INTRODUCTION

Schizophrenia is generally a chronic and disabling mental health condition associated with positive (psychotic symptoms such as delusions, hallucinations), negative (such as anhedonia, asociality) and cognitive symptoms (such as impaired working memory and executive function) [1]. The first positive symptoms typically develop after cognitive and negative symptoms [1].

Excessive loss of synapses has been hypothesised to lead to the disorder, and may also occur during the disorder, contributing to long-term disability [2–4]. It has the potential to explain a number of aspects of the pathophysiology, epidemiology and clinical presentation of the disorder [5].

There are two key bodies of in vitro evidence supporting the hypothesis that there is lower synaptic density in schizophrenia. Firstly, post-mortem studies of brain samples from patients with schizophrenia have been used to investigate synaptic markers. This includes measuring protein and mRNA levels of synaptophysin, a presynaptic protein considered the in vitro gold standard marker for synaptic density [6]. Upon meta-analysis, synaptophysin levels have been shown to be significantly lower in the cingulate cortex (predominantly anterior part), frontal cortex and hippocampi of patients relative to controls [6]. In addition to this, markers of postsynaptic density are also lower across a number of brain regions in patients with schizophrenia relative to control samples [7]. Studies that use electron microscopy and manual counting also show lower synaptic spine levels in cortical regions [8–10].

Secondly, studies of neurones cultured from induced pluripotent stem cells (iPSCs) from patients with schizophrenia have investigated synaptic markers, generally, relative to non-isogenic control lines. These studies show impaired branching and synaptic formation [11, 12], as well as providing evidence of excessive elimination of synapses in vitro associated with schizophrenia genotypes [13, 14].

However, whilst these findings provide evidence for lower synaptic markers in schizophrenia, it is not clear if this is the case in vivo. To address this, we aim to review and critique in vivo neuroimaging findings that potentially capture information about synaptic density or synaptic activity to consider the nature of the brain changes in schizophrenia and address the question of whether there is lower synaptic density in schizophrenia. We consider structural imaging approaches using magnetic resonance imaging (MRI) measures of gyri
cation index, grey matter volume, grey matter density and cortical thickness, because changes in these have been interpreted as reflecting synaptic loss in schizophrenia [15–18]. We first focus on findings in patients with
chronic schizophrenia, then in first episode psychosis and genetically and clinically high-risk individuals, and review longitudinal data where available. We then overview findings from positron emission tomography (PET) imaging of regional glucose metabolism, and magnetic resonance spectroscopy (MRS) measures of neuronal metabolic function in patients with schizophrenia. Finally, we review PET imaging of synaptic protein 2A in schizophrenia, outlining remaining questions and identify areas for future research.

**METHODS**

We conducted a series of literature searches to identify relevant studies using PubMed and Google Scholar databases (search from 1st January 1966 to 31st March 2022) and supplemented these with hand-searching of reference lists. We identified the most recent meta-analyses and summarise these to provide an overview of the magnitude and consistency of findings for each imaging approach. A summary of the imaging techniques included can be seen in Fig. 1. Where meta-analyses were not available, we identified the most recent systematic reviews or, where these were not available, the largest studies available to date. The search terms and numbers of key publications included can be found in the supplementary materials. Effect sizes throughout are defined as small if Hedges’ g/Cohen’s d in the [0.2 – 0.5] range, medium effect sizes include Hedges’ g/Cohen’s d < |0.2|, medium effect sizes include large if Hedges’ g/Cohen’s d > |0.5|.

**Gyrification and gyration index**

Gyrification is the folding of the cerebral cortex which gives rise to characteristic peaks (gyri) and troughs (sulci). Gyrification increases the brain’s surface area:volume ratio, maximising the number of neurones and the efficiency of their communication [19]. The gyrification index (GI) is the ratio of the length of the complete (i.e. folded) cortical contour to the length of the outer (i.e. smooth) brain surface. Thus, a higher GI indicates more extensive cortical folding [20].

The only meta-analysis of GI studies to date found a lower local GI in schizophrenia patients than controls in fronto-temporal regions with a small effect size (Hedges’ g = −0.2) [21]. However, it included data from just six cross-sectional patient cohorts, partly because it only included studies published between 2010 and 2020, and it should be recognised that studies not included have found evidence for higher GI in schizophrenia [22, 23]. These inconsistencies may be at least partly explained by the stage of illness, as studies in younger patients (typically in their first episode) and those at high risk of psychosis predominantly show evidence for higher gyrification in the frontal cortex [22–27], whilst studies of patients with chronic illness tend to show lower gyrification relative to controls [27, 28].
In addition, longitudinal studies have shown that GI reduces with duration of psychosis in the same subjects [29, 30]. Thus, higher gyriﬁcation early in schizophrenia, followed by a process leading to reductions in GI in chronic illness, could explain the apparently conﬂicting ﬁndings between studies. Indeed, this idea is supported by a recent mega-analysis of data from over 670 individuals [27].

How might GI changes reﬂect synaptic changes? Synaptic density reﬂects the balance between synaptogenesis and synapse loss and is additionally affected by synaptic spine dynamics such as synaptic remodelling and stabilisation. Synaptogenesis increases rapidly early in neurodevelopment, exceeding the rate of synaptic loss, so that synaptic density increases markedly post-partum until it starts to level-off in early childhood [31–33]. Following this period, synaptic pruning is thought to exceed synaptogenesis, so that synaptic density declines into the third decade of life before plateauing from the fourth decade until older age. This process varies by brain region, with higher-order regions such as the prefrontal cortex maturing later [31–34]. Two large studies of over 1100 healthy individuals aged 3–83 years found that GI was highest at around 3 years and gradually declined throughout adulthood, similar to the trajectory of synaptic changes [35, 36]. Synaptic pruning may release tethering connections between sulci and gyri, causing sulcal widening and gyral peakedness [19]. Supporting this, computational work shows that cortical folding in primates is determined through mechanical forces arising from synaptic connections between migrating axons [37]. These “tension-based” mechanisms are considered key to cortical folding during neurodevelopment [38]. Importantly, this process could be exaggerated in schizophrenia, which may explain the longitudinal ﬁndings of GI reductions as the disease progresses [30].

