool for the clinic and the practice of precision medicine in patients with schizophrenia.

The fifth chapter reviews contributions from MRI investigations to the identification of heterogeneous patterns of progression of brain changes over the longitudinal course of schizophrenia after the initial onset of symptoms, their relevance to the outcome of the illness, and the relationship with treatment.

The sixth chapter provides a comprehensive coverage of neuroimaging research in at-risk mental states. It reviews diagnostic methods, neuroimaging techniques and paradigms, structural, functional, and neurochemical findings, highlights methodological limitations, and discusses the risks of characterizing mental disorders purely by their biological inherency.

The seventh chapter deals with the impact of antipsychotic drugs on brain structure and function and contributes to the lively debate on the role played by antipsychotic treatment on the progressive trajectory of brain abnormalities. It also reviews current evidence relevant to changes of positive and negative symptoms (both primary and secondary) under treatment, with respect to brain structural, functional, and neurochemical correlates.

The eighth chapter summarizes very recent neuroimaging findings across schizophrenia spectrum disorders in order to provide an insight into the current trends for research in this area and highlights the progress in our understanding of this disorder spectrum.

In the light of the reviewed literature and of the limitations of current diagnostic categories, the ninth chapter addresses the potential of neuroimaging research for translation into psychiatric clinical practice and suggests the need for further investigations with multicenter and multimodal imaging design, integrating clinical measures and imaging data, applying new multivariate approaches, such as different combined machine learning algorithms, to consolidate promising findings and finally lead to the translation into clinical practice.

The book represents a unique opportunity for researchers, clinicians, and trainees in psychiatry to improve their knowledge on neuroimaging findings from different techniques, in the frame of a transnosographic approach that takes into account psychopathological dimensions common to the examined group of disorders, different features of at-risk states, and treatment implications and also provides different pathophysiological perspectives. The clear and informative update of neuroimaging research on primary psychotic disorders and its potential for translation into psychiatric clinical practice may guide future research in this area aimed at reducing the gap between current clinical practice and precision psychiatry.

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Neuroimaging: Diagnostic Boundaries and Biomarkers

1

Silvana Galderisi, Giulia Maria Giordano, and Lynn E. DeLisi

1.1 Introduction

Neuroimaging research has shown that the abnormalities of brain structure and function, as well as the receptor pharmacology, are associated with psychiatric disorders but do not reflect boundaries of current diagnostic categories. Though this has disappointed scientists and clinicians searching for biomarkers supporting current diagnostic categories, neuroimaging findings are being reconsidered in the light of recent proposals for research aimed at identifying at-risk patients with an early diagnosis, predicting the treatment response and reconceptualizing classification systems in psychiatry (e.g., the Research Domain Criteria, https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml).

The present chapter will focus on the use of neuroimaging to identify biomarkers for the wide spectrum of psychotic disorders, with a focus on schizophrenia and other primary psychotic disorders. The state of the art of neuroimaging techniques as diagnostic tools will be depicted; main pitfalls and innovative perspectives will be highlighted. In particular, main contributions provided by neuroimaging techniques in the characterization of schizophrenia and other primary psychotic disorders will be examined for the purposes of diagnosis, prediction of outcome, treatment response, and onset of psychosis in subjects with "at-risk mental state." Brain abnormalities that might contribute to separate subjects with schizophrenia from healthy controls are observed even before the disease onset and are predictive of illness course [1, 2]. The future of neuroimaging in psychiatry will depend on the possibility to move from the evidence of differences between groups to measures at the individual level, meaningful in the clinical

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practice, supporting diagnosis, and enabling prediction of illness course and response to treatment.

1.2 Biomarkers: Definition and Application in Psychiatry

1.2.1 Definition

Different medical disciplines have adopted biomarkers in order to measure specific characteristics, provide a diagnosis, and predict treatment response or outcome of a disease. A variety of terms, such as biological marker, biomarker, surrogate marker, surrogate endpoint, and intermediate endpoint, can be found in the literature. In order to standardize the relevant terminology, the biomarkers definitions working group on "biomarkers and surrogate endpoints preferred definitions and conceptual framework" [3], convened by the National Institutes of Health, and proposed preferred definitions for terms such as biomarker, clinical endpoint, and surrogate endpoint.

A biological marker (biomarker) is 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" [3]. For instance, in the clinical medical practice, blood glucose level represents the cornerstone of diagnosis and management of diabetes. Therefore, a biomarker can be used as a measure of normal or abnormal biological functions or as a measure of treatment response. For these purposes, different biological parameters, such as receptor structure, electrophysiological correlates, and imaging-related measures, may represent a biomarker.

Biomarkers have a great importance in preclinical studies (such as in vitro studies conducted on tissue samples or *in vivo* studies conducted in animal models) and in the early phase of clinical trials. Furthermore, in clinical practice they can be used for (1) disease staging; (2) diagnosis, i.e., identification of patients with a specific disease or an abnormal condition; (3) prognosis, i.e., to categorize patients according to the risk for disease progression; and (4) prediction of response to treatment.

A *clinical endpoint* represents a clinical measure of disease characteristics used in clinical trials to assess the ratio benefits/risks related to a therapeutic intervention. A *surrogate endpoint* is defined as a biomarker that might substitute for a clinical endpoint in order to predict the efficacy of therapeutic intervention trial. The use of a biomarker as a surrogate endpoint is based on the *accuracy* (the correlation between clinical endpoint and surrogate endpoint) and *reproducibility* values. In drug development, approval by the US Food and Drug Administration (FDA) is based specifically on the effects that the drug produces on a specific surrogate endpoint or on a clinical endpoint, other than survival or irreversible morbidity [4].

Validation and *qualification* processes are crucial aspects to assess the utility of a surrogate endpoint (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf). The *validation* process refers to the performance of a surrogate endpoint in terms of sensitivity, specificity, and

reliability. The *qualification* process is important to determine the ability of a biomarker in predicting the clinical outcome in order to verify its relevance to drug development.

In general, in the medical practice, the validity of a biomarker is verified through the evaluation of its sensitivity, specificity, positive predictive value, and negative predictive value [5].

The sensitivity and specificity refer to the ability of a biomarker to determinate, respectively, the cases of patients with disease or the healthy cases correctly. The *positive predictive value* is the probability that subjects with a positive test truly have the disease, while the *negative predictive value* refers to the probability that subjects with a negative test truly do not have the disease.

The Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease [5, 6] suggested that a perfect diagnostic biomarker should identify only true positive cases and no false-negative one in order to reflect accurately the prevalence of the disease of interest. Furthermore, it should have sensitivity and specificity no less than 80% and a positive predictive value around 90%. Moreover, it should be reliable, reproducible, noninvasive, and inexpensive. Finally, it should be confirmed as a valid biomarker by at least two independent studies. A well-established biomarker developed for the β-amyloid pathology in the Alzheimer disease is the [F-18] florbetapir-PET, validated on the basis of relationships between [F-18] florbetapir-PET data antemortem and the β-amyloid in postmortem tissues. Clark and colleagues reported that the results rated as positive or negative for β-amyloid were confirmed in 96% of 29 subjects assessed in the autopsy cohort; in the secondary cohort (the non-autopsy cohort) [F-18], florbetapir-PET allowed to rate as amyloid negative 100% of healthy subjects, suggesting the high negative predictive value of this measure [7].

1.2.2 Neuroimaging Biomarkers

In psychiatry, uncertainties about the pathophysiology of different mental disorders as well as about the relationship between identified biological abnormalities and pathophysiological mechanisms have contributed to make the search for biomarkers quite unsuccessful, so far. Historically, neuroimaging biomarkers were developed to allow the discrimination between primary mental disorders and secondary mental disorders caused by lesions such as neoplasm, hematoma, hydrocephalus, atrophy, or cerebrovascular diseases. However, these conditions explained the etiopathogenesis of a low percentage of mental disorders. Therefore, the use of neuroimaging data to differentiate primary and secondary mental disorders did not lead to a large use of biomarkers in the clinical practice.

Until now, the diagnosis of mental disorders has been based mainly on the description of subject's behavior (subjective-descriptive classification). The identification of neuroimaging biomarkers is crucial to move into the era of objective brain measures [8] and, maybe, to genes (see Chap. 4). Indeed, neuroimaging techniques, such as positron emission tomography (PET), as well as single-photon emission computed

tomography (SPECT) and magnetic resonance spectroscopy (MRS), might be used to study variations in cells and molecular targets, while diffusion tensor imaging (DTI) and structural and functional magnetic resonance imaging (sMRI and fMRI, respectively) might investigate anatomical and functional circuitry [9]. Functional MRI is a measure of the blood-oxygenation-level-dependent (BOLD) change in levels of blood deoxyhemoglobin that is a measure of variation in brain activity. MRS allows the study of brain metabolism, providing a measure of different metabolites levels within different brain regions, in the absence of structural brain changes. Finally, DTI is based on diffusion characteristics of water molecules and offers a measure of white matter integrity and connectivity between brain regions. All these methods can be used at a single time point or in longitudinal studies, which are useful to follow progressive brain changes across time.

Currently, in Europe and the USA, neuroimaging is not recommended to diagnose a primary mental disorder, and more research is needed to change this picture and develop biomarkers capable to support the diagnostic work-up, predict illness course and treatment response, and develop new effective treatments.

1.2.2.1 Steps for Neuroimaging Biomarker Discovery

The first step in the development of neuroimaging biomarkers consists in defining a clinical relevant question with the aim to improve patients' quality of life. Biomarkers of the conversion to psychotic disorders in subjects at clinical high risk represent a good example of such a goal [10, 11]. The second step is crucial to ensure that a specific biomarker is linked to brain phenotypes directly associated with physiological mechanisms of interest, and not to the consequences of the disease, treatments, or other confounding factors such as age and personality traits [12]. The third step requires the validation of the biomarker in order to ensure sufficient positive and negative predictive value. Multicenter studies, conducted in independent samples with an adequate size, are needed to achieve this goal. Finally, in the fourth step, researchers have to indicate the clinical utility and costs/benefits of a specific biomarker. To this aim, the biomarker should improve the ability to establish a diagnosis, clinical outcomes, and quality of life (Fig. 1.1). In addition, it has been suggested that longitudinal studies might be crucial to establish a final diagnosis in subjects with unclear presentation of a mental disorder and to examine progressive brain changes [13] that could be related to the pathophysiology of the disease [14], antipsychotic treatments [15], or to substance and alcohol abuse [16].

1.3 Primary Psychotic Disorders and Neuroimaging Findings: Which Biomarkers for Psychotic Disorders?

Schizophrenia is a severe disease that affects approximately 0.5–1% of the general population. Since the first descriptions of schizophrenia [17, 18], it has been observed that patients are unaware of their symptoms, disconnected from reality, and exhibit negative symptoms that affect both high-level and basic cognitive functions. Over a hundred years ago, Emil Kraepelin differentiated dementia praecox, to

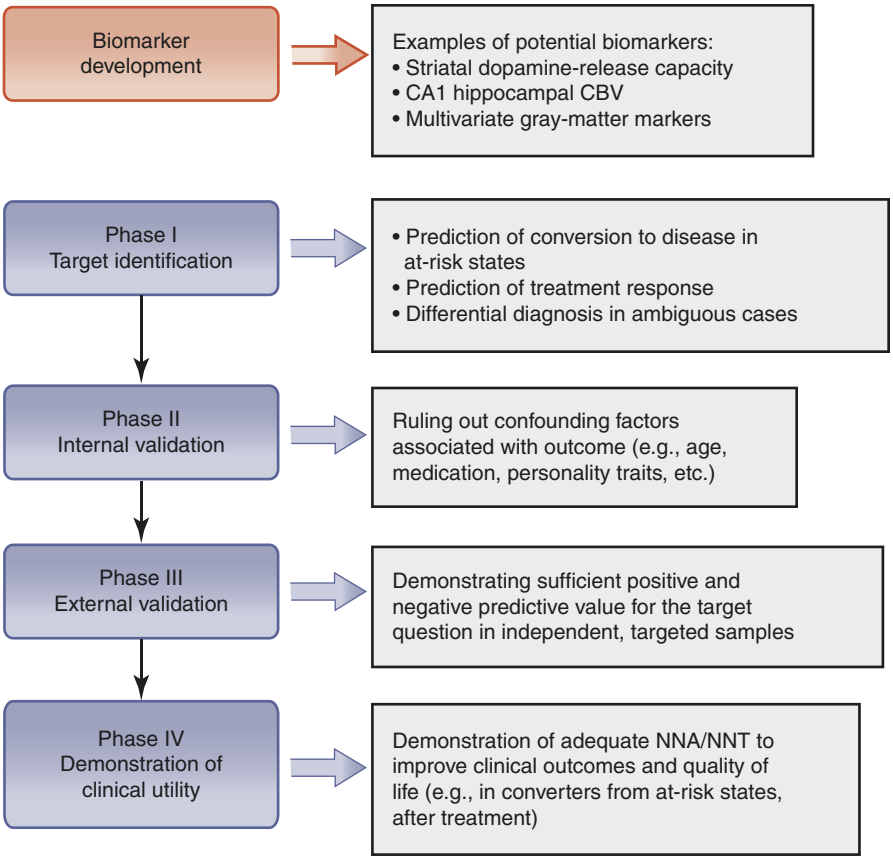

Fig. 1.1 Steps for biomarkers development. On the left, steps for biomarkers development. On the right, examples of potential biomarkers. From Fig. 2 in Abi-Dargham and Horga Abi-Dargham [8]

be called schizophrenia later on, from manic-depressive insanity, later termed bipolar disorder [17]. Conceptualization of endogenous psychoses as two distinct categories and the separation between primary psychotic disorders and primary affective disorders are still highly debated. Moreover, the schizophrenia spectrum disorder includes other categories characterized by psychotic symptoms such as delusions and hallucinations, i.e., schizoaffective disorder, delusional disorder, schizotypal personality disorder, schizophreniform disorder, and brief psychotic disorder. Actually, relation and boundaries between affective and schizophrenia spectrum disorders remain at the center of the debate. A spectrum model points that psychosis severity varies on a continuous scale with schizophrenia and affective disorders at opposite ends and schizoaffective disorder in between. Structural and functional neuroimaging techniques can uncover the neurobiological underpinnings of clinically defined entities, such as schizophrenia, and draw a likely delimitation with respect to bipolar disorder or schizoaffective disorder. In addition, they might

identify brain alterations that occur since the onset, or even before the onset, of the disease and predict illness course, treatment response, and functional outcome.

1.3.1 Diagnostic Biomarkers

1.3.1.1 Structural Gray and White Matter MRI Findings

In subjects with chronic schizophrenia (SCZ) or other schizophrenia spectrum disorders (SSD), the brain structural abnormalities consistently observed include the volume increase of the third and lateral ventricles and the decrease of intracranial and total brain volume [19, 20]. Volume decrease in cortical gray matter (GM), predominantly in prefrontal cortex (PFC) and inferior frontal gyrus, has also been confirmed repeatedly [19]. In antipsychotic-naïve patients (AP-naïve), the volume reductions in the caudate and thalamus seem to be more pronounced than in medicated patients, while less extensive total gray matter loss is detected [19]. A volume decrease in the right and left thalamus is also observed in first-episode schizophrenia (FES) subjects [21], indicating the presence of the abnormality since the early development of the disorder. Several replicated findings indicate the presence of a significant reduction in the right hippocampal volume, corpus callosum area (CC), and total GM and an increase in the right, left, and total lateral ventricle volumes in FES relative to healthy controls (HC) [22–25]. Some structural abnormalities seem to progress over time in schizophrenia. In particular, with the progressive manifestation of the disorder in FES subjects, a pattern of progressive loss of the whole cerebral GM volume, involving frontal, temporal, and parietal lobes, occurs. In chronic conditions, a significant volume loss affects the total cortical GM, primarily in the left superior temporal gyrus (STG), left anterior STG, left Heschl gyrus, left planum temporale, and posterior STG bilaterally [26]. In addition, a volume decrease in frontal, parietal, and temporal white matter [27] and a volume increase in lateral ventricles were found [13, 27, 28]. The possibility to identify structural abnormalities as candidate biomarkers is hindered by the variability of mentioned abnormalities in relationship with illness stage, treatment regimen, and image acquisition.

Results from sMRI meta-analyses in psychotic disorders are described in Table 1.1.

The diagnostic value of a biomarker also depends on whether it differs between the population of interest and other diagnostic categories. SCZ and subjects with schizoaffective disorder, for instance, show a widespread cortical gray matter volume decrease in numerous and overlapping areas, such as frontal, limbic, and subcortical areas [31–33], while gray matter reduction is observed in anterior cingulate and insular cortex in bipolar disorder (BPD) subjects [34]. In direct comparison with BPD subjects, SCZ showed a reduced right amygdala volume and a larger increase in right and left lateral ventricle volumes, while BDP subjects were characterized by whole brain and prefrontal lobe volume reductions, as well as by an increase in the volume of the globus pallidus [30]. By contrast, these differences appeared less pronounced when comparing first-episode bipolar disorder and schizophrenia subjects. In this case, similar abnormalities including a reduction in

Table 1.1 Structural gray and white matter MRI findings in psychotic disorders

Study	Sample	Medication	Brain imaging technique, study design	Findings
Vita et al. [23]	340 FES; 422 HC	Medicated	Meta-analysis of 21 structural MRI (sMRI) studies	Significant overall effect sizes for lateral and third ventricular volume increase and for volume reduction of whole brain and hippocampus, but not for temporal lobe, amygdala, and total intracranial volumes
Boos et al. [29]	679 SCZ; 1100 HC; 1065 FHR	Unknown	Meta-analysis of 25 sMRI studies	Smaller hippocampal volume in relatives than in controls. Reduced GM and increased third-ventricle volume in relatives versus HC. Smaller hippocampal volume in SCZ compared to first-degree relatives
Arnone et al. [24]	894 SCZ/SSD/FES; 809 HC	Medicated	Meta-analysis of 28 sMRI	Corpus callosum area reduced in SCZ in comparison to HC, especially in first-episode patients
Arnone et al. [30]	1823 BPD; 670 SCZ; 29 SSD; 1940 HC	Medicated	Meta-analysis of 72 sMRI studies	Whole brain and prefrontal lobe volume reductions, as well as increased volume of the globus pallidus and lateral ventricles volumes in BPD versus HC. Smaller lateral ventricular volume and enlarged amygdala volume in BPD than in SCZ
Adriano et al. [21]	449 FES/SCZ; 508 HC	Medicated	Meta-analysis of 13 sMRI studies (six studies of first-episode patients only and seven studies of chronic patients)	Significant bilateral thalamus volume reduction in both FES and SCZ compared to HC. Left thalamus smaller than right thalamus in both SCZ and HC
Kempton et al. [13]	473 SCZ/patients with psychotic disorders (schizoaffective disorder, schizophreniform, psychoses not otherwise specified); 348 HC	Unknown	Meta-analysis of 13 longitudinal sMRI studies (median duration of follow-up unknown)	Increased rates of lateral ventricle dilation over time in patients compared to HC (effect size $g = 0.449$, 95%CI 0.192–0.707, $p = 0.0006$). No significant effect of age of onset, duration of illness, or age at baseline scan was found

(continued)

Table 1.1 (continued)

Study	Sample	Medication	Brain imaging technique, study design	Findings
Olabi et al. [27]	928 SCZ; 867 HC	Unknown	Meta-analysis of 26 sMRI studies	Significantly greater decreases over time in whole brain volume, whole brain GM, frontal GM and WM, parietal WM, and temporal WM volume, as well as larger increases in lateral ventricular volume in SCZ than in HC
Vita et al. [26]	813 FES/SCZ; 718 HC	Unknown	Meta-analysis of 19 sMRI studies	Significantly higher volume loss over time of total cortical GM, left STG, left anterior STG, left Heschl gyrus, left planum temporale, and posterior STG bilaterally in SCZ. FES showed greater progressive loss of cerebral GM volume involving the frontal, temporal, and parietal lobes, and left Heschl gyrus than HC
De Peri et al. [25]	1198 FES; 315 FE BPD; 1382 HC	Medicated	Meta-analysis of 45 sMRI studies	Significant overall effect sizes ($Q = 43.39$, $p = 0.02$) for intracranial, whole brain, total GM, and WM volume reduction, as well as for lateral ventricular volume increase at disease onset in both schizophrenic and bipolar patients
Adriano et al. [22]	1669 FES/SCZ; 2130 HC	Medicated	Meta-analysis of 13 structural MRI studies of FEP and of 22 chronic patient studies	Significant bilateral hippocampal volume reduction in patients as compared with HC. Similar hippocampal volume reduction in FES and SCZ. Left smaller than right hippocampus in patients with respect to HC

Table 1.1 (continued)

Study	Sample	Medication	Brain imaging technique, study design	Findings
Fusar-Poli et al. [28]	1046 SCZ,; 780 HC	Medicated	Meta-analysis of 30 longitudinal sMRI studies (Median duration of follow-up of 72.4 weeks)	At baseline, whole brain volume reductions and enlarged lateral ventricle (LV) volumes; no volumetric abnormalities in the GM and WM volumes, cerebrospinal fluid, and caudate nucleus in SCZ compared to HC. Progressive GM volume decreases and LV volumes enlargements in patients than in HC
Haijma et al. [19]	8327 medicated SCZ/SSD; 771 antipsychotic-naive patients	Medicated; AP naïve	Meta-analysis on cross-sectional volumetric (MRI) brain alterations in both medicated and antipsychotic-naïve patients	Significant decrease of intracranial and total brain volume and increase of third and lateral ventricles in medicated versus AP-naïve patients; volume decreases in cortical GM, prefrontal GM, and inferior frontal gyrus in medicated versus drug-naïve patients. Volume reductions in caudate nucleus and thalamus more pronounced in AP naïve than in medicated patients. White matter volume decreased to a similar extent in both groups; gray matter loss less extensive in AP-naïve patients

SCZ subjects with schizophrenia, *SSD* schizophrenia spectrum disorder, *FES* first-episode schizophrenia, *FHR* familial high risk, *FEP* first-episode psychosis, *BPD* subjects with bipolar disorder, *HC* healthy controls, *sMRI* structural magnetic resonance imaging, *WM* white matter, *GM* gray matter, *STG* superior temporal gyrus

intracranial, whole brain, and total gray and white matter volumes, as well as an increase in lateral ventricular volume, were observed in both patient groups [25]. Interestingly, similar results were reported in a study based on a dimensional approach to psychosis that included first-degree relatives of bipolar and schizophrenia or schizoaffective subjects. Psychosis probands and relatives with psychosis spectrum personality disorders showed diffuse gray matter reductions in

overlapping cortical regions, including the frontotemporal, parietal, cingulate, and insular cortices, and the cerebellum. Unaffected relatives did not show any abnormality. Furthermore, psychotic bipolar probands had gray matter volume reductions primarily localized in the frontotemporal, cingulate, and insular cortices, albeit less extensive than probands with schizophrenia or schizoaffective disorder, who showed a widespread cortical and subcortical GM volume reduction [32]. This might indicate a partially divergent GM phenotype across disease categories, with SCZ and schizoaffective disorder subjects demonstrating more generalized decrease in neocortical and subcortical gray matter regions and BPD subjects showing limited reductions in frontotemporal regions. Volume reductions in thalamus and hippocampal subcortical areas were also consistently reported in psychosis spectrum disorders [35–38], with a greater volume loss in SCZ as compared to BPD subjects [35, 39, 40]. Actually, recent evidence suggests that a decreased thalamus volume is present in SCZ but not in BPD subjects [32, 41]. Findings relevant to the amygdala and basal ganglia volumes are more inconsistent. In fact, volume decreases limited to schizophrenia, as well as decreases in both SCZ and BPD but more prominent in SCZ than in BDP, or no decrease in either diagnostic groups, or even increased volumes in SCZ, were reported [31, 42–50]. Few studies provided data on correlations between structural brain abnormalities and clinical characteristics of SCZ and SSD subjects. In line with Ivleva et al. findings supporting the notion of the psychosis spectrum [32], a negative correlation was observed between the severity of delusions and frontal gray matter volumes, as well as between the severity of hallucinations and right uncus gray matter volume along a continuum across diseases [49]. Furthermore, findings obtained by studying first-episode psychosis (FEP) subjects, such as FES, FEP SSD, and FEP BPD, indicated a direct association of the negative dimension with lateral and third ventricle volume enlargement and of the positive dimension with thalamus and ventral diencephalon nuclei volume increase [20, 51]. It is worth highlighting that the most significant ventricular and basal ganglia enlargement and the greatest frontotemporal cortical volume deficits were reported in subjects with an earlier onset of a schizophrenia spectrum disorder, while the least extensive cortical deficits were found in mood disorder subjects [46].

1.3.1.2 Diffusion Tensor Imaging Findings

Increasing evidence suggests regional disconnectivity and white matter (WM) pathology of bundles connecting cortical and subcortical areas in the brain of SCZ subjects [52–54]. Anatomical disconnectivity and myelination abnormalities were confirmed also in postmortem and genetic studies in schizophrenia [55, 56]. DTI analysis, enabling the study of this kind of WM alterations, revealed their presence since the early stages of the disorder [57–59]. Evidence of frontotemporal abnormalities in FEP subjects and fronto-temporo-limbic impairments in subjects with schizophrenia has been provided [57, 59–64]. In FEP, lower fractional anisotropy (FA) values were observed in corpus callosum (CC), uncinate fasciculus (UF), anterior cingulum (AC), superior longitudinal fasciculus (SLF), and fornix (FX). Specifically, in FES subjects decreased FA in medial and middle frontal lobe, precuneus and parietal lobe, anterior and posterior cingulate cortex, and

predominantly in the temporal lobe confirmed that changes of cortical-subcortical WM integrity occur early at the onset of the disorder. Furthermore, in the same subjects, FA reductions were found in the anterior and posterior internal capsule, external capsule, and bilateral hippocampal gyri [65]. Interestingly, these WM alterations were correlated with specific cognitive deficits in verbal and spatial working memory, as well as with positive more than negative symptoms in FES subjects. The correlation between microstructure abnormalities and psychopathology is yet scant, but recent studies showed that lower FA values in the right SLF, right inferior longitudinal fasciculus (ILF), right arcuate fasciculus (AF), left UF, right cingulum bundle, inferior fronto-occipital fasciculus, and right fornix correlate with negative symptom severity [59, 66–70]. Overall, schizophrenia studies consistently reported decreased FA and WM abnormalities localized preferentially within the fiber bundles connecting prefrontal and temporal lobes, including UF, cingulum bundle, arcuate fasciculus, and genu of the corpus callosum [71, 72].

Results of meta-analyses or reviews of DTI studies in psychotic disorders can be found in Table 1.2. Figure 1.2 shows the trajectories of uncinate fasciculus, arcuate fasciculus, genu, fornix, cingulum, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus [74].

However, these features cannot be regarded as available biomarkers for schizophrenia diagnosis, especially when we consider the overlap between findings obtained in SCZ and those reported in BPD samples [73, 75–79]. Nevertheless, the disrupted intra- and interhemispheric structural WM connections in SCZ provide a solid evidence for the conceptualization of the disconnectivity syndrome. Indeed, widespread alterations observed in WM bundles connecting heteromodal association cortices (HASC), such as ventral prefrontal cortex and superior temporal gyrus, could explain the disruption in the coordination of those association areas and the cognitive and behavioral deficits observed in schizophrenia [57, 80–82].

1.3.1.3 Functional Neuroimaging Findings

Several functional neuroimaging studies reported that HC and subjects with psychotic disorders during task performance engage the same brain networks but with a differential magnitude of activation [83, 84]. Multiple meta-analyses and systematic reviews exploring working memory, executive function, emotion recognition, or positive symptoms have highlighted the differential activation of the prefrontal cortex [84–88], anterior cingulate cortex (ACC) [84, 87, 89], insula [86, 89, 90], thalamus [84, 91], and superior temporal gyrus [86, 87, 89] in SCZ as compared to HC. In particular, SCZ subjects showed reduced activation in the left dorsolateral prefrontal cortex (DLPFC), rostral/dorsal ACC, left thalamus, and inferior and posterior cortical areas, which should support executive task performances [92]. A hyperactivation was observed, instead, in several midline regions, such as ventrolateral prefrontal cortex (VLPFC), posterior temporal and parietal cortices, amygdala, and insula. The largely confirmed hypoactivation of DLPFC and ACC is consistent with an impairment in the cognitive control network that could be associated with the executive dysfunction in SCZ [84]. Most probably, the reduced top-down regulation provided by the DLPFC leads to a relatively greater activity in

Table 1.2 DTI findings in psychotic disorders

Study	Sample	Medication	Brain imaging technique, study design	Findings
Patel et al. [72]	202 SCZ; 213 HC	Medicated	2 meta-analyses on DTI studies investigating the genu and splenium of the corpus callosum	Lower FA in the splenium in patients (modest effect size) than in HC
Ellison-Wright and Bullmore [62]	407; SCZ/SSD; 383 HC	Medicated	The ALE method hybridized with the rank approach used in genome scan meta-analysis (GSMA) on DTI studies	Significant FA reductions in the left frontal deep WM and temporal deep WM
Kuswanto et al. [65]	FES; HC	Medicated; assessment PANSS; Sternberg item recognition task	Review of 22 DTI studies	Decrease of FA predominantly in the temporal lobe (superior temporal gyrus, inferior temporal gyrus, temporal-occipital region, and posterior temporal regions) but also in medial and middle frontal lobe, precuneus and parietal lobe, anterior and posterior cingulate cortex in patients as compared to HC. FA reductions in the anterior and poster internal capsule, in the fornix, and in bilateral hippocampal gyri in FES. Changes in white matter integrity correlated with specific cognitive deficits (verbal and spatial working memory) as well as psychopathology (positive more than negative symptoms) in patients with FES

SCZ subjects with schizophrenia, *SSD* schizophrenia spectrum disorder, *FES* first-episode schizophrenia, *FHR* familial high risk, *FEP* first-episode psychosis, *BPD* subjects with bipolar disorder, *HC* healthy controls, *ALE* activation likelihood estimation, *WM* white matter, *FA* fractional anisotropy, *DTI* diffusion tensor imaging

the middle regions as compensatory response or alternative strategies to support task performance [84, 93, 94]. Furthermore, findings of reduced amygdala activation for emotion perception, reduced modulation of visual processing areas, as well as contemporary hyperactivity in the cuneus, superior temporal gyrus, parietal lobule, and precentral gyrus may reflect an aberrant connectivity in networks processing emotional stimuli in SCZ [87, 95]. This suggests that patients have a difficulty in modulating integrative brain areas underlying complex socio-emotional stimuli processing, such as ACC, dorsomedial PFC and occipital pole, and a compensatory recruitment of nonemotional regions [96–98]. The detected functional alterations

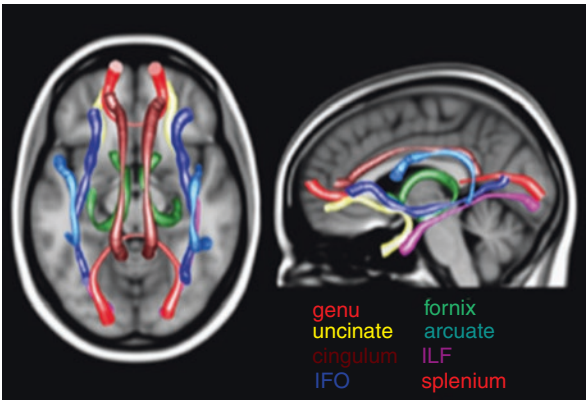

Fig. 1.2 Uncinate fasciculus, arcuate fasciculus, genu, fornix, cingulum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus. *ILF* inferior longitudinal fasciculus, *IFO* inferior fronto-occipital fasciculus. From Fig. 1 in Boos et al. [73]

in SCZ frequently involve the same brain areas in which structural abnormalities are observed since the onset of the disorder [89], thus supporting the possibility to use these structural aberrations as biomarkers for early diagnosis. An example is provided by the increased activation in bilateral cortical areas involved in speech generation, i.e., the Broca's area, the associative auditory cortices of the Wernicke's convolution, as well as the areas involved in verbal memory, i.e., the left hippocampus/parahippocampal region, demonstrated in SCZ subjects experiencing auditory verbal hallucinations (AVHs) [90]. The involvement of these language-related perceptual and motor areas in AVHs in functional neuroimaging studies is consistent with the correlation between hallucination severity and gray matter volume reductions in the left superior and middle temporal gyri or altered microstructure of white matter bundles (such as superior longitudinal fasciculus) connecting Broca's and Wernicke's regions, reported by structural imaging studies [99–101]. When comparing distinct psychosis categories, SCZ subjects showed a pronounced impairment in both neural networks involved in verbal and visuospatial working memory, while schizoaffective disorder subjects were impaired in visuospatial processing only [102]. Similarly, more subtle or no abnormality was seen in BDP subjects with respect to SCZ, when studying activation patterns of networks engaged in working memory tasks [103, 104].

Resting state functional MRI enabled the identification of connectivity patterns in brain areas typically conceptualized as part of the default mode network (DMN). This is a large-scale brain network involved in self-referential thinking, active at rest that recruits the medial PFC, left hippocampus, posterior cingulate cortex, and precuneus [105]. It has been suggested that disorders included in the psychosis spectrum share the connectivity reductions in the DMN; the reduction, however, is more pronounced in SCZ, and selective nodes are differentially affected in different disorders [106]. Specifically, SCZ seems to be characterized by abnormal recruitment of the frontopolar cortex and the basal ganglia [107]. SCZ and schizoaffective disorder subjects show the same degree of altered connectivity, revealing greater coherence in the left frontopolar cortex, right DLPFC, and multiple regions within basal ganglia, compared to HC. BPD subjects, compared to HC, show significantly more coherence in other regions within DMN, i.e., the left parietal cortex, left

fusiform gyrus, right visual and auditory association cortices, left frontopolar cortex, and the pons [107]. A DMN dysfunction, i.e., reduced deactivation of the medial frontal gyrus, was observed during working memory tasks in acute [108] and in clinical remission [109] phases in subjects with schizoaffective disorder as compared to HC, thus indicating a trait like feature of schizoaffective disorder [110]. Similar results of a failure to deactivate the medial frontal cortex were observed also in bipolar disorder and schizophrenia, supporting the concept of DMN dysfunction as shared feature across the diseases [110–113] (Fig. 1.3).

Findings suggesting increased or no aberrant functional connectivity at rest between frontal and mesolimbic areas of the DMN in schizophrenia and affective psychoses were also reported [105, 114, 115].

Interestingly, the aforementioned brain regions found to be dysfunctional in studies cited in this paragraph correspond to those revealing structural abnormalities, such as PFC, DLPFC, temporal and occipital cortex, or hippocampal nuclei.

For more details on the findings described in this paragraph, reader is referred to Table 1.3, reporting results of fMRI meta-analyses in psychotic disorders.

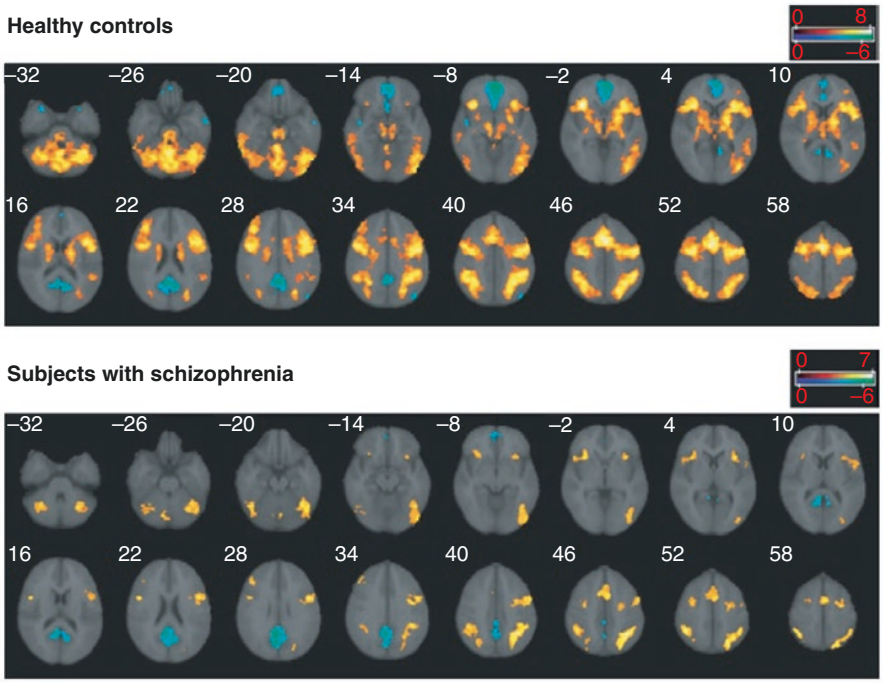

Fig. 1.3 DMN in subjects with schizophrenia and healthy controls. Brain regions showing a significant effect of the two-back versus baseline contrast in healthy controls and in subjects with schizophrenia. Yellow colors indicate a positive association with the two-back memory task. Blue colors are for areas where the task led to a decrease in the blood oxygenation level-dependent (BOLD) response (areas of deactivation). Numbers refer to Talairach z coordinates of the slice shown. The right side of each image represents the left side of the brain. Color bars indicate z scores from the group-level analysis. From Fig. 1 in Pomarol-Clotet et al. [111]

1.3.1.4 Other Neuroimaging Findings

An extensive body of research provided substantial evidence of abnormal

Table 1.3 fMRI findings in psychotic disorders

Study	Sample	Assessment	Brain imaging technique, study design	Findings
Minzenberg [84]	SCZ; HC	Delayed match to sample or delayed response (including Sternberg item recognition), go/no-go (including AX-CPT), Mental arithmetic, N-back, oddball, sequence recall, Stroop, Wisconsin card sort, and word generation tasks were used to explore the executive functions	Meta-analysis of 41 fMRI/PET studies published prior to February 2007	In within-group analyses, activation of a similarly distributed cortical-subcortical network prominently include the DLPFC, ventrolateral PFC, ACC, and thalamus in HC and SCZ. In between-group analyses, reduced activation in the left DLPFC, rostral/dorsal ACC, left thalamus (with significant co-occurrence of these areas), and inferior/posterior cortical areas, in patients than in HC. Increased activation in several midline cortical areas in patients than in HC
Jardri et al. [90]	SCZ/SSD experiencing AVHs during scanning	Patients press online button during auditory verbal hallucinations	10 meta-analysis of fMRI/PET studies	Significantly increased activation likelihoods in a bilateral neural network, including the Broca's area, anterior insula, precentral gyrus, frontal operculum, middle and superior temporal gyri, inferior parietal lobule, and hippocampus/parahippocampal region in patients experiencing AVHs

(continued)

Table 1.3 (continued)

Study	Sample	Assessment	Brain imaging technique, study design	Findings
Taylor et al. [87]	450 SCZ; 422 HC	Tasks aimed to assess (1) emotion perception (2) Emotion experience (3) Emotion valence-specific processing	Meta-analysis of 26 fMRI/PET studies	For emotional experience, greater activation in the left occipital pole in HC than in SCZ. For emotional perception, reduced activation in bilateral amygdala, visual processing areas, ACC, DLPFC, medial frontal cortex, and subcortical structures in SCZ than in HC. Greater activation in the cuneus, parietal lobule, precentral gyrus, and superior temporal gyrus in SCZ than in HC Reduced specific reactivity of the amygdala in emotion-neutral contrast and decrease in ACC activity throughout contrasts in SCZ versus HC
Radua et al. [89]	sMRI: 965 FEP; 1040 HC; fMRI: 362 FEP; 403 HC; [FEP included both schizophrenia spectrum psychoses (schizophrenia, schizoaffective, schizophreniform) and affective psychoses (bipolar psychosis and psychotic depression)]	Cognitive tasks assessing attention, processing, speed, verbal fluency, working memory, visual memory	Multimodal meta-analysis of 43 structural (VBM) and functional (fMRI, PET, SPECT) studies	Conjoint structural and functional differences between FEP and HC in the insula/superior temporal gyrus and the medial frontal/anterior cingulate cortex bilaterally. In the same regions, large and robust decreases in gray matter volume were found with either reduced or enhanced activation. Specifically, the anterior parts of the insula and the dorsal part of the mF/ACC showed hypoactivation; the posterior parts of the insula and the ventral part of the mF/ACC showed reduction in deactivation in FEP

SCZ subjects with schizophrenia, *SSD* schizophrenia spectrum disorder, *FES* first-episode schizophrenia, *FEP* first episode psychosis, *BPD* subjects with bipolar disorder, *HC* healthy controls, *VBM* voxel-based morphometry, *SPECT* single-photon emission computed tomography, *PET* positron emission tomography, *fMRI* functional magnetic resonance imaging, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *PFC* prefrontal cortex, *mF* medial frontal

neurometabolite levels in schizophrenia and affective disorders. An increased striatal dopamine synthesis in both caudate and putamen regions has been reported by several PET studies in SCZ and SSD subjects [85]. On the other hand, magnetic resonance spectroscopy provided new insights about glutamatergic neurotransmission. Reductions of *N*-acetylaspartate (NAA) and glutamate (glu) concentrations have been found in frontal lobe, thalamus, and basal ganglia in SCZ and FES subjects [116, 117], while an increase in glutamine (gln) was observed in frontal regions [118]. Furthermore, both glu and gln levels in the frontal region show a greater progressive decrease with age in patients as compared to healthy controls, suggesting a progressive loss of synaptic activity. These findings are consistent with an increased glutamate turnover in frontal regions among patients that leads to a faster reduction of glu and gln concentrations with age [118]. Moreover, an extensive meta-analysis suggested that the decrease of NAA involves the frontal lobe, hippocampus, thalamus, and basal ganglia in SCZ, while it is limited to the basal ganglia and frontal lobe in BDP [116]. However, no difference was found among SCZ, BPD, or schizoaffective subjects in the degree of NAA reduction in the DLPFC [119]. See Table 1.4.

1.3.2 Biomarkers of Schizophrenia Subtypes: Deficit and Non-deficit Schizophrenia

The wide heterogeneity of schizophrenia in clinical picture, symptomatic and functional outcomes, as well as neurobiological correlates has led to the identification of different subtypes within the syndrome. To date, although DSM-5 does not include any schizophrenia subtype, deficit schizophrenia (DS), i.e., schizophrenia with primary and enduring negative symptoms [120–122], is largely regarded as the most validated schizophrenia subtype. With respect to non-deficit schizophrenia (NDS), DS is associated to poor response to pharmacological treatment [123], worse functional outcome [122, 124, 125], and greater impairment of neurocognitive functions [124–126].

1.3.2.1 Structural and Functional Neuroimaging Findings

Results of MRI studies demonstrated that DS was not associated with lateral ventricular enlargement [127–129]. These findings are surprising since the lateral ventricular enlargement has often been reported in association with negative symptoms and poor outcome. A discrepant finding reported by Arango and colleagues [130] showed an increased ventricular volume in DS subjects, in comparison with HC, without differences between NDS and DS subjects or HC. These discrepant results might be explained by differences in methodological aspects, such as MRI analysis methods and the inclusion in the latter study of the third and fourth ventricles too.

Different studies reported greater abnormalities in temporal lobe in DS than in NDS subjects, including an increase of left temporal cerebrospinal fluid volume [131], smaller right temporal lobe volume [127], and reduced gray matter volume in the superior [132, 133] and middle temporal gyrus [133]. In a study conducted in DS, NDS, and BPD subjects and HC, the authors, evaluating network-level properties of cortical thickness, found higher interregional coupling, associated with high regional

Table 1.4 Other neuroimaging findings in psychotic disorders

Study	Sample	Medication	Brain imaging technique, study design	Findings
Brugger et al. [117]	SCZ; FEP; HC	Medicated	Meta-analysis of 97 ^{1}H-MRS studies	Significant reductions in NAA levels in frontal lobe, temporal lobe, and thalamus in both patient groups as compared to HC
Marsman et al. [118]	647 SCZ/ FEP; HC	Medicated/ antipsychotic naive	Meta-analysis of 28 1H-MRS studies that examined differences in glutamate and glutamine concentrations	Decreased glutamate and increased glutamine in medial frontal region in SCZ as compared with HC. In SCZ, glutamate and glutamine concentrations decreased at a faster rate with age as compared with HC
Fusar-Poli and Meyer-Lindenberg [85]	113 SCZ/ SSD; 131 HC	Medicated	11 striatal (caudate and putamen) PET studies were included in a quantitative meta-analysis of dopamine synthesis capacity	Increased striatal (both caudate and putamen) DSC in SCZ as compared with HC
Kraguljac et al. [116]	SCZ; FEP; BPD	Medicated	Meta-analysis of 146 studies evaluating *N*-acetylaspartate choline and creatine assessed with -MRS in SCZ and bipolar disorder up to September 2010	Decreased NAA levels in the basal ganglia and frontal lobe in SCZ versus HC, decreased NAA levels in the basal ganglia in BPD versus HC

SCZ subjects with schizophrenia, *SSD* schizophrenia spectrum disorder, *FES* first-episode schizophrenia, *FEP* first-episode psychosis, *BPD* subjects with bipolar disorder, *HC* healthy controls, *MRS* magnetic resonance spectroscopy, *DSC* dopamine synthesis capacity, *NAA N*-acetylaspartate, *Cho* choline, *Cr* Creatine, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex

centrality in the inferior frontal, inferior parietal, and middle and superior temporal cortices, in DS subjects as compared to the other groups [134]. These results are in contrast with previous studies conducted in other (NDS) groups of subjects with schizophrenia, which reported reduced frontotemporal and frontoparietal connectivity (see [135] for a review). Wheeler's et al. findings [134] suggested that DS might represent a subtype of schizophrenia with a diffuse neurodevelopmental disorder of brain connectivity, since the increased network density could be linked to a reduction of networks differentiation during neurodevelopment. As to DTI data, different studies investigated white matter tracts connecting frontal, parietal, and temporal lobes [66–68] in DS and reported WM abnormalities in frontoparietal and frontotemporal circuits involving the superior longitudinal fasciculus [66], left uncinate fasciculus [67, 68], right inferior longitudinal fasciculus, and right arcuate fasciculus [67]. The disruption of the left uncinate fasciculus, right inferior longitudinal fasciculus,

and right arcuate fasciculus was reported in DS subjects, as well as in FEP subjects with a "deficit-like" disease [67], suggesting that these abnormalities might represent a neurobiological feature of DS and do not depend on other factors such as pharmacological treatment or duration of illness. These results are in line with studies that showed in DS subjects impairment of emotion expression, social cognition, and socio-emotional functioning, associated with fronto-temporal-parietal circuit [51]. Furthermore, WM abnormalities in DS subjects could be related to the increased density of interstitial cells of WM found in postmortem studies, thus suggesting an abnormal development of WM tracts [136]. However, these findings await replication since these studies were conducted in small samples.

Only few functional neuroimaging studies were carried out in DS subjects, and results are not as consistent as expected [51]. The most replicated findings involved abnormalities in the frontoparietal circuit in DS subjects as compared to NDS subjects [51, 135]. In different studies using PET or SPECT, authors reported glucose hypometabolism or hypoperfusion in the frontal and parietal cortices in subjects with DS as compared to those with NDS [51, 135]. In a recent fMRI study, using a monetary incentive delay task to investigate the reward processing, the authors reported a reduced activity of the dorsal caudate during reward anticipation in DS subjects as compared with NDS subjects and healthy controls [137].

On the whole neuroimaging studies, investigating neurobiological correlates of DS refuted the hypothesis of the association between DS and lateral ventricles enlargement and indicated that DS is not just the more severe end of the schizophrenia severity spectrum [51]. However, they failed to produce a coherent picture and identify a robust biomarker.

1.3.3 Prognostic and Predictive Biomarkers

1.3.3.1 Prediction of Treatment Response

Several longitudinal MRI studies investigated brain changes associated to early-, medium-, and long-term outcomes of SCZ, either clinical (number of subsequent psychotic episodes, severity of symptoms, hospitalizations, duration of remission, and response to treatment) or functional outcomes (the ability to live independently, maintain employment, or be in a relationship) [138–154] (Table 1.5).

Results from these studies have demonstrated that the presence of brain alterations at the baseline is related to worse clinical and functional outcome at follow-up and that these alterations tend to progress in patients with poor outcome. However, both the chronicity of the illness and the effect of medication should be taken into account. In fact, after the illness onset, most patients are treated with antipsychotics; patients with a poor course of illness are more likely to be exposed to a long period or high doses of medications that could have an impact on brain measures [156].

Similar considerations concerning the effects of medication apply to medium and long-term follow-up studies conducted in FEP subjects [157, 158] or in children and adolescents with early onset first-episode schizophrenia (CAFEP) [139]. In a 4-year follow-up study conducted in FEP subjects, Manè and colleagues [157]

Table 1.5 Relationship between brain structure alterations and medium- and long-term clinical and functional outcomes

Study	Sample	Assessment	MRI technique	Findings
Wassink et al. [138]	63 SCZ	SANS; SAPS; CASH; PSYCH BASE Outcome evaluated after 7 years	sMRI, manual tracings	Negative association of cerebellar volume at baseline with negative and positive symptom duration, as well as psychosocial impairment, after a 7-year follow up
Van Haren et al. [155]	109 SCZ (89 FEP; 20 s psychotic episode)	CASH; SCAN Outcome evaluated after 2 years	sMRI	No association of brain volume parameters with clinical and functional outcome after a 2-year follow-up
Mitelman et al. [150]	104 SCZ (GF and PF); 41 HC	CASH Outcome evaluated after about 4 years	DTI	Reduced overall WM integrity of the prefrontal and temporal areas in SCZ as compared to HC in both PF and GF but more pronounced in PF than in GF
Van Haren et al. [153]	96 SCZ; 113 HC	PANSS; CASH Outcome evaluated after 5 years	sMRI	Decreases in GM density in the left superior frontal area, left STG, right caudate nucleus, and right thalamus in SCZ as compared to HC. Correlation between GM density reduction in the superior frontal cortex and increased number of hospitalizations, 5 years after the onset
Van Haren et al. [154]	96 SCZ; 113 HC	PANSS; CASH Outcome evaluated after 5 years	sMRI	More pronounced cortical thinning in SCZ in temporal regions associated with poor outcome, 5 years after the onset
Jaaskelainen et al. [147]	54 SCZ	PANSS; SOFAS Outcome evaluated after 16 years	sMRI	Increased density of frontal and limbic areas associated with better clinical and functional outcome at follow-up
Friedman et al. [142]	34 SCZ and SCZ-AFF	BPRS; clozapine Treatment response evaluated after 6 weeks	CT	Prefrontal sulcal enlargement associated with poor response to clozapine
Honer et al. [140]	39 SCZ; 3 SCZ-AFF	CGI; clozapine Treatment response evaluated after 6 weeks	CT	Prefrontal sulcal enlargement associated with poor response to clozapine

Table 1.5 (continued)

Study	Sample	Assessment	MRI technique	Findings
Molina et al. [148]	24 SCZ	SAPS; SANS Neuroleptics; clozapine Treatment response evaluated after 6 months	SPECT, rCBF	During treatment with neuroleptics, subjects who later responded to clozapine showed higher thalamic, left basal ganglia, and right prefrontal perfusion, than nonresponders. As compared to HC, in nonresponders, lower perfusion in prefrontal cortex, while in responders higher perfusion in the left basal ganglia and thalamus. Subcortical perfusion of responders decreased when they received clozapine
Molina et al. [149]	39 SCZ	SAPS; SANS Neuroleptics, clozapine Treatment response evaluated after 6 months	SPECT, rCBF	During neuroleptic treatments nonresponders to clozapine showed lower rCBF in comparison with responders in the thalamus, basal ganglia, and DLPFC After clozapine intake, perfusion reduction in thalamus and basal ganglia in responders only
Konicki et al. [141]	36 SCZ (26 GO and 10 PO)	CGI; clozapine Treatment response evaluated after 6 weeks	CT	Prefrontal sulcal enlargement associated to poor response to clozapine
Arango et al. [143]	75 SCZ	SANS; BPRS; SARS; clozapine; haloperidol Treatment response evaluated after 10 weeks	sMRI, ROI	Increased GM volume associated with good treatment response in clozapine-treated patients but with poor treatment response in haloperidol-treated patients
Molina et al. [144]	25 SCZ	SANS; SAPS; clozapine Treatment response evaluated after 6 months	sMRI-PET	Positive symptom improvement associated with temporal GM volume; disorganization symptom improvement inversely related to intracranial volume and hippocampal volume. Patients with high baseline DLPFC volume and metabolic activity more likely to experience improvement in negative symptoms

(continued)