Gray Matter Involvement in Schizophrenia: Evidence from Magnetic Resonance Imaging Studies

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2.1 Schizophrenia-Related Gray Matter Alterations

A number of analytical approaches have been used to assess case-control differences in structural MRI studies (see Chap. 1 for more details). Univariate analyses of group differences in neuroimaging typically employ either a region-of-interest (ROI) approach or voxel-based morphometry (VBM). In the former, case-control differences are estimated at the level of anatomical regions defined using brain atlases while the latter involves a voxel-wise comparison of

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brain tissue concentration or density between two groups. In meta-analyses of ROI-based studies, the pooled effect size of case-control differences is commonly expressed either as Cohen's *d* (Cohen 1977) or Hedges' *g* (Hedges 1981). Meta-analyses of VBM studies examine whether the brain-coordinates of case-control differences derived from the primary literature are statistically likely to cluster within specific brain regions. The Anatomical Likelihood Estimation (ALE) (Eickhoff et al. 2012) and Signed Differential Mapping (SDM) (Radua and Mataix-Cols 2009) are the most widely used algorithms for VBM-based meta-analyses. Univariate analyses, although informative, ignore potential covariation among brain regions or voxels. By contrast multivariate analyses are concerned with the identification of case-control differences in the spatial patterns of brain structural covariation. Several multivariate methods have been employed and these mainly include source based morphometry and machine learning algorithms. Source-based morphometry (SBM) (Xu et al. 2009) extracts spatially independent components (i.e., clusters) from MRI-derived voxelwise measures of gray matter concentration or volume. Machine learning approaches examine the predictive value of brain phenotypes in discriminating patients from healthy individuals and commonly include a recursive feature elimination framework (Guyon et al. 2002; Saeys et al. 2007). Multiple machine learning algorithms are available with support vector machines (SVM), discriminant and sparse canonical analyses, multiple kernel learning, deep learning and multiview learning being the most popular choices (Arbabshirani et al. 2017; Veronese et al. 2013).

2.1.1 Cross-Sectional Studies

2.1.1.1 Univariate Analyses in Patient Samples Unselected for Illness Duration

The consortium for Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) (http://enigma.ini.usc.edu/) is the largest international collaborative initiative in brain imaging.

ENIGMA is organized in disorder-specific working groups which aim to quantify case-control differences in brain phenotypes extracted from MRI data using harmonized analysis and quality assurance protocols across all participating sites (Thompson et al. 2014, 2017). The ENIGMA schizophrenia working-group has leveraged the data within the consortium to create one of the largest datasets of gray matter ROIs in patients with schizophrenia and healthy individuals. Studies from the ENIGMA consortium (Chap. 21) have established that schizophrenia is associated with replicable but subtle case-control differences in the volume of subcortical structures (patients = 2028 and healthy individuals = 2540) (van Erp et al. 2016) (Fig. 2.1) and in regional cortical thickness and area (patients = 4474 and healthy individuals = 5089) (van Erp et al. 2018) (Fig. 2.2). Specifically, compared to healthy individuals, patients had smaller hippocampus ($d = −0.46$), amygdala ($d = −0.31$), thalamus ($d = −0.31$), accumbens ($d = −0.25$) and intracranial volumes ($d = −0.12$) and larger pallidum ($d = 0.21$) and lateral ventricles ($d = 0.37$) and global bilateral reductions in cortical thickness (left: $d = −0.53$; right: $d = −0.51$) and surface area (left: $d = −0.25$; right: $d = −0.25$) (Fig. 2.1). When controlling for these global effects, patients showed further regional changes in cortical thickness but not area. This accentuated regional cortical thinning was most pronounced in the fusiform gyrus, but was also present in multiple temporal regions (inferior, middle and superior temporal gyri and parahippocampal gyrus), in the ventrolateral prefrontal cortex (PFC; lateral orbitofrontal and inferior frontal gyrus), in the insula, and in the posterior anterior cingulate cortex (ACC) (Fig. 2.3). Notably, the motor (precentral gyrus), somatosensory (postcentral gyrus), and parietal (superior and inferior parietal cortex and paracentral lobule) cortices as well as the rostral ACC were significantly thicker in patients than in healthy individuals (Fig. 2.3). The findings of ENIGMA have been replicated in an independent Japanese sample of 884 patients with schizophrenia and 1680 healthy individuals from the consortium of the Cognitive Genetics Collaborative Research Organization (COCORO) (Okada et al.

Fig. 2.1 Subcortical volume differences between patients with schizophrenia and healthy individuals. Mean and standard error of the effect size (Cohen's d) of regional case-control differences in subcortical volume (van Erp et al. 2016). The effect size for each subcortical volume was corrected for sex, age and intracranial volume (ICV). The effect size for ICV was corrected for sex and age. (From https://www.ncbi.nlm.nih.gov/pubmed/26283641)
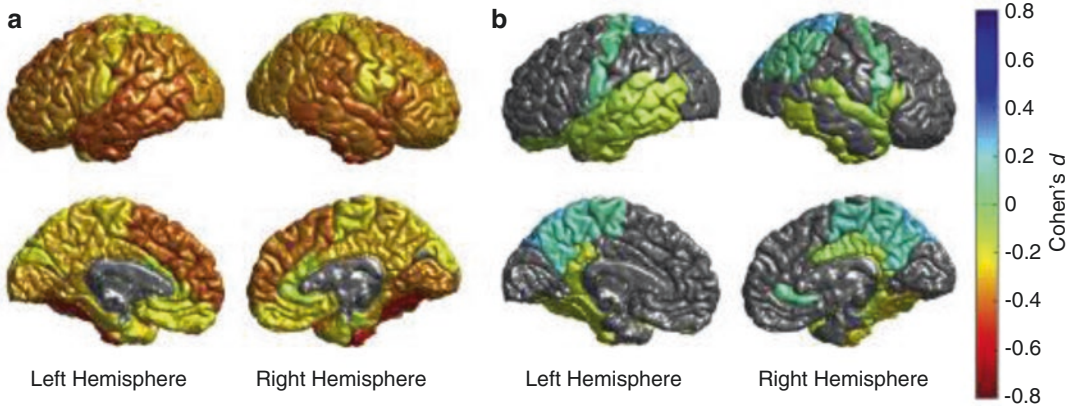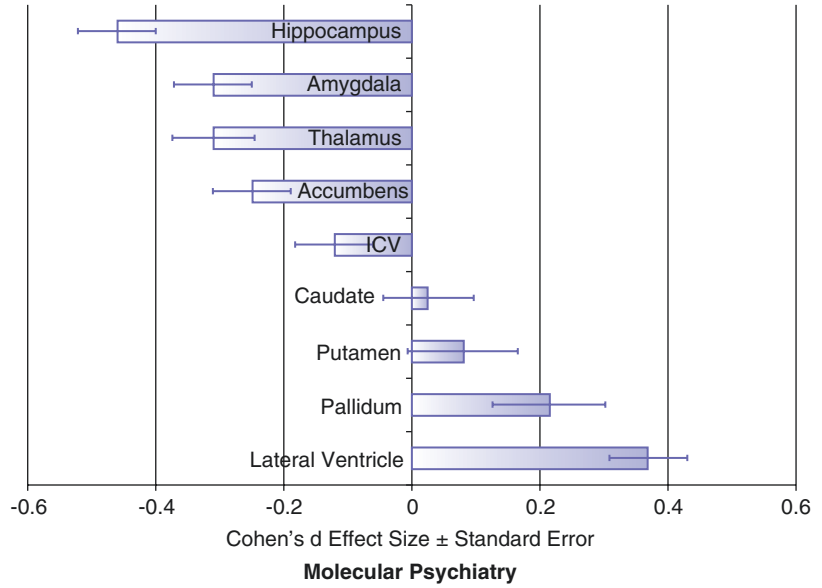

Fig. 2.2 Cortical map of differences in cortical thickness between patients with schizophrenia and healthy individuals. Cortical map of regional effect size (Cohen's d) of case-control differences in regional cortical thickness controlling for age and gender (**a**) and age, sex, and global cortical thickness (**b**) (van Erp et al. 2018). (From https://www.ncbi.nlm.nih.gov/pubmed/29960671)

2016) and are aligned with meta-analyses based on pooled effect size of case-control differences from 317 studies comprising over 18,000 patients (Haijma et al. 2013).

Two meta-analyses, published a year apart used ALE to map gray matter changes in schizophrenia. Glahn et al. (2008) used data from 31 VBM studies, comprising 1195 patients with schizophrenia and 1262 healthy volunteers, while Fornito et al. (2009) used data from 37 VBM studies that collectively compared 1646 patients to 1690 healthy individuals. Not surprisingly the primary studies in these two meta-analyses showed significant overlap, which extended to the results reported. Schizophrenia-related reductions were more consistent for gray matter concentration than for volume although the findings largely converged (Fornito et al. 2009). The regions where gray matter density reductions in patients were most likely to be reported comprised the ACC, the parahippocampal, middle frontal and postcentral gyri, and the thalamus;
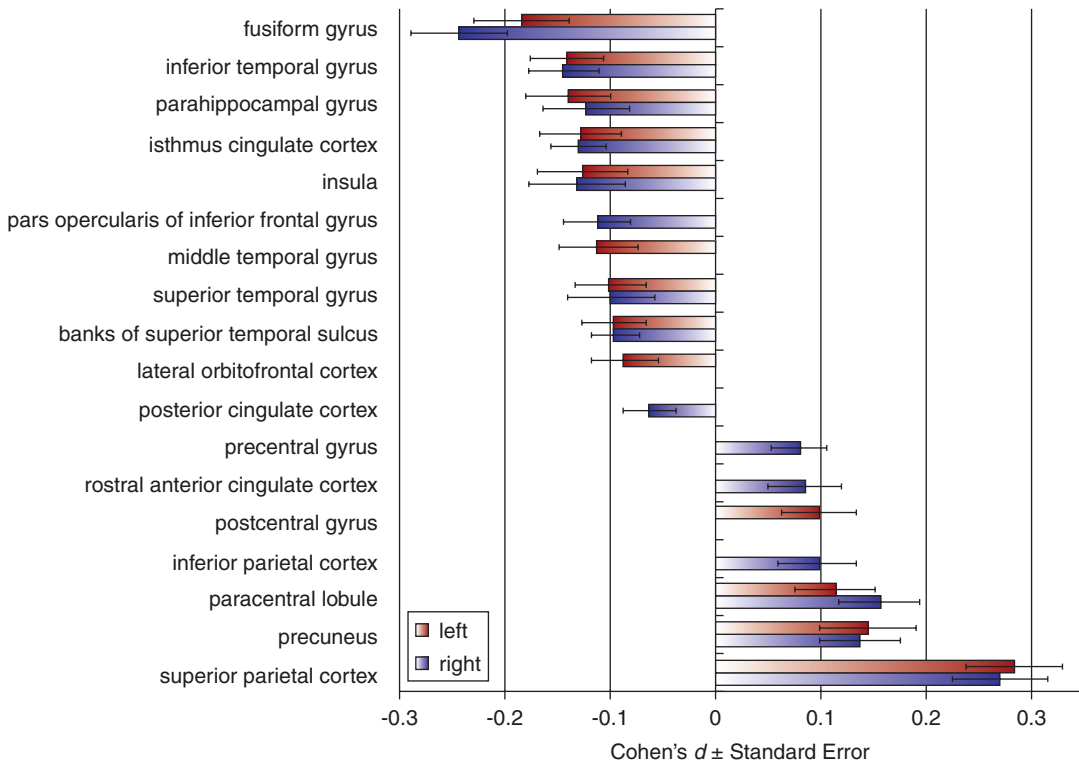
Fig. 2.3 Regional differences in cortical thickness between patients with schizophrenia and healthy individuals. Mean and standard error of the effect size (Cohen's d) of regional case-control differences in cortical thickness after controlling for age, sex, and global mean cortical thickness (van Erp et al. 2016). (From https://www.ncbi.nlm.nih.gov/pubmed/29960671)

conversely, patients had increased gray matter density in striatal regions (Fornito et al. 2009; Glahn et al. 2008). These findings were updated by Bora et al. (2011) who applied SDM to MRI data from 49 VBM studies comparing 1999 patients with schizophrenia and 2180 healthy individuals. Gray matter volume reductions were more likely to be located bilaterally in the ACC, the medial and inferior PFC, the superior temporal gyrus, the precentral gyrus and insula. Amongst the subcortical regions, schizophrenia-related reductions were also noted in the thalamus and the amygdala extending to the red nucleus in the midbrain.

2.1.1.2 Univariate Analyses in First-Episode Patients

Three separate meta-analyses have identified brain changes seen in patients with first-episode schizophrenia. Vita et al. (2006) and Steen et al.

(2006) examined case-control differences in a very limited number of volumetric ROIs. The former study used data from 21 studies involving 551 first-episode patients with an approximate mean age of 25 years and 680 demographically matched healthy individuals. The latter extracted data contrasting 1424 patients with first-episode schizophrenia, with an approximate average age of 26 years, to 1315 matched healthy individuals. Although both studies found larger ventricles and smaller hippocampi, effect sizes were only provided by Vita et al. (ventricles: $d = 0.39$; hippocampi right $d = -0.47$ and left: $d = -0.65$). Radua et al. (2012) used SDM to analyse data from 25 VBM studies, contrasting 965 patients with first-episode psychosis, with an approximate mean age of 24 years, to 1040 matched healthy individuals. In patients, gray matter volume decrements clustered in the insula, operculum, the superior temporal gyrus and the medial

frontal and anterior cingulate cortices while gray matter increased clustered in the precentral gyri.

2.1.1.3 Univariate Analyses in Early-Onset Schizophrenia

A relatively small number of studies primarily conducted by the National Institutes of Mental Health (NIMH) in the USA and centres in the Norway, Spain, and the UK have examined brain alterations in patients with childhood-onset (onset before the age of 13 years) or adolescent-onset (onset between the ages of 13–18 years) schizophrenia, henceforth jointly referred to as early onset psychosis (EOP). Although EOP patients represent less than 4% of schizophrenia cases arising from any birth cohort (Cannon et al. 1999), their study has the potential to provide information about the interaction between schizophrenia-related mechanisms and developmental processes that occur during adolescence (Giedd et al. 1999).

Studies in adolescent-onset schizophrenia have found reductions in total brain volume (Collinson et al. 2003; Matsumoto et al. 2001) and gray matter volume particularly within the frontal lobe (Moreno et al. 2005; Reig et al. 2011; Yoshihara et al. 2008) but no such differences in subcortical volumes (James et al. 1999; Juuhl-Langseth et al. 2012; Matsumoto et al. 2001).

Nearly all studies on childhood-onset schizophrenia derive from the NIMH cohort and collectively have found that patients, compared to age-matched healthy children, have lower total brain and thalamic volumes and larger caudate and globus pallidus (Frazier et al. 1996a, b; Jacobsen et al. 1996; Kumra et al. 2000).

2.1.1.4 Multivariate Pattern Analyses in Patients Unselected for Illness Duration

The study of Gupta et al. (2015) is of particular interest as they applied SBM to the largest MRI dataset to date comprising 936 healthy individuals and 784 patients with schizophrenia. Following age and sex regression, both decrements and increments in gray matter concentration were observed in schizophrenia. Decrements clustered within the superior, middle, medial and inferior frontal gyri, the superior and inferior temporal gyri, the fusiform gyrus, the insula, the cuneus and precuneus, and the cerebellar vermis and declive while increments were located in the brainstem (pons and ventral tegmental area).

Further, Kambeitz et al. (2015) conducted a meta-analysis of studies (n = 20) that applied machine learning to MRI data from patients with schizophrenia from healthy individuals. They found that, regardless of the specific algorithm, patients with schizophrenia could be distinguished from healthy individuals with a sensitivity of 76.4% and a specificity of 79.0%.

Similar findings were reported in two of the largest studies conducted to-date that applied machine learning algorithms to structural MRI data to discriminate healthy individuals from patients with first episode schizophrenia (n = 127) and from patients with schizophrenia (n = 387) at different stages of their illness (Rozycki et al. 2018; Squarcina et al. 2017). In both studies, regions within the medial prefrontal, temporo-limbic and peri-Sylvian cortex, together with ventricular and pallidal enlargement, showed the higher discriminative power but the accuracy of diagnostic classification was modest and ranged from 72 to 77% (Rozycki et al. 2018).

2.1.2 Longitudinal Studies

Several studies have assessed gray matter morphometry in patients with a first episode psychosis or chronic schizophrenia at multiple time points after illness onset as well as examined the association of the longitudinal changes identified to clinical outcome. The challenge in this line of research is to disentangle brain alterations related to disease mechanism versus those that may be more closely associated with medication exposure and side-effects, substance use, and suboptimal lifestyle choices.

2.1.2.1 First-Episode Psychosis

Multiple research groups, mostly based in Australia, Europe, and North America have contributed to the literature on brain alterations following the first psychotic episode in adult

(Andreasen et al. 2011; Cahn et al. 2002; DeLisi et al. 1997, 2004; Haukvik et al. 2016; Lieberman et al. 2001; Nakamura et al. 2007; Puri et al. 2001; Takahashi et al. 2009; Whitworth et al. 2005) and in EOP patients (Arango et al. 2012; Fraguas et al. 2012; Jacobsen et al. 1998; James et al. 2004; Keller et al. 2003; Reig et al. 2009; Sporn et al. 2003; Thompson et al. 2001). There is significant variability in the results reported, even between studies using cohorts with similar characteristics. Nevertheless, key meta-analyses of the literature have identified some consistent findings.

Fraguas et al. (2016) focused specifically on early onset psychosis. Their meta-analysis included longitudinal MRI studies (with a mean inter-scan of 2.46 years) that collectively involved 156 EOP patients (mean age at baseline 13.3–16.6 years) and 163 demographically matched healthy youth. They used a ROI approach to derive the effect size of case-control differences in longitudinal changes in total brain volume, total gray matter volume and in the gray matter volume of each cerebral lobe. Compared to healthy youth, EOP patients showed accelerated volume reduction in all the gray matter ROIs examined; the largest effect sizes were noted for the gray matter volume of the frontal ($g = -0.43$) and the occipital lobes ($g = -0.79$). These results resonate with the longitudinal changes in cortical thickness reported by Greenstein et al. (2006) in the NIMH cohort which only comprises youth with childhood-onset schizophrenia (n = 70) and healthy youth (n = 70) scanned repeatedly between the ages of 14 and 22 years. At younger ages, patients showed greater cortical thinning in anterior and posterior cortical regions. This pattern became more localized in the superior, middle, medial, and lateral orbital frontal gyri and in the superior and middle temporal gyri when the patients reached adulthood. Additionally during the follow-up period, the rate of cortical thinning in the superior parietal and postcentral gyri "normalized" while that in the superior and middle temporal gyri did not. Collectively, these findings have been interpreted as an exacerbation of the developmental changes taking place during adolescence (Thompson et al. 2001); in typically developing youth, there is a posterior-to-anterior wave of reduction in cortical volume and thickness which is assumed to reflect brain maturational processes in frontal and occipital regions that precede similar maturational changes in the lateral temporal cortex (Giedd et al. 1999; Gogtay et al. 2004).

Although EOP studies are informative, the typical onset of schizophrenia is in the third decade of life and therefore adult-onset datasets are more representative of the clinical population with schizophrenia. A meta-analysis by Vita et al. (2012) identified nine longitudinal studies of adults patients scanned within the first 24 months from onset that provided ROIs measures of gray matter of the whole-brain, the cerebral lobes and the auditory cortex on Heschl's gyrus (HG). Compared to healthy individuals (n = 337), patients (n = 341) showed reduction of moderate effect size (range of d: −0.30 to −0.58) in all the gray matter measures examined with the exception of the HG where the effect size of case-control differences was large (right: $g = -1.13$; left: $g = -1.33$).

We also highlight the contribution of the Iowa Longitudinal Study that stands out based on sample size and duration of follow-up. The Iowa Longitudinal Study was conducted between 1987 and 2007 that recruited 542 patients at their initial psychotic presentation at a mean approximate age of 24 years. Repeated MRI scans (minimum 2 and maximum 5 scans) were available from 202 patients and 125 healthy individuals; the mean interval between first scan and last available scan was 7.2 years (Andreasen et al. 2011). Patients showed accentuated decrease in whole-brain and regional gray and white matter volume and increased enlargement of the lateral ventricles. With regards to gray matter volume, the slope of decline in patients was greater for the frontal lobe and the thalamus (Andreasen et al. 2011). However, progressive brain changes did not occur uniformly in patients or in healthy individuals. For example, 47% of patients were losing at least 0.5% and 34% were losing at least 1% of frontal gray matter volume (as compared with 36% and 23% in healthy individuals, respectively). The interaction between time and

diagnostic group on all brain measures was statistically significant at the first inter-scan interval, which was at 2 years after intake, but not thereafter. Increased attrition with longer follow-up may have reduced the power to detect case-control differences. However, these findings raise the possibility that disease-mechanisms affecting brain integrity may indeed be most active during the early stages of schizophrenia. This interpretation may need to be considered in the context of a study by Schaufelberger et al. (2011) who conducted a 1-year follow-up of 39 patients with first-episode psychosis and 52 healthy individuals enrolled in a population-based case-control study. Although the sample size was small and the follow-up period was brief, the authors reported a significant group by time interaction in the superior temporal gyrus and the hippocampus due to gray matter increase in patients in these brain regions while no change was observable in the control group. This "gain" in patients was associated with prolonged remission suggesting that if disease mechanisms are indeed active in the early stages of the illness this effect may be limited to a subset of patients likely to have a more severe illness.

2.1.2.2 Patient Samples Unselected for Illness Duration

Several studies have examined progressive brain changes in patients of schizophrenia at different stages of their illness beyond the first episode (Mathalon et al. 2001; Mitelman et al. 2009; van Haren et al. 2008, 2011, 2016; Veijola et al. 2014; Wood et al. 2001) as have several reviews (Hulshoff Pol and Kahn 2008; Zipursky et al. 2013). Several meta-analyses have also provided a synthesis of the emerging patterns (Haijma et al. 2013; Kempton et al. 2010; Olabi et al. 2011).

More specifically, Kempton et al. (2010) focused their meta-analysis on the issue of lateral ventricular enlargement as an indirect measure of progressive brain loss; they included 13 studies that had measured the lateral ventricles or entire ventricular system at a minimum of two time points in a cumulative sample of 473 patients and 348 healthy individuals. Patients showed greater

progressive ventricular enlargement than healthy individuals with a mean effect size $g = 0.45$; the effect size of case-control differences was similar for early stage ($g = 0.49$) and chronic ($g = 0.41$) patients.

Olabi et al. (2011) conducted a meta-analysis using data from 27 patient cohorts comprising 928 patients and 867 healthy individuals for whom baseline and follow-up a ROI volumetric data were available. The mean duration of illness at the baseline scan was 6.2 years (range: 0.3–18.7 years) and the mean inter-scan interval was 3.49 years. Greater progressive changes in patients were noted for the whole brain volume ($d = -0.40$) and the ventricular volume ($d = 0.53$). The slope of decline was steeper in patients for all gray matter ROIs but reached significance for the whole-brain ($d = -0.52$) and frontal lobe ($d = -0.34$). No significant time by diagnosis interaction was noted for subcortical structures although the reported confidence intervals were large, suggesting significant inter-study heterogeneity.

The results of these meta-analyses resonate with the findings from one of the largest longitudinal MRI datasets of patients with schizophrenia at the University Medical Center Utrecht (Hulshoff Pol et al. 2001). At baseline, the cohort comprised 159 patients with schizophrenia (with a mean duration of illness of 13.7 years) and 158 healthy participants. At intake, patients had smaller amygdala, hippocampus and thalamus and larger caudate and globus pallidus. They also showed evidence of cortical thinning in the inferior frontal, superior temporal and ventral occipital regions and in the precuneus, insula and posterior cingulate cortex (Hulshoff Pol et al. 2001) and greater volume in the superior parietal lobule and occipital pole (van Haren et al. 2011). After a mean interval of approximately 5 years, 96 patients and 113 healthy individuals were rescanned. At follow-up, both diagnostic groups showed progressive reductions in whole-brain and cerebral lobe gray matter volume (van Haren et al. 2008) and thickness, but the slope was steeper in patients particularly in frontal and temporal regions (van Haren et al. 2011). Subcortical progressive volumetric reductions

were more pronounced in patients' caudate, puta-men, hippocampus, and amygdala (van Haren et al. 2016).

2.2 Associations Between Gray Matter Morphometry and the Clinical Features of Schizophrenia

Gray matter alterations in schizophrenia are thought to underpin disease expression but this association is complex. Several clinical features seem to correlate with symptom severity in cross-sectional investigations and the prognostic value of neuroimaging for clinical and functional outcomes. Outcomes were commonly defined using consensus criteria for clinical remission (e.g., Andreasen et al. 2005), type of course (e.g., non-remitting versus remitting) or overall function based on the General Assessment of Functioning (GAF) score. We focus on associations between gray matter morphometry and disease expression that were reported in the studies discussed in the preceding sections when such information was available. Additionally we highlight notable findings from the wider literature.

2.2.1 Cross-Sectional Studies

2.2.1.1 Associations Between Gray Matter Changes and Symptom Severity

In the ENIGMA studies, the association between gray matter ROIs and symptoms was assessed using both whole-brain and hypothesis-led ROI methods. In the whole-brain analyses, greater positive symptom severity correlated with cortical thickness in the left fusiform gyrus (r = 0.60), the left pars triangularis (r = −0.08), the left superior frontal gyrus (r = −0.07), the right inferior (r = −0.07), and the bilateral middle frontal gyrus (left r = −0.08; right r = −0.10) and middle temporal gyrus (left r = −0.07; right r = −0.06) (van Erp et al. 2018). Greater negative symptom severity correlated with widespread cortex thinning bilaterally (left and right r = −0.08) and larger lateral

ventricular volume (van Erp et al. 2016, 2018). The hypothesis-led analyses focused on the superior temporal gyrus (STG) given its involvement in auditory hallucinations (Lee et al. 2018) and on PFC regions because of their association with negative symptoms (Millan et al. 2014). In these analyses, positive symptom severity was negatively related to STG thickness bilaterally (left: βstd = −0.05; right: βstd = −0.07) (Walton et al. 2017) while negative symptom severity negatively related with the thickness of the left medial orbitofrontal cortex (βstd = −0.07) and to a lesser extent with the thickness of the left lateral orbitofrontal gyrus and the pars opercularis (Walton et al. 2018).

However, the ENIGMA findings are only partially supported by other meta-analyses. The meta-analysis by Bora et al. (2011) reported a link between negative symptom severity and reduced gray matter density in the medial and lateral orbital PFC (as well as the insula) but only in chronic patients. Fusar-Poli et al. (2012), who focused on first-episode mediation-naïve patients, found a negative between reduced STG gray matter volume and overall psychopathology. Therefore the magnitude of the associations between gray matter changes and psychopathology is generally small and perhaps it is not surprising that such associations have not been always detectable (e.g., Gupta et al. 2015).

The complexity of the links between gray matter phenotypes and psychopathology is highlighted by the contradictory findings from machine learning studies. Kambeitz et al. (2015) found that diagnostic accuracy based on machine learning analysis of structural MRI data was better for patients with predominantly positive symptoms while Rozycki et al. (2018) reported better diagnostic classification accuracy for patients with greater negative symptom severity.

2.2.1.2 Associations Between Gray Matter Changes and Outcome

In childhood-onset schizophrenia, whole-brain mean cortical thickness at baseline was positively associated with remission at 3 months post-scan (Greenstein et al. 2008). This finding was partially confirmed by Doucet et al. (2018) who

used a machine learning approach to evaluate the predictive value of gray matter phenotypes for symptomatic improvement at 6-months in adult patients (n = 100) in the early stages of schizophrenia (duration of illness <5 years). Although symptomatic improvement showed moderate correlations with global cortical thickness and subcortical volumes, none of these phenotypes had significant prognostic value.

Two notable studies attempted to test whether machine learning applied to brain structural features can distinguish between patients with remitting versus non-remitting outcomes (also see Chap. 17). Zannetti and colleagues (2013) used MRI data from 62 patients with first-episode of schizophrenia and an equal number of matched healthy individuals; the diagnostic accuracy of the classifier was modest in distinguishing cases from controls (73.4%), but failed to discriminate between patients with remitting and non-remitting course, as the diagnostic accuracy achieved was marginally above chance (58.3%). Nieuwenhuis et al. (2017) expanded upon this effort by using data from a substantial sample of patients with first episode psychosis (n = 386) from centres in Australia, Brazil, the Netherlands, Spain, and the UK. Classification accuracy according to outcome was modest in some of the participating centres but did not generalize across centres; in fact when data from all the centres were analyzed into one model, the classification accuracy was at chance level.

2.2.2 Longitudinal Studies

None of the major meta-analyses of longitudinal studies have addressed the association with clinical outcome (Fraguas et al. 2016; Olabi et al. 2011; Vita et al. 2012) so we focus on the findings of the two largest longitudinal studies, the Iowa Longitudinal Study, which followed-up first-episode psychosis (Andreasen et al. 2011, 2013), and the study coordinated by the University Medical Center Utrecht that examined patients with schizophrenia at different stages of their illness (Hulshoff Pol et al. 2001; van Haren et al. 2008, 2011, 2016). The Iowa

Longitudinal Study focused on the association between remission (defined as in Andreasen et al. 2005), relapse (defined as in Csernansky et al. 2002) and the rate of progressive brain changes in patients (n = 202). Over an average period of 7 years, the mean duration of relapse was 1.34 years. The early phases of the illness were characterized by multiple relapses of relatively short duration; as time progressed, the number of relapses decreased while their length increased. The length of the period spent in relapse (but not the number of relapses) was associated with greater loss in whole-brain and frontal gray matter volume (Andreasen et al. 2013). In the cohort from the University Medical Center Utrecht, patients (n = 96) were followed-up for an average period of 5 years at which point the median GAF score was used to divide patients into those with good (GAF = 66.7) and those with poor outcome (GAF = 38.2). The outcome groups did not differ in age, sex, scan interval, socioeconomic status, illness duration, or antipsychotic medication intake. However, compared to patients with good outcomes, those with poor outcomes showed more pronounced progressive cortical thinning in multiple temporal regions (superior and middle temporal and Heschl gyri), in the ACC and in the visual cortex (cuneus).

2.3 Potential Moderators

2.3.1 Sex

There are no consistent reports of a differential effect of sex on schizophrenia-related brain structural alterations either in cross-sectional or longitudinal studies. Whenever an effect of sex has been found it has been associated with greater brain structural deviance in male patients. For example, the ENIGMA studies found no interaction between diagnosis and sex on subcortical volume when correcting for multiple comparisons; at a nominal uncorrected statistical threshold, the proportion male patients was associated with more pronounced case-control differences in the accumbens and the amygdala (van Erp et al. 2016). Moreover, meta-analyses that examined

the effect of sex found no interactions with diagnosis (Fraguas et al. 2016; Haijma et al. 2013; Kempton et al. 2010; Olabi et al. 2011) with the exception of Bora et al. (2011), who reported that male sex was associated with greater deviance in the gray matter of the PFC, the insula, the amygdala and the thalamus.

2.3.2 Age

Age and illness duration are commonly highly correlated and their independent contribution to schizophrenia-related gray matter morphometry can be difficult to disentangle. Age is a significant determinant of gray matter morphometry; a substantial body of literature suggests that gray matter regions cortical thickness and volume peak during late childhood and decrease thereafter (Ducharme et al. 2015; Good et al. 2001; Raz et al. 2005, 2010). The association between age and brain morphometry in schizophrenia is likely to involve complex interactions between age-related brain changes, primary effects of disease mechanisms, and secondary effects of prolonged medication exposure and patients' suboptimal lifestyle. There is some evidence that the magnitude of case-control differences in schizophrenia may be influenced by developmental age (Chap. 15). As previously noted, the slope of cortical thinning was steeper in adolescence in the NIMH cohort of childhood-onset schizophrenia but became similar to that of healthy youth as patients approached adulthood (Greenstein et al. 2006). The evidence for older adults is somewhat conflicting. Kambeitz et al. (2015) found that machine learning algorithms attained better diagnostic sensitivity for chronic compared to first-episode patients indicating that case-control differences in schizophrenia may become more distinctive with age. By contrast, in the University Medical Center Utrecht cohort, excessive gray matter volume decrease in patients with schizophrenia over a 5-year follow-up was significant for those aged 18–46 years but not in older patients (van Haren et al. 2008). This observation has not been replicated in other studies including a further study

from the same cohort that examined cortical thickness (van Haren et al. 2011).

2.3.3 Antipsychotic Medication

The effect of antipsychotic medication on brain morphology is subject to intense scrutiny and debate (See also Chap. 18). Antipsychotic drugs are the mainstay pharmacological treatment of schizophrenia and reduce dopaminergic neurotransmission albeit to a variable degree. The first-generation antipsychotics (FGA) are high-affinity antagonists of dopamine D_2 receptors while the second-generation (SGA) antipsychotics have lower affinity for D_2 receptors but different affinities for serotonergic, adrenergic, acetylcholine, and histamine receptors (Miyamoto et al. 2005). Antipsychotic exposure and illness severity are not independent because patients with a more severe illness are more likely to receive medication for longer periods and at higher doses. Disambiguating the effects of medication on gray matter integrity from those attributable to primary disease mechanism is the greatest challenge as most MRI studies include medicated patients.

2.3.3.1 Effect of Antipsychotic Medication on Striatal Volumes

Striatal enlargement has been associated with antipsychotic treatment in multiple studies (Gupta et al. 2015; Ho et al. 2011; van Haren et al. 2016) and meta-analyses (Haijma et al. 2013) and is absent in studies of medication-naïve patients (Fusar-Poli et al. 2012, 2013). The first indication that antipsychotics may causally affect striatal structure was provided by Chakos and colleagues in 1994 who reported an increase in the volume of the caudate nucleus in patients with first-episode schizophrenia following initiation of treatment with haloperidol, a prototypical FGA. Subsequent studies found that caudate enlargement can be reversed following withdrawal of antipsychotic medication or substitution of FGAs with SGAs (Chakos et al. 1995; Frazier et al. 1996b; Corson et al. 1999). Because the caudate is rich in dopamine D_2 receptors, this FGA-induced enlargement has been attributed

to remodelling caused by strong dopaminergic blockade which can induce ultrastructural changes in striatal neurons (Benes et al. 1985; Chakos et al. 1998; Meshul et al. 1992) and alterations in the dendritic morphology of cortical neurons (Lidow et al. 2001; Selemon et al. 1999) and in fronto-striatal connectivity (Tost et al. 2010).

Antipsychotics may also influence progressive striatal changes. In the University Medical Center Utrecht cohort, the cumulative annual intake of FGAs was inversely associated with progressive volume loss in the putamen (rho = 0.46) and caudate (rho = 0.38) over a 5-year period (van Haren et al. 2016); similarly, in the Iowa Longitudinal Study, higher antipsychotic doses were inversely associated with progressive volume loss in the caudate and putamen over a 7-year period (Ho et al. 2011).

2.3.3.2 Antipsychotic Treatment and Volume Changes in Other Subcortical Regions

The most convincing evidence for an association between antipsychotic exposure and subcortical volumes derives from the ENIGMA dataset (van Erp et al. 2016). Specifically, the proportion of medication-naive patients was negatively associated with the effect size of case-control differences in hippocampal volume. The effect size of case-control difference in ventricular enlargement was negatively associated with the proportion of patients treated with SGA and positively associated with the mean current antipsychotic dose in chlorpromazine equivalents (CPZE).

2.3.3.3 Antipsychotic Treatment and Changes in Cortical Thickness or Volume

Preclinical studies suggest several mechanisms that may lead to cortical thinning following exposure to both FGAs and SGAs. These include antipsychotic-induced microstructural changes in dendritic morphology (Dorph-Petersen et al. 2005; Vernon et al. 2011), which can be reversed upon discontinuation (Vernon et al. 2012). FGAs may compromise gray matter integrity by reducing cerebral flow and metabolism (Goff et al.

1995; Lahti et al. 2004; Miller et al. 1997; Molina et al. 2003; Wright et al. 1998) and by increasing oxidative stress and excitotoxicity (Goff et al. 1995; Wright et al. 1998). Conversely, SGAs (such as olanzapine and clozapine) may preserve cortical gray matter integrity by reducing excitotoxicity (Duncan et al. 2000) while enhancing dendritic resilience (Wang and Deutch 2008), neurogenesis (Halim et al. 2004; Wakade et al. 2002; Wang et al. 2004), and neurotrophic factor expression (Bai et al. 2003; Fumagalli et al. 2003). The association between antipsychotic dose and class has therefore been examined in multiple MRI studies comparing patients to healthy individuals and patients treated with FGAs or SGAs.

The ENIGMA consortium found evidence for an association between antipsychotic exposure and mostly global measures of cortical thickness (van Erp et al. 2018). In particular, mean hemispheric cortical thickness was inversely associated with exposure to FGAs or combinations of FGAs and SGAs. In addition, higher dose in CPZEs inversely correlated with cortical thickness in almost all cortical regions but more prominently in the superior frontal gyrus, the pars triangularis, the superior, middle and inferior temporal gyri, and the supramarginal gyrus. The magnitude of these associations however was small ($|r| < 0.2$). The meta-analysis by Radua et al. (2012) has provided further information about the localization of cortical changes associated with antipsychotic medication in first-episode patients. In a series of meta-regression analyses they found that the gray matter volume in medial PFC, the ACC, and the insula were significantly lower in medicated patients compared to healthy individuals. This reduction was greater than that observed in the same regions in a subgroup analysis that included only samples with antipsychotic-naïve patients. The meta-analysis by Haijma et al. (2013) focused on more global measures and reported that higher antipsychotic dose at the time of scanning was associated with lower whole-brain gray matter volume for both FGAs and SGAs. Importantly, a sub-analysis of antipsychotic-naive samples found that the effect-size of case-control differences was approxi-

mately 75% of that seen in medicated samples, indicating that the most significant reduction in whole-brain gray matter volume may predate treatment initiation.

Two key single-cohort studies have examined the association between antipsychotic exposure and progressive cortical changes. In the Iowa Longitudinal Study, patients were divided into those that received high (mean dose, 929.4 CPZE mg), intermediate (mean dose, 391.7 CPZE mg), and low daily antipsychotic dose (mean dose, 111.5 CPZE mg) (Ho et al., 211; Andreasen et al. 2013). Patients in the top tertile had smaller frontal gray matter volume compared to those in the lowest tertile; this association however was independent of follow-up duration. Conversely, in the University Medical Center Utrecht longitudinal cohort, cortical thickness reduction over the 5-year follow-up period was associated with antipsychotic class (van Haren et al. 2011), being more pronounced in those treatment with FGAs. The main SGA prescribed in this cohort was olanzapine; higher exposure to olanzapine over the follow-up period (in mg per year) was associated with a non-significant increase in whole-brain gray matter volume. A different pattern was observed in patients with emergent treatment resistance that were prescribed clozapine at any point during the follow-up period. These patients showed more pronounced cortical thinning in the left superior temporal cortex compared to all other patients, and those prescribed higher doses of clozapine (in mg per year) showed further thinning in the PFC and ACC.

Similar results were reported by Vita and colleagues who examined the association between antipsychotic dose and class (FGA or SGA) on ROIs involving whole-brain, frontal, temporal, and parietal gray matter volume derived from 18 longitudinal studies (range of follow-up: 1–7 years) yielding a cumulative sample of 1155 patients with schizophrenia and 911 healthy individuals (Vita et al. 2015). Patients treated with FGAs or a combination of FGAs and SGAs showed reductions in all gray matter measures over time; the greater the exposure to FGAs during the inter-scan period, both in terms of cumulative and mean daily dose, the greater

the reduction in whole-brain gray matter volume. By contrast, the higher the mean daily dose of SGAs during the follow-up, the lower the reduction in whole brain gray matter volume. A larger ROI-based meta-analysis by Fusar-Poli et al. (2013) of 30 studies comprising MRI data from of 1046 schizophrenia patients and 780 controls over a median follow-up period of over 1-year, also confirmed that progressive whole-brain gray matter volume decreases and lateral ventricular enlargement were associated with greater cumulative exposure to higher antipsychotic doses. This meta-analysis however did not consider antipsychotic class.

The study by Lieberman et al. (2005) merits special attention because their sample of patients with first-episode schizophrenia (n = 263) was randomized to double-blind treatment with the SGA olanzapine, 5–20 mg/day, or the FGA haloperidol, 2–20 mg/day, for up to 104 weeks. This random assignment enabled investigators to disentangle the effect of antipsychotic class from patient- and physician characteristics that may drive medication regimes in clinical settings. Patients were assessed by MRI at weeks 0 (baseline), 12, 24, 52, and 104 and were compared to 58 healthy study participants. At study end, the sample with available data comprised 239 patients with a baseline MRI, and 161 patients with at least one follow-up assessment. By week 12, patients' rate of whole-brain gray matter volume reduction was steeper in the haloperidol- versus the olanzapine-treatment group and the magnitude of this difference remained largely constant to the study end. These group differences were driven by volume loss in haloperidol-treated patients, which was absent in the olanzapine-treated patients. The same pattern was noted for frontal, temporal, and parietal gray matter volumes. The volume of the caudate showed greater enlargement in the haloperidol- compared with the olanzapine-treatment group beginning at week 24.

2.3.3.4 Gray Matter Alterations in Medication-Naïve Patients

Studies on medication-naïve patients are particularly useful in disentangling disease- versus medication-related brain structural changes.

Fusar-Poli et al. (2012) identified 14 studies with structural MRI data, collectively contrasting 206 antipsychotic-naive patients with first-episode psychosis (mean age of 26.4 years) to 202 healthy individuals. They found consistent and significant gray matter reductions ($g = 0.83$) (but no increases) in patients compared to healthy individuals that clustered within the superior temporal gyrus, the insula, and the cerebellum. These findings were largely replicated in a further meta-analysis by Haijma et al. (2013) who also found that medication-naïve patients, compared to healthy individuals, had smaller intracranial ($d = -0.14$), whole-brain ($d = -0.21$), whole-brain gray matter ($d = -0.36$), thalamic ($d = -0.68$), and caudate ($d = -0.38$) volumes.

2.3.4   Substance Use

Substance use, and particularly cigarette smoking, cannabis and alcohol, is highly prevalent in schizophrenia, affecting approximately 40% of patients (de Leon and Diaz 2005; Hunt et al. 2018). In MRI studies of non-psychotic populations, cannabis (Martín-Santos et al. 2010), cigarette smoking (Gallinat et al. 2006), and alcohol abuse (Zahr and Pfefferbaum 2017) have all been associated with diminished brain tissue volumes. Therefore substance abuse has the potential to exacerbate volume reductions in schizophrenia. Supporting evidence has been provided mainly from the University Medical Center Utrecht cohort, by Rais et al. (2008) who reported that first-episode patients who continued to use cannabis over the 5-year follow-up period showed greater reduction in gray matter volumes and increased ventricular enlargement compared to those that did not abuse cannabis. The effect of cannabis was most pronounced in regions rich in cannabinoid receptors (CB1) within the dorsolateral PFC, the ACC, and the occipital cortex (Rais et al. 2010). However, in a review of the literature, Malchow et al. (2013) cautioned that the effect of cannabis on brain structure in patients with schizophrenia is inconsistent and is likely to be small. Finally, a meta-analysis of the relevant literature, showed that alcohol abuse in patients with schizophrenia was associated with thinner cortex and enlarged ventricles but the magnitude of this effect was commensurate to that seen in non-psychotic individuals (Lange et al. 2017).

2.3.5   Stress and Cardiometabolic Risk Factors

There is substantial support for elevated baseline activity of the hypothalamic-pituitary-adrenal (HPA) axis, the central stress response system, in patients with psychosis (Borges et al. 2013; Walker et al. 2008). It is generally known that HPA hyperactivity is associated with microstructural abnormalities and volume loss in the hippocampus, which is a key target region for glucocorticoids (Sapolsky 2003). At present, the link between hippocampal volume reduction and HPA activity is based on a sample of 24 patients with first-episode schizophrenia where an inverse association was found with cortisol levels both cross-sectionally and at 3-month follow-up (Mondelli et al. 2010).

Patients with schizophrenia are at risk of developing cardio-metabolic disease for several reasons including genetic predisposition to diabetes (Ryan et al. 2003), reduced physical activity (Rosenbaum et al. 2014), and the metabolic side-effects of antipsychotic medications (Mitchell et al. 2013). It has been estimated that at least a quarter of all medicated patients meet criteria for metabolic syndrome (Mitchell et al. 2013). In non-psychotic populations (Doucet et al. 2018; Medic et al. 2016; Yates et al. 2012), the presence of metabolic syndrome (comprising insulin resistance, obesity, dyslipidemia and hypertension), or merely increased body mass index (BMI), is associated with cortical thinning. There are only two studies that have addressed the effect of BMI on brain morphometry in patients with schizophrenia. Jørgensen et al. (2017) obtained MRI data from patients with first-episode schizophrenia (n = 78) and healthy individuals (n = 119) at intake and then 1 year later. Increases in BMI over the follow-up period showed a small negative association ($\beta = -0.19$) with whole-brain and whole-brain gray matter volume change, which was however similar in magnitude in both groups. Moser et al.

(2018) used a multivariate machine approach to examine the effect of BMI on MRI measures from 100 patients with recent-onset schizophrenia (illness duration <5 years) while simultaneously modelling correlations with clinical and cognitive symptoms, substance use, psychological trauma, physical activity, and medication (Fig. 2.4). Even after accounting for these multiple variables, BMI was negatively and significantly associated the cortical thickness (r = −0.28).
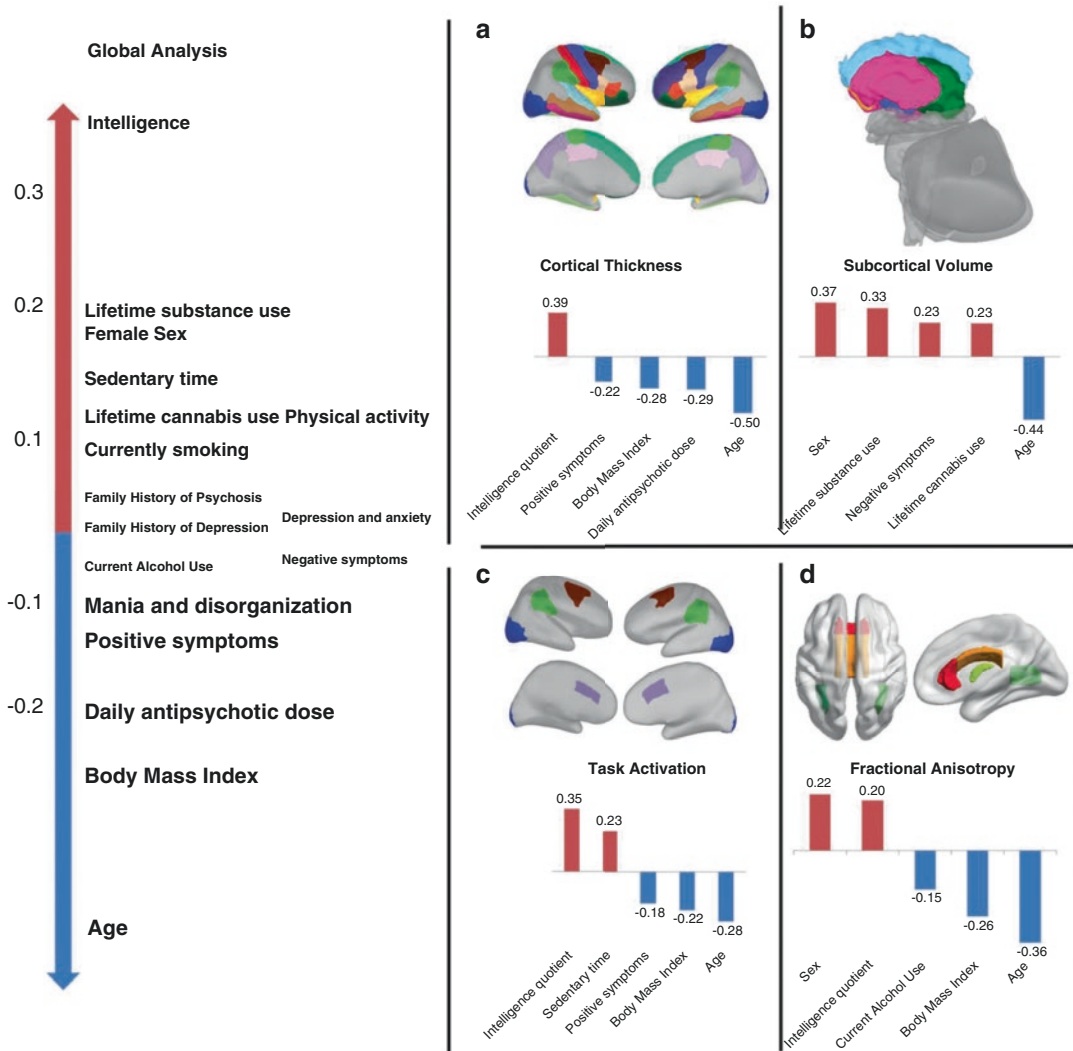

Fig. 2.4 Multivariate associations between behavioral, clinical and multimodal imaging phenotypes in psychosis. Right Panel: Association between neuroimaging and non-imaging variables across all imaging modalities. Left Panel: (**a**): Regional cortical thickness measures correlated most highly with non-imaging variate (top) and correlations between non-imaging variables and cortical thickness variate (bottom). (**b**): Subcortical volumetric measures correlated most highly with non-imaging variate (top) and correlations between non-imaging variables and subcortical volumes variate (bottom). (**c**): Regional task-related brain activation correlated most highly with non-imaging variate (top) and correlations between non-imaging variables and task-related brain activation variate (bottom). (**d**): Regional fractional anisotropy measures correlated most highly with non-imaging variate (top) and correlations between non-imaging variables and fractional anisotropy variate (bottom) Results from sparse canonical correlation analyses from Moser et al. (2018). (From https://www.ncbi.nlm.nih.gov/pubmed/29516092)

2.4   Overview of Findings

The studies presented in the preceding sections provide evidence for the following statements: (1) schizophrenia-related gray matter alterations consist mostly of subtle and widespread reductions in cortical and subcortical gray matter density and volume and in cortical thickness; these gray matter alterations occur in the context of a small but significant reduction in intracranial volume (ICV) in patients with schizophrenia (effect size −0.2) (Haijma et al. 2013); (2) tissue loss is most prominent in the temporal (inferior, middle and superior temporal and parahippocampal gyri), the occipital and the frontal (lateral orbitofrontal and inferior frontal gyrus) cortex, in the posterior ACC, and in the insula; notably regions within the motor (precentral gyrus), somatosensory (postcentral gyrus), and parietal (superior and inferior parietal cortex and paracentral lobule) cortex may show tissue gain; (3) gray matter tissue reductions are largely present at the time of the first psychotic episode and may be greatest early in the course of illness, mirroring the social and occupational deterioration which seems more pronounced in the early stages of psychosis (Häfner and Maurer 2006); (4) after illness onset, the slope of age-related decline in cortical regions appears to be steeper in patients with schizophrenia than in healthy individuals but of small magnitude; it is estimated that the cumulative loss of brain tissue after 20 years of illness is approximately 3% (Hulshoff Pol and Kahn 2008; Wright et al. 2000); (5) the association between gray matter alterations and clinical outcome is complex; the general pattern suggests that whole-brain gray matter reductions are more pronounced in patients that are more symptomatic and have poor clinical and functional outcomes; (6) sex differences in schizophrenia-related gray matter alterations are small, and when present they indicate greater deviance in male patients; (7) antipsychotic drugs, and particularly FGAs, have been associated with progressive striatal and ventricular enlargement and diffuse cortical thinning; (8) several factors including HPA dysregulation, substance abuse, stress, higher BMI, and cardiometabolic risk are likely to contribute to the gray matter alterations observed in schizophrenia (Fig. 2.5).

2.5   Mechanistic Implications and Future Directions

Structural MRI as applied to the studies described above lacks the resolution to inform us about the nature of pathogenetic processes underlying gray matter changes in schizophrenia. Furthermore, the processes involved may not affect all patients in the same fashion. Studies that have applied multivariate clustering techniques to multimodal datasets from patients with schizophrenia (i.e., datasets that include clinical, genetic, cognitive and brain phenotypes) hint at the presence of multiple, partially overlapping syndromes that may be associated with a discrete set of risk factors (Arnedo et al. 2015; Zheutlin et al. 2018). No systematic examination, however, has been undertaken to date to examine the association between gray matter integrity and risk-conferring gene variants or other non-genetic risk factors. A meta-analyses of the limited neuroimaging studies available have implicated a four-marker haplotype in G72, a microsatellite and single nucleotide polymorphism in NRG1, DISC1, CNR1, BDNF, COMT and GAD1; these associations were of small or medium magnitude and were most frequently observed in frontal regions (Harari et al. 2017).

The gray matter changes in patients with schizophrenia should be considered in the context of ICV reduction, a consistent finding in MRI studies of schizophrenia (Haijma et al. 2013). The expansion of the skull, which determines ICV, is driven by brain growth (O'Rahilly and Müller 2001) and reaches its maximum size at approximately 13 years of age (Blakemore 2012). The reduced ICV in patients suggests that the biological process leading to overt disease may be active early in development. As already discussed, there are progressive post-onset changes in brain and gray matter volume that are indicative of on-going disease related mechanisms that lead to further compromise in brain structural integrity.
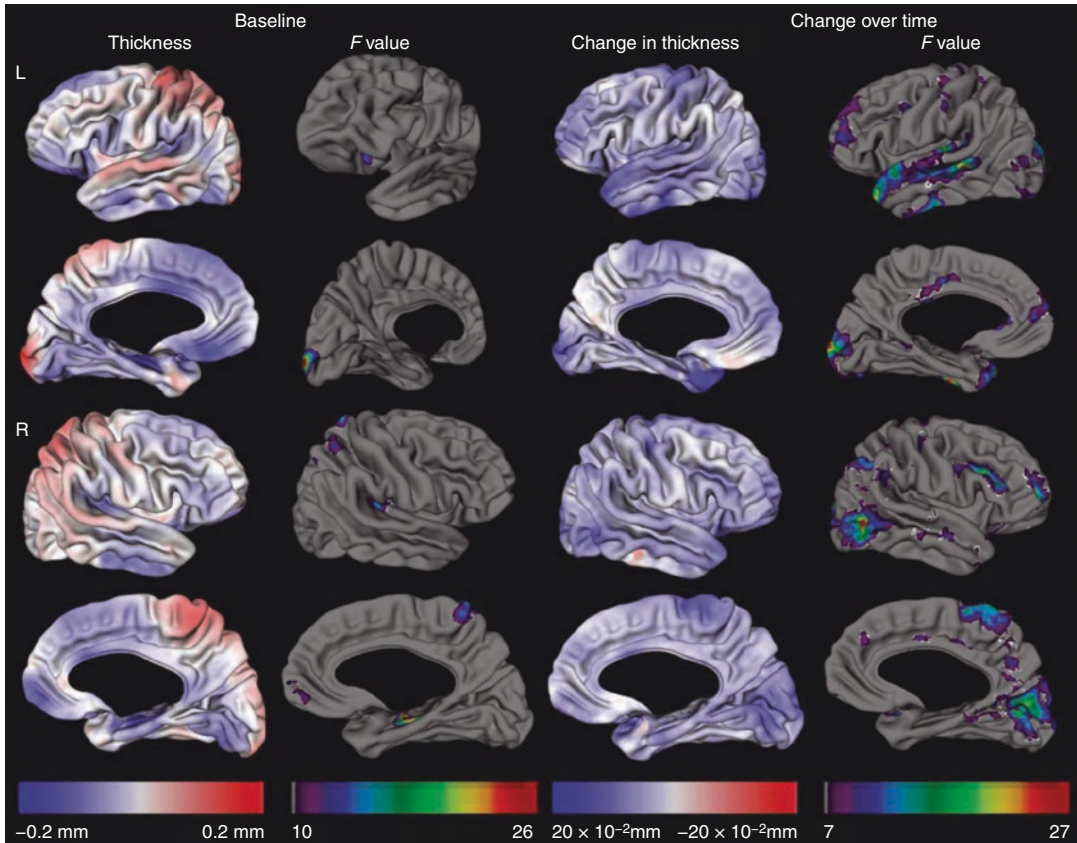
Fig. 2.5 Maps of change in cortical thickness in millimeters and F values, showing reduction (blue) or excess (red) at study entry (patients with schizophrenia = 154, controls = 156) and during the 5-year interval (patients = 96, controls = 113) (van Haren et al., 2011; https://www.ncbi.nlm.nih.gov/pubmed/21893656)

Traditional models of schizophrenia emphasize neurotransmitter abnormalities mostly in the dopaminergic (Howes and Kapur 2009) and glutamatergic systems (Moghaddam and Javitt 2012). According to the dopamine hypothesis, schizophrenia is characterized by hyperactive transmission in the striatal areas and hypoactive transmission in the prefrontal cortex as proposed by Davis and colleagues in 1991 and updated more recently by Howes and Kapur in 2009. In vivo and in vitro studies suggest that excess dopamine can trigger inflammation, oxidative stress, apoptosis, and mitochondrial impairment (Junn and Mouradian 2001). For example, prolonged stimulation of cortical neurons by excessive dopamine can induce calcium-related excitotoxicity and mitochondrial dysfunction through mitochondrial complex I inhibition (Ben-Shachar 2017). With respect to glutamate,

the primary excitatory neurotransmitter, gray matter pathology in schizophrenia may be linked to excitotoxic injury through excessive Ca2+ influx via the N-methyl-d-aspartate (NMDA-R) receptor (Moghaddam and Javitt 2012). Further, Ca2+ toxicity targets mitochondria leading to dysfunction, either directly or through oxidative inhibition of mitochondrial complexes I, II and V, ultimately activating death signals (Nicholls 2009; Davis et al. 2014).

Several other mechanisms have been proposed to explain the gray matter alterations observed in schizophrenia with most of the data derived from post-mortem studies. To-date, there is no convincing evidence that schizophrenia is associated with gliosis or neuronal cell loss or other histopathological changes commonly seen in degenerative disorders (Arnold et al. 1998; Baldessarini et al. 1997; Heckers

et al. 1991; Pakkenberg 1993; Thune et al. 2001; Walker et al. 2002). By contrast, decreased cortical neuropil, relative to specimens from psychiatrically-healthy individuals, has been one of the most replicable post-mortem findings in schizophrenia (Selemon and Goldman-Rakic 1999). This reduction has been observed in multiple brain regions including primary sensory and associative cortices (Casanova et al. 2008). In a parallel line of research, replicable reductions have been noted in synaptic protein and mRNA levels in multiple cortical regions, although the precise distribution of these changes cannot be fully evaluated because of limited brain coverage of the available data. The most robust, modest, reductions have been noted for synaptophysin (a neuron-specific presynaptic protein) particularly within the hippocampus, but also in dorsolateral PFC and ACC as these regions are preferentially sampled in schizophrenia research (Osimo et al. 2018). Additional but smaller reductions in other synaptic proteins (i.e., SNAP-25, PSD-95, synapsin and rab3A) have also been consistently noted in the hippocampus while data for other brain regions are very limited (Osimo et al. 2018). Whether these changes are developmental or whether they occur later in life remains unknown as post-mortem studies are restricted to chronic cases.

Some researchers have proposed that mitochondrial dysfunction (either primary or induced) may contribute to the neuronal, dendritic, and synaptic abnormalities seen in schizophrenia. While the brain comprises less than 2% of the human body mass, it consumes 20% of the energy expensed. ATP production is therefore crucial for cellular homeostasis, electrical conductivity, and synaptic function; neurons are critically dependent on the mitochondria to generate the requisite amounts of ATP. Evidence of abnormal energy generation in schizophrenia has been known since Looney and Childs (1934) who reported increased lactate and decreased glutathione in blood samples from schizophrenic patients. In post-mortem brain tissue from patients with schizophrenia, mitochondria are differentially affected depending on the brain region, cell type, and subcellular location. The overall pattern

however indicates that mitochondria, particularly in or near the synapses and neuropil, are functionally compromised (Roberts 2017).

Mitochondrial DNA is susceptible to damage from reactive oxygen species (Corral-Debrinski et al. 1992) while release of mitochondrial DNA during cell stress can trigger inflammatory responses (López-Armada et al. 2013; Naik and Dixit 2011; Oka et al. 2012). There is substantial evidence implicating oxidative/nitrosative stress pathways in the pathophysiology of schizophrenia as recently shown in a meta-analysis of 61 independent cohorts comprising blood samples from 3002 patients with first-episode schizophrenia and 2806 healthy individuals; patients had lower total antioxidant status and docosahexaenoic acid (DHA) levels and higher levels of homocysteine, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (Fraguas et al. 2018). Moreover, a recent meta-analysis of post-mortem studies (n = 41; 783 patients and 762 controls) by van Kesteren et al. (2017) confirmed that despite significant inter-study heterogeneity, both microglia density and the concentrations of pro-inflammatory proteins are increased in schizophrenia. These changes were particularly evident in temporal cortical regions. Direct in-vivo evidence that these mechanisms operate centrally is currently lacking. Neuroimaging studies attempting to quantify case-control differences in central pro-inflammatory markers have focused on the activation state of microglia. Activated microglia expresses higher levels of the 18-kDa translocator protein (TSPO) (Cosenza-Nashat et al. 2009) which can be measured in vivo using positron emission tomography (PET) radiotracers. Studies using this methodology have thus far failed to provide consistent support for an increase of TSPO in schizophrenia (Plaven-Sigray et al. 2018; Marques et al. 2018), and the heterogeneity between studies is at least partly attributable to on-going methodological challenges (Plavén-Sigray and Cervenka 2019).

Finally, there is also evidence for myelin-related dysfunction in schizophrenia, which could also account for the observed decreases in brain tissue. Maturational changes in intracortical myelination occur in late adolescence

and early adulthood and coincide with the peak period of risk for schizophrenia (Bartzokis 2002; Paus et al. 2008; Rapoport et al. 2005; Weinberger 1987). Several oligodendrocyte/myelin related genes, such as neuregulin and its receptor ERBB4, are genetically associated with schizophrenia (Karoutzou et al. 2008; Norton et al. 2006). Post-mortem studies in schizophrenia have reported compromised integrity of the myelin sheath (Uranova et al. 2001), abnormal oligodendrocyte density and morphology (Uranova et al. 2004), and expression of genes associated with oligodendrocytes and myelin in multiple brain regions (Dratcheva et al. 2006; Hakak et al. 2001; Katsel et al. 2005). These findings do not seem attributable to antipsychotic exposure (Hakak et al. 2001; Konopaske et al. 2008). In vivo neuroimaging studies of intracortical myelination in schizophrenia have yielded variable results. Nevertheless, reduced intracortical myelin has been found in the prefrontal cortex (Bagary et al. 2003; Bohner et al. 2012; Price et al. 2010), temporal lobes (Foong et al. 2000) and primary/association visual cortex (Bachmann et al. 2011; Palaniyappan et al. 2013). A more recent and larger study reported myelin reduction in patients with schizophrenia compared to controls in the sensorimotor cortex, the transverse temporal gyri, the cuneus, and in the visual cortex (Jørgensen et al. 2016).

The small effect size of case-control differences in gray matter integrity and the multiplicity of potential mechanisms and moderators argue that future research efforts will require adequately powered large-scale projects comprising multiscale measures (e.g., genetic, molecular, neuroimaging, clinical, and cognitive) from patients and healthy individuals. It is widely accepted that adolescent mental health problems arise from complex interactions between these factors. Examination of these interacting influences requires advanced multivariate modelling and significant computing power in order to simultaneously handle high-dimensional datasets. This is an emerging field with multiple groups endeavoring to define optimal statistical algorithms and to test the validity of the resultant models (e.g., Nymberg et al. 2013).

Summary

- Gray matter alterations in schizophrenia comprise subtle and widespread reductions in cortical and subcortical gray matter density and volume and in cortical thickness in the context of reduction in intracranial volume.
- Gray matter tissue reductions seem to occur at the time of the first psychotic episode and may mirror the social and occupational deterioration observed in the early stages of psychosis.
- After illness onset, the slope of age-related decline in cortical regions appears steeper in patients with schizophrenia than in healthy individuals; these age-related changes may be exacerbated by the use of first-generation antipsychotics.
- Factors that may contribute to gray matter abnormalities in schizophrenia also include substance abuse, stress, and cardiometabolic dysregulation.

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