However, there are two key limitations of GI measures and their application to the synaptic hypothesis. Firstly, there are inconsistent ﬁndings, particularly regarding whether ﬁrst episode patients show higher or lower gyriﬁcation relative to controls, indicating that further work, particularly longitudinal studies in ﬁrst episode patients, is needed. Secondly, GI is not a direct measure of synaptic density. Neuronal loss and demyelination, which are uncontrolled in most in vivo studies of gyriﬁcation [39], may contribute to altered GI [31, 40]. Moreover, the relationship between changes in GI and synaptic markers (such as synaptophysin or SV2A) remains unprobed. Thus, although GI differences in schizophrenia are consistent with synaptic alterations, they may not be due to synaptic alterations and further research is needed to establish the exact relationship between synaptic loss and GI changes.

**Grey matter volumes and cortical thickness**

*Studies of schizophrenia groups.* Over the last three decades there have been more than 500 structural MRI studies including over 38,000 volunteers comparing brain volumes between people with schizophrenia and healthy controls [41–49]. Fortunately, these ﬁndings have been synthesised in a series of comprehensive meta-analyses. Comparisons between groups can be made between volumes of deﬁned regions of interest, generally based on anatomically deﬁned structures, or at the level of the voxel. These provide complementary information, with the former allowing hypotheses concerning particular anatomical structures to be tested, whilst the latter are not generally constrained by anatomical delineations and so may detect the pattern of differences across the whole brain and within regions.

In 2019, Kuo & Pogue-Geile undertook a meta-analysis comparing brain volumes between people with chronic schizophrenia and healthy controls [41]. Their results, summarised in Table 1 below, demonstrate statistically signiﬁcant increases in lateral and third ventricle volumes, and signiﬁcantly lower intracranial, total brain and total grey matter volumes, as well as smaller volumes of a number of grey matter brain structures, including bilateral frontal lobes, bilateral prefrontal lobes, bilateral superior temporal gyri, bilateral hippocampi, bilateral fusiform and left insula in schizophrenia [41]. The increases in ventricular volume are generally assumed to reﬂect loss of volume in grey matter, and potentially other structures, given evidence that intra-cranial volume is, if anything, smaller in people with schizophrenia [50].

These results are consistent with those from a voxel-wise, coordinate-based meta-analysis by Glahn et al. [45], which included data from 1195 schizophrenia patients and 1262 healthy control subjects. They found lower grey matter density relative to controls in a network of regions, which included the bilateral insular cortex, anterior cingulate gyrus, left parahippocampal gyrus, middle frontal gyrus, postcentral gyrus and the thalamus [45]. Interestingly, data from 15 of the 31 studies analysed demonstrated increased grey matter density in some brain areas, notably striatal regions such as the left and right putamen and the right head of the caudate. As many of the patients in these studies had taken antipsychotic treatment for many years, and given that all antipsychotic drugs bind to D₂ receptors, which are highly expressed in the striatum [51, 52], this could be an effect of antipsychotic treatment.

To exclude potentially confounding effects of antipsychotic use on grey matter morphology in schizophrenia, Gao et al. compiled evidence from 15 structural MRI studies comprising 486 drug-free patients and 485 healthy controls in 2018 [44]. In this analysis, researchers observed signiﬁcantly lower grey matter volumes in four main neuroanatomical regions in patients with schizophrenia versus controls: left fusiform gyrus, left inferior frontal gyrus, right superior temporal gyrus and left supramarginal gyrus. These regions overlap with the regions identiﬁed in the other meta-analyses that included antipsychotic treated patients. Interestingly, this antipsychotic-free schizophrenia group did not show increased grey matter volume in the striatum but did show increases in right lingual gyrus and right superior frontal gyrus (orbital part) volumes. However, it should be noted that, antipsychotic-free subjects included in this study were not necessarily antipsychotic-naïve, as some patients had been treated but had undergone a medication wash-out prior to scanning, so it remains possible that prior treatment has had some inﬂuence on ﬁndings [44]. Notwithstanding this, the predominant ﬁndings are of decreased grey matter volumes in cortical and subcortical regions in schizophrenia, in conjunction with smaller areas of modest increases in grey matter volumes. These studies were predominantly in patients with chronic illnesses. This raises the question of whether grey matter volume alterations are present early in the course of illness or only emerge later. Findings by Brugger and Howes show statistically signiﬁcant higher ventricular volumes and lower mean volumes of the amygdala, anterior cingulate cortex, frontal lobe, hippocampus, temporal lobe and thalamus in ﬁrst episode psychosis when compared to controls (see Table 1 and Fig. 2 for details) [42]. Overall, the ﬁndings indicate reduced grey matter volume across several regions, particularly frontal and temporal cortical regions, in schizophrenia, and that these are also evident in the ﬁrst episode psychosis subgroup, and after accounting for confounding factors such as the effects of long-term antipsychotic use. This raises the question of whether alterations are also seen in people at risk for schizophrenia. To address this, we now consider brain volume abnormalities observed in genetically and clinically high-risk populations.

*Studies of people at familial and genetic high-risk of schizophrenia.* The ﬁrst-degree relatives of people with schizophrenia may carry genetic risk variants associated with schizophrenia. They are also likely to have shared similar environments. In 2019, de Zwarte et al. [53] showed that, after correction for intracranial volume, ﬁrst-degree relatives of patients with schizophrenia had signiﬁcantly smaller total brain (Cohen’s d = −0.16, q < 0.05, corrected), total
Table 1. Summary of structural MRI findings by brain region for grey matter volumes in schizophrenia/people at risk of schizophrenia relative to healthy controls unless otherwise stated from recent meta-analyses, giving effect sizes (< indicates lower in schizophrenia).

| ROI | Mean effect size (d) corrected for ICV | p | Mean effect size (g) | p | Mean effect size (g) | p | Mean effect size (d) | p |
|-----|--------------------------------------|---|----------------------|---|----------------------|---|----------------------|---|
| Accumbens | −0.05 | Not significant [95% CI: −0.13, 0.02] | | | | | | |
| Amygdala | 0.00 | Not significant [95% CI: −0.11, 0.11] | | | −0.46 | <0.001 |
| Anterior cingulate cortex (left) | | | | | −0.26 | 0.006 |
| Anterior cingulate cortex (right) | | | | | −0.39 | 0.0005 |
| Caudate | −0.03 | Not significant [95% CI: −0.11, 0.04] | | | −0.11 | Not significant (p = 0.23) |
| Frontal lobe | −0.47 | <0.001 | | | −0.31 | <0.001 | −0.31 | 0.003 |
| Fusiform (left) | | | | | −0.60 | <0.005 |
| Fusiform (right) | | | | | −0.45 | | |
| Grey matter (total) | −0.81 | <0.001 | | | | | −0.38 | <0.001 |
| Grey matter (cortical) | −0.11 | q < 0.05 corrected | | | | | | |
| Hippocampus | −0.06 | Not significant [-0.14, 0.02] | | | −0.66 | <0.001 | −0.49 | <0.001 |
| Insula (left) | | | | | −0.46 | 0.045 |
| Insula (right) | | | | | | | Not significant |
| Intracranial volume | n/a | | | | −0.12 | <0.001 |
| Lateral ventricles | 0.09 | p < 0.05 uncorrected | 0.40 | <0.001 | 0.44 | <0.001 |
| Prefrontal lobe | | | | | −0.40 | <0.001 |
| Pallidum | −0.05 | Not significant [95% CI: −0.12, 0.02] | | | | | | |
| Putamen | −0.07 | Not significant [95% CI: −0.14, 0.01] | | | −0.31 | 0.11 |
| Superior temporal gyrus (left) | | | | | −0.57 | 0.01 |
| Superior temporal gyrus (right) | | | | | −0.38 | 0.0008 | −0.90 |
| Temporal lobe | −0.84 | <0.001 | −0.22 | 0.001 | −1.09 | 0.029 |
| Thalamus | −0.13 | q < 0.05 corrected | | | −0.36 | 0.001 |


| ROI | Mean effect size (d) for ICV | Mean effect size (p) | p | Mean effect size (g) | p | Mean effect size (d) | p | Mean effect size (d) | p |
|-----|-----------------------------|----------------------|---|----------------------|---|----------------------|---|----------------------|---|
| Third ventricle | 0.15 | q < 0.05 corrected |     | 0.12 | < 0.05 corrected |     | 0.52 | < 0.001 |
| Total brain volume | −0.96 | < 0.001 |     | 0.43 | < 0.001 |     | −0.25 | < 0.001 |

Dark grey boxes indicate data not reported, light grey boxes indicate no significant difference, and white boxes show significant differences.

ICV, intracranial volume; GMV, grey matter volume; ROI, region of interest.

In conclusion, the meta-analyses to date of those at familial and/or genetic risk of schizophrenia demonstrate lower grey matter volume relative to controls. The only subcortical subregion to demonstrate consistent grey matter differences across all studies is the thalamus (d = −0.12, g = 0.05, corrected) and cerebellar grey matter (d = −0.11, g = 0.05, corrected). These findings suggest that grey matter volume differences are relatively specific to schizophrenia, and may be a marker of increased risk for the development of psychotic disorder.
above) in the right temporal lobe ($g = −0.38$) and anterior cingulate/paracingulate cortex ($g = −0.39$) relative to CHR participants who did not develop a disorder during the studies (Table 1) [43]. This suggests that lower grey matter volumes in fronto-temporal regions are associated with the prodrome to schizophrenia rather than the expression of sub-clinical symptoms, indicating specificity to the development of the disorder.

**Longitudinal structural imaging studies.** Given that, in absolute terms, the effect sizes for lower grey matter volumes are larger in people with chronic schizophrenia than in first episode samples (Table 1), a key question, then, is whether structural brain changes are progressive. However, there are other potential explanations, such as cohort effects. For example, first episode cohorts typically include a proportion of patients who recover and stay well, and are thus not included in samples of patients with chronic illness [59, 60]. It is possible that this subgroup has less marked grey matter alterations, although this remains to be tested. However, if this is the case, the failure to include the sub-group with a good outcome in studies of patients with chronic illness may explain the larger grey matter changes relative to controls than are seen in first episode studies. Longitudinal studies have addressed this issue by measuring changes in grey matter volumes over time in the same subjects.

In 2012, Vita et al. meta-analysed data from 813 subjects with schizophrenia and 718 healthy controls. They found that the schizophrenia group demonstrated a statistically significant greater volume loss over time in total cortical grey matter and in other brain regions, including the left superior temporal gyrus, left anterior superior temporal gyrus; left Heschl gyrus; left planum temporale; and posterior superior temporal gyrus bilaterally [61]. As can be seen in Fig. 3, these differences are subtle, with about a 0.5% greater loss of total grey matter each year in the schizophrenia group than healthy controls. Longitudinal studies have addressed this issue by measuring changes in grey matter volumes over time in the same subjects.

![Fig. 2](image-url) **Brain volume differences in patients with first episode psychosis relative to controls.** Meta-analytic results of regional brain volume differences between patients with first episode psychosis and healthy control subjects, adapted with permission from Brugger and Howes (2017). ACC anterior cingulate cortex.

These studies thus indicate that there is greater reduction in grey matter volumes in schizophrenia over time than in controls, but, as they predominantly included patients with chronic illness, it was unclear if this was present from illness onset. This was addressed in a systematic review by Gallardo-Ruiz et al. that focussed on studies of first episode patients. This found evidence for progressive grey matter volume loss in frontal, temporal (especially superior temporal regions), parietal cortices and a number of subcortical areas in patients from their first episode psychosis [62]. Similarly, further temporal analysis by Vita et al. in 2012 revealed that grey matter volume loss was most pronounced in the first episode psychosis subgroup with significant reductions observed in frontal, temporal and parietal lobes, and the left Heschl gyrus, compared to healthy controls. With respect to the clinical high-risk population, a 2021 systematic review by Merritt et al. echoed these findings, demonstrating that those suffering from psychotic experiences demonstrated a progressive decline in regional grey matter volumes, with changes most marked in the temporal, frontal, cingulate and parietal cortices [63].

**Antipsychotic use and volumetric findings.** Meta-analyses have shown that greater antipsychotic exposure is associated with greater case-control differences in both cross-sectional and longitudinal studies (46–49 see supplement for discussion). However, findings from longitudinal studies that adjust for antipsychotic exposure indicate that antipsychotic treatment is unlikely to account for all of the excess volume changes in schizophrenia [47, 48].

Overall, the longitudinal evidence demonstrates regions of greater progressive grey matter volume loss, particularly in fronto-temporal regions, in schizophrenia relative to controls from early in the illness, and antipsychotic use may contribute to this. However, whilst further work is needed to determine the potential contribution of other factors to excess changes in schizophrenia, several large longitudinal studies to date indicate that there is excess grey matter loss in schizophrenia that is not entirely accounted for by antipsychotic use.

**Cortical thickness**

Cortical thickness refers to the depth of the cortical grey matter in the orthogonal plane from the surface of the cortex, demarcated by the pia mater superficially and the white matter below. Regional variation in cortical thickness ranges from 1 mm (typically in Brodmann’s area 3) to 4.5 mm (generally Brodmann’s area 4) [64]. In 2018, van Erp et al. conducted a meta-analysis of cortical thickness and surface area abnormalities in schizophrenia. They collated data collected from 4474 individuals with schizophrenia and 5098 healthy volunteers. The schizophrenia individuals were found to have thinner cortices than healthy controls (right/left hemisphere: $d = −0.52/−0.53$ respectively) and in fronto-temporal...
regions (d < −0.40). Specifically, the largest negative effect sizes were in the fusiform gyri (right $d = −0.54$, left $d = −0.49$); superior temporal gyri (right $d = −0.44$, left $d = −0.44$); middle temporal gyri (right $d = −0.38$, left $d = −0.44$); inferior temporal gyri (right $d = −0.44$, left $d = −0.45$); left superior frontal gyrus ($d = −0.43$); right pars opercularis ($d = −0.42$) and insula cortex (right $d = −0.41$, left $d = −0.41$). With the exception of findings in the left superior frontal gyrus, most of the fronto-temporal differences remained statistically significant after controlling for global cortical thickness, which suggests lower cortical thickness in schizophrenia is particularly seen in fronto-temporal regions. Furthermore, there was a negative correlation between increasing age and bilateral temporal pole thickness, which was stronger in the schizophrenia group than in the healthy volunteers, suggesting an underlying process of progressive cortical thinning in schizophrenia consistent with the evidence for longitudinal grey matter volume loss, as outlined above [65].

As has been acknowledged elsewhere in this review, MRI findings can be influenced by multiple factors in addition to brain structure, and these need to be considered in their interpretation. In the case of cortical thickness, Weinberger & Radulescu (2021) outline that MRI findings suggestive of lower cortical thickness may, in fact, reflect increased myelin, which decreases T1 time and, in turn, the MRI measurement [66]. Thus, it is important to recognise that lower cortical thickness in schizophrenia may reflect alterations in other brain constituents rather than grey matter differences.

Neurite orientation dispersion and density imaging

Neurite Orientation Dispersion and Density Imaging (NODDI) is a type of diffusion weighted MRI that can distinguish between microstructural components in grey and white matter. It can be applied to imaging of grey matter regions to extract measures such as the Neurite Density Index (NDI) and Orientation Dispersion Index (ODI). NDI characterises the density of neurites by modelling the intra-neurite space, whilst ODI models the space between axons to calculate the angular variation of neurites, cell membranes, somas and glial cells [67–69]. Since the method was first published in 2012 [67], we identified only one study that has used it to investigate grey matter microstructure in patients with chronic schizophrenia [70, 71]. Patients showed lower NDI relative to healthy controls in the temporal pole, anterior hippocampal gyrus and hippocampus [70]. Studies of patients with psychotic disorders including schizophrenia additionally report lower ODI relative to healthy controls in the anterior cingulate cortex and medial frontal gyrus [72] and lower NDI in lateral prefrontal cortex, superior/medial frontal gyrus, central sulci, superior temporal gyrus, and middle temporal gyrus [73]. However, given that these studies include some patients with affective psychosis, these findings must be interpreted with caution in relation to schizophrenia [73]. Finally, one study carried out in first episode psychosis patients, taking medication, that focussed on the hippocampus as the only region of interest, found no differences in ODI or NDI [74]. Together these studies suggest that schizophrenia may be associated with disrupted grey matter microstructures, but there are inconsistencies. Further studies are required to replicate these findings, and to investigate the potential contribution of confounding factors such as antipsychotic use. Notwithstanding these caveats, lower NDI could partly reflect lower levels of pre/post-synaptic elements. However, it is not a direct measure of synaptic elements, and changes could reflect alterations in other microstructural elements, such as lower density or atrophy of myelinated axons [75, 76].

Summary of structural MRI findings and consideration of their implications

Meta-analyses demonstrate lower cortical and subcortical grey matter volumes and cortical thickness in patients with schizophrenia relative to healthy controls, with small to moderate effect sizes, although absolute volume differences are modest (~7% in fronto-temporal regions, and ~2% for whole brain grey matter [77]). Grey matter changes are progressive over time, from early in the course of the illness. Furthermore, grey matter loss in clinically at-risk groups is linked to subsequent transition to psychosis [43]. There are a number of potentially confounding factors in addition
to antipsychotic treatment, including higher rates of substance misuse and higher incidence of physical and psychiatric comorbidity in patients with schizophrenia than in healthy controls, which could putatively contribute to findings [50], although we were not able to find evidence to support their effects in the meta-analyses so it remains unclear how much they might contribute to findings, if at all. There are also important methodological considerations in addition to those already raised. In particular, people with schizophrenia show increased motion in scanners compared to healthy control subjects [78]. Whilst a variety of methods have been used to correct for motion, small differences in motion are difficult to fully correct and could contribute to case-control differences [79, 80]. Additionally, around 80% of the studies in the meta-analyses we have considered used 1.5 Tesla (T) scanners [41], which may underestimate volume differences compared to 3 T scanners [81].

Another important consideration for interpreting findings is whether gender differences may impact the conclusions. While studies typically control for the male:female ratio between patients and controls, most also include more male participants (e.g. ~66% male in Kuo and Pogue-Geile, 2019, and 67.4% male in Brugger & Howes, 2017) [41, 42]. On average males have greater total brain volume than females, with regional differences in both volume and density [82]. Several studies also suggest that there may be effects of gender on grey matter differences in schizophrenia in some regions but not others [83], highlighting the importance of investigating and controlling for gender effects in neuroimaging studies.

Notwithstanding these issues, what do these MRI measures reflect at the cellular level?

Given the huge number of human MRI studies that measure grey matter parameters, there has been surprisingly little work to investigate what cellular constituents make up MRI grey matter measures [84]. Bennett has provided some estimates for the constituents of 1 mm³ of human cortical grey matter derived from a review of the literature, summarised in Fig. 4 [15]. This highlights that axons and dendrites make up the largest proportion of grey matter, and synapses make up a relatively small component by volume (around 6%). An important caveat is that these are estimates for average grey matter, and may vary across the brain. Moreover, human data for some structures, such as the volume of axon collaterals, are not available so were estimated from data from other species such as cat [15].

A related question is what changes in cellular structure can lead to grey matter volume change. A number of studies have investigated this using animal models. Kassem et al. used restraint stress, which is known to cause brain structural changes, to investigate this using MRI in mice [85]. They found stress resulted in grey matter volume loss of the order of 10–15% in some, but not all, brain regions investigated. The grey matter volume loss occurred in the absence of loss of cells, but with reductions in synaptic spine density and dendritic volume. Moreover, change in grey matter volume was directly correlated with change in dendritic volume. Another study used a learning paradigm, auditory fear conditioning, in mice to show this was associated with both increases in spine density and greater grey matter volumes in the same brain regions [86]. Moreover, these were directly correlated (Fig. 5), but there was no significant relationship between nuclei density and the VBM signal in the same region. The R² was ~0.2, indicating that ~20% of the variance in the MRI signal was related to differences in synaptic spine density. Similar findings have been seen in other species as well. For example, a non-human primate study using a stroke model [87] showed lower grey matter volumes on MRI and decreased levels of synaptic markers in the same region in the absence of cell loss. These studies were cross-sectional so do not show relationships with change in MRI signal. To address this, Asan et al. used a longitudinal neuroimaging approach to investigate age related...
changes in grey matter volume and cellular constituents [84]. Mice received structural MR imaging and two-photon in vivo imaging (2pii) at three timepoints over 12 weeks. 2pii was employed to measure a range of parameters including cellular shrinkage (or expansion) over time; nucleus count and cell density; distances between cell nuclei (thus cell clustering); and mean nuclei volume (as a marker for transcriptional activity). Interestingly, they found grey matter reductions over time, but that changes in cell number were not correlated with grey matter volume across imaging volumes capturing all cortical layers, as is typically the case in human imaging. Unfortunately, they do not report data for synaptic density or volumes.

One important methodological consideration is that animals are typically anaesthetised during MRI studies, in contrast to the human studies, and physically restrained in other studies. Both factors reduce the potential for movement artefacts that may affect human imaging. We were unable to find studies that quantified both pre- and postsynaptic elements as well as grey matter volumes in the same animal. Future studies that do this would be useful to fully quantify the relationship between grey matter volume measures and synaptic measures. Nevertheless, while there is limited translational evidence, taken together, the findings from the studies we have discussed show that grey matter volume is partly related to synaptic spine density, and changes can occur in grey matter volumes without changes in cell number. Of course, this merely indicates it is possible that lower grey matter volumes in schizophrenia could be related to synaptic loss, but does not provide evidence that this is the case [84].

Indeed, a number of researchers, including Lerch et al. [88] and Weinberger & Radulescu [66], have called for caution before drawing molecular and cellular conclusions from in vivo MRI imaging data. MRI findings reflect the local magnetic properties of the tissue being imaged [66]. As such, structural MRI findings can be influenced by alterations in water content, tissue perfusion, cholesterol levels, and imperceptible head motion, any of which may be different between groups [66]. Although dimensional MRI findings indicative of altered grey matter volume are often interpreted in terms of the synaptic hypothesis, it is important to recognise that these other factors could account for alterations, and the need for more specific measures of synapses in patient studies.
selected three primary regions of interest based on frontal and anterior cingulate cortices and hippocampus [6]. They examined, including dorsolateral prefrontal and temporal cortices (found significantly lower [11 C]UCB-J uptake in frontal cortex, including the anterior cingulate cortex, as well as in the hippocampus, occipital, parietal and temporal cortices of patients with schizophrenia.

Both studies included patients taking antipsychotic treatment. However, neither study found a relationship between cumulative antipsychotic dose and [11 C]UCB-J uptake [117, 118]. Moreover, Onwordi et al. tested if sub-chronic haloperidol or olanzapine exposure affected SV2A markers in rodents, showing that binding of [3H]UCB-J and levels of other SV2A markers were unaffected by the antipsychotic administration [117]. Thus, the data to date suggest that antipsychotic treatment is not confounding these findings. Nonetheless, confirming whether patients with schizophrenia who are not taking any medication have lower SV2A levels remains an outstanding question.

**DISCUSSION**

Our review summarises findings from meta-analyses of brain imaging studies in over 50,000 subjects (including over 28,000 patients), identifying alterations in a number of structural, synaptic protein and metabolic markers relevant to understanding whether there are synaptic alterations in schizophrenia (Table 3). This shows that, in comparison to control subjects, grey matter volumes are lower in patients with chronic schizophrenia, in first episode patients and, to lesser degrees, in people with risk factors for schizophrenia. These differences are typically most pronounced in the frontal and temporal cortices both in chronic schizophrenia and first episode patients and, to some extent, in clinically high-risk individuals who go on to develop psychosis, who have lower grey matter volumes of the superior temporal gyrus. The grey matter findings in schizophrenia are based on meta-analyses of over 600 studies and more than 23,000 patients. It would take a large number of negative findings for these structural findings to be nullified, meaning that we can be confident that schizophrenia is associated with lower grey matter volumes in a number of cortical and subcortical brain regions, particularly in frontal and temporal cortical regions. Longitudinal structural MRI findings also show that grey matter volume loss is accelerated in schizophrenia in comparison to healthy controls, and that this is at least partially independent of antipsychotic exposure, although more studies are warranted to further test this (see supplement for further discussion).

Gyrification is lower in studies of older patients with chronic illness, but there are inconsistent findings in first episode patients, indicating that there is a need for more, ideally longitudinal, studies early in the course of illness to determine the trajectory of change. Measures of brain metabolism are also lower in schizophrenia, particularly in frontal regions, but effects are most marked in patients with chronic illness.

Finally, two recent studies using [11 C]UCB-J PET find evidence for lower levels of the synaptic terminal protein SV2A, in frontal and temporal cortices of patients with schizophrenia. The SV2A PET imaging in schizophrenia thus extends post-mortem findings of lower protein and mRNA levels of synaptophysin and other presynaptic markers in samples from patients in these regions [6, 117, 118].

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**Table 2.** [11 C]UCB-J imaging studies in patients with schizophrenia, summarising sample details.

| Studies                     | Sample size | Mean age ± SEM | Mean illness duration (SCZ) |
|-----------------------------|-------------|----------------|---------------------------|
| Onwordi et al. (2020)       | 19 (3 F)    | 41.5 ± 2.7     | 17.4 years                |
| Radhakrishnan et al. (2021) | 13 (3 F)    | 40.52 ± 3.1    | 17.3 years                |

**CTR** control subjects, **SCZ** patients with schizophrenia, **F** female.

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![Fig. 6 Whole brain maps of the mean [11 C]UCB-J volume of distribution (V_t) in schizophrenia (left) and healthy control (right) groups, indicating lower levels of the synaptic vesicle protein 2 A (SV2A) marker in schizophrenia particularly in fronto-temporal regions, consistent with lower synaptic density in schizophrenia](image-url)
Table 3. Summary of imaging findings in schizophrenia and people at risk for schizophrenia, from the literature discussed in this review, and key considerations for understanding if there are synaptic density changes in the disorder.

| Modality and measure | Main findings in genetically (GHR) and clinically high risk (CHR) | Main findings in first episode psychosis (FEP) | Main findings in chronic schizophrenia | Longitudinal findings | Effects of antipsychotic medication | Limitations |
|----------------------|---------------------------------------------------------------|-----------------------------------------------|--------------------------------------|----------------------|-----------------------------------|-------------|
| Structural MRI: gyrification index | No meta-analysis: studies generally support ↑ | No meta-analysis: studies generally support ↑ | Meta-analysis shows ↓ globally (systematic review generally supports this, especially in older patients) | No meta-analysis: some studies show faster rate of decrease in schizophrenia | No meta-analysis: limited indirect evidence for widespread ↓ from longitudinal studies | Limited number of studies, particularly in early illness and of longitudinal change. No studies yet link Gi to synaptic markers |
| Structural MRI: cortical grey matter (GM) volume | GHR: ↓ thalamus ↑ ventricles ↔ amygdala ↔ hippocampus ↔ pallidum ↔ putamen | ↓ amygdala ↓ anterior cingulate ↓ hippocampus ↓ thalamus ↓ temporal lobe ↔ caudate ↔ putamen | ↓ frontal lobe ↓ fusiform ↓ hippocampus ↓ insula (L) ↓ prefrontal lobe ↓ superior temporal gyrus ↓ temporal lobe ↓ total brain volume ↓ ventricles | Greater volume loss of: total cortical GM, superior temporal gyrus, Heschl gyrus (L), planum temporale (L), frontal cortex, temporal cortex, thalamus, caudate nucleus, insula, periventricular area, putamen, cingulate cortices Rate of GM volume loss most pronounced early in illness | Drug free patients: ↓ fusiform gyrus (L) ↓ inferior frontal gyrus (L) ↓ superior temporal gyrus (R) ↓ supramarginal gyrus (L) ↑ lingual gyrus (R) ↑ superior frontal gyrus (R) ↑ progressive cortical GM volume loss associated with ↑ daily antipsychotic intake in patients taking at least one first-generation APD vs. those taking second-generation only | Not specific to synapses, and could include differences in glia, neuronal soma volumes, dendrites and other structural components |
| Structural MRI: cortical grey matter density | n/a | n/a | ↓ insular cortex (bilateral) ↓ anterior cingulate ↓ parahippocampal gyrus (L) ↓ middle frontal gyrus ↓ postcentral gyrus ↓ thalamus ↓ putamen ↑ caudate (R) | n/a | n/a | Not specific to synapses, and could include difference in glia, neuronal soma volumes, dendrites and other components |
| Structural MRI: cortical thickness | n/a | n/a | ↓ hemispheric cortical thickness bilaterally ↓ fusiform (bilateral) ↓ superior, middle and inferior temporal gyri (bilateral) ↓ superior frontal gyrus (L) ↓ pars opercularis (R) ↓ insula (bilateral) | Stronger negative correlation between increasing age and bilateral temporal pole thickness in schizophrenia than in controls | ↓ frontal lobe ↓ parietal lobe ↓ temporal lobe ↓ insula ↓ isthmus of cingulate gyrus (in medicated vs unmedicated and vs controls) | Not specific to synapses, and could include difference in glia, neuronal soma volumes, dendrites and other components |
| Neurite orientation dispersion and density imaging | n/a | ↔ hippocampus n/a for other ROIs | ↓ temporal pole ↓ anterior hippocampal gyrus ↓ hippocampus | n/a | n/a | Not specific to synapses and could include differences in myelination of axons |
| FDG PET: glucose utilisation | n/a | ↓ frontal cortex in chronic schizophrenia | ↓ frontal cortex | n/a | ↓ frontal cortex in medicated/mixed | Changes in FDG uptake may represent changes in neuronal activity (not... |
Strengths and limitations
We were able to identify meta-analyses synthesising data from large numbers of studies for many of the measures. However, for some measures meta-analyses were not available (see Table 3), generally because there were insufficient studies. This was notably the case for gyrification measures, cortical thickness and grey matter density measures, where there were no meta-analyses of studies in first episode patients or high-risk groups, and for SV2A studies at all stages of schizophrenia. This limits the conclusions that can be drawn for these groups and measures. This was also the case for longitudinal studies in general. This limits the conclusions that can be drawn about whether there are progressive changes in many measures, and highlights the need for more longitudinal studies in schizophrenia.

What do the imaging findings say about whether there is lower synaptic density in schizophrenia? The preclinical studies that we reviewed show that interventions that alter ex vivo synaptic markers are also associated with changes in MRI measures. This indicates that the MRI findings in schizophrenia could reflect lower synaptic density. However, only a few studies have investigated the relationship between MRI imaging signals and synaptic measures, and these have predominantly been conducted in rodent models. There is a need for further studies to determine if these rodent findings can be replicated, and for studies in humans (such as post-mortem studies combining MRI imaging and synaptic measures). Furthermore, as shown in Fig. 4, over 50% of grey matter volume is estimated to comprise dendrites and axons, 18% is extracellular space, and the remaining volume includes neuronal soma, synapses, astrocytes, oligodendrocytes and glia. Given that synapses are estimated to comprise only ~6% of total grey matter volume, and grey matter volume differences in schizophrenia are similar in magnitude (~5–11% in some fronto-temporal regions [77]) and it is implausible all synapses are lost in schizophrenia, synaptic loss alone is unlikely to explain all of the grey matter and cortical thickness differences seen in schizophrenia. Moreover, whilst post-mortem studies do not generally find lower density of neurons or other cells in brain regions of interest in schizophrenia, there are reports of lower number and volume of neurons in some regions [61, 119–124], which could contribute to the grey matter MRI differences. Nevertheless, although lower synaptic density is unlikely to account for all of the grey matter differences in schizophrenia, this does not preclude synaptic loss being a driver of changes in other constituent, such as dendritic volume, that might also contribute to volume loss. As discussed earlier, NAA and FDG measures are also not specific to synapses. Thus, whilst the alterations in these and the structural measures are consistent with lower levels of synapses, they cannot be taken as establishing this. In this respect, imaging of SV2A provides the most specific measure of synaptic density currently available.

Gaps in evidence and the interpretation of SV2A findings in terms of lower synaptic density
Box 1 summarises a number of the key outstanding areas for further work identified by our review of imaging findings in schizophrenia. The gaps in evidence and outstanding questions are considered further in this section before we then consider the potential mechanism that could underlie lower synaptic terminal density. The fact that lower [11]CUCB-J levels have been reported in two independent cohorts of patients provides some confidence that there are lower SV2A levels in schizophrenia. Nevertheless, it will be important for further studies to confirm findings in additional cohorts to determine the generalisability of findings, and to include antipsychotic free patients (Box 1). Both [11]CUCB-J studies to date were of patients with chronic schizophrenia. It is thus unclear at what stage of illness these deficits arise and whether differences in SV2A reflect earlier loss of synapses, the
Box 1. Key next steps

- Further longitudinal studies of grey matter volumes from the first episode of schizophrenia controlling for antipsychotic use
- Additional studies of monozygotic and dizygotic relatives of patients with schizophrenia to determine the shared genetic and environmental components to grey matter differences in schizophrenia
- Further studies in first episode patients and of longitudinal changes in gyral and cortical thickness
- SV2A imaging in additional cohorts of patients with schizophrenia to test generalisability of findings
- Investigation of the relationship between SV2A and structural and functional imaging measures in schizophrenia
- SV2A imaging in first episode schizophrenia to determine if differences are present early in the course of illness

effects of disease progression or potentially both. The evidence for longitudinal changes in grey matter volumes from first episode suggests there may be early and progressive changes in neuropil, which might include synaptic loss, in schizophrenia, but multimodal studies earlier in the course of illness are required to determine the degree to which synaptic differences contribute to this (Box 1).

As discussed earlier, SV2A is a presynaptic vesicular protein expressed in synaptic terminals. However, whilst the SV2A findings could reflect a selective loss of synaptic terminals, or even just vesicle proteins, in schizophrenia, when they are taken with the post-mortem evidence for lower levels of pre- and postsynaptic markers in the same regions in schizophrenia, the most likely interpretation is that they reflect lower synaptic density in the disorder. This supports the synaptic hypothesis of schizophrenia [2, 3, 5]. Nevertheless, confirming that there is loss of postsynaptic elements in vivo will require the development of new PET tracers or other imaging approaches. In the meantime, further post-mortem studies to investigate the levels of synaptic vesicle proteins, the number of SV2A molecules per vesicle and the number of vesicles per terminal in schizophrenia, would be useful to aid interpretation of the in vivo findings.

SV2A is expressed at both excitatory and inhibitory synapses [101]. Whilst this means it is a good marker of total synaptic terminal, density, a limitation of [11 C]UCB-J imaging is that it provides little information about what type of synapses may be affected in schizophrenia. Recent work by Onwordi et al. combined [11 C]UCB-J with MRS of glutamate levels to investigate the relationship between the two measures [125]. The study found that glutamate levels were correlated with the SV2A measure in the anterior cingulate cortex of control subjects, but not in the patient group, which, taken together with lower SV2A levels in this region, suggests excitatory synaptic terminals may be particularly affected in schizophrenia [125]. However, while the highest brain glutamate concentrations are found in glutamatergic nerve terminals, the glutamate MRS signal also reflects glial and extracellular glutamate levels, potentially limiting the interpretation of these findings [126].

As also discussed earlier, the structural MRI differences in schizophrenia could reflect alterations in other neuropil components, such as dendrites, unmyelinated axons, glial cells and not just synapses. They could also reflect differences in other grey matter constituents, including cell body number and volume, in addition to neuropil. Supporting this, neither [11 C]UBC-J PET study found SV2A levels were related to grey matter volumes. However, given that, at most, synaptic differences will only account for a proportion of structural brain differences in the same regions, the samples for these studies were likely under-powered to detect relationships. Moreover, neither study included other structural or metabolic measures, such as cortical thickness or FDG PET. Thus, larger studies that investigate the relationships between the structural and metabolic measures are needed to understand the degree to which synaptic changes could underlie the structural and metabolic brain changes we review in schizophrenia (Box 1).

Some questions remain about the effects of antipsychotic medication. While neither UCB-J study found effects of cumulative antipsychotic dose on SV2A levels, this does not exclude an effect of antipsychotic drugs. Thus, studies of SV2A levels in antipsychotic untreated patients are needed to rule this out. In addition to this, use of other drugs such as cannabis or cocaine may influence findings [127, 128]. While both UCB-J studies in schizophrenia excluded participants who tested positive for drugs of abuse, cohorts of patients with schizophrenia typically have higher frequency of past drug use, which could confound findings [129]. However, recent work shows SV2A levels are more likely to reflect recent use rather than be correlated with past substance use history, although this has only been tested for cocaine to date [127]. Whilst this suggests that past substance use is not likely to be a major confound, further work is warranted to determine if this holds for other substances in addition to cocaine.

Finally, grey matter loss, cortical thinning and lower SV2A levels have been found in other neuropsychiatric disorders, such as major depression, substance use disorders, post-traumatic stress disorder, and others [111, 127, 128]. This raises a number of questions, including how specific the alterations we have considered are to schizophrenia, and whether the same mechanism underlies alterations across disorders. Key differentiators may be the underlying mechanisms and the circuits involved.

What mechanism could underlie synaptic loss? Immune-mediated excessive synaptic pruning has been proposed as one possibility [130, 131]. Supporting this, numerous post-mortem studies have demonstrated increased density of microglial cells (with a hypertrophic morphology indicating an activated phenotype) in the brains of schizophrenia patients compared with healthy controls, particularly in the frontal and temporal lobes [130, 132–134]. Microglial cells are the immune cells of the central nervous system, which play a major role in synaptic pruning and phagocytosis of synaptic material in the brain [135, 136]. In vitro studies further show increased engulfment of synaptosomes by microglia cultured from patients with schizophrenia in comparison to controls [13], suggesting a schizophrenia genetic background to controls [13]. For example, juvenile stress exposure in rodents has been shown to result in increased microglial pruning and synaptic loss, particularly in the prefrontal cortex and the hippocampus [138–146]. Adolescent stress is additionally considered a risk factor for developing schizophrenia, potentially implicating the same pruning mechanism [147]. Thus, aberrant microglial activation is a potential mechanism that could account for lower synaptic density in schizophrenia, and disrupt cortical function (see [5] for a further discussion of this). However, there is inconsistency within the in vivo findings on microglial markers in schizophrenia, potentially due to methodological factors [148], and the link between microglial mediated pruning and brain imaging changes in vivo remains to be established. Further studies are also required to investigate the effects of stress on SV2A levels, and to relate this to schizophrenia pathophysiology. Notwithstanding these caveats, this suggests potential targets for interventions [137].

CONCLUSIONS
Neuroimaging techniques have been widely used to investigate the pathophysiology of schizophrenia, providing evidence for a range of structural and metabolic differences in schizophrenia, including lower grey matter volumes, cortical thickness, gyralization and NAA and FDG levels with moderate effect sizes in chronic schizophrenia in cortical regions, particularly in fronto-temporal areas. Effects are also seen in first episode schizophrenia, with the possible exception

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of gyration. Moreover, evidence indicates grey matter changes are progressive from the first episode of illness. These findings are consistent with, but do not prove, lower synaptic density in the disorder. Moreover, it is clear that synaptic differences alone cannot account for the magnitude of the grey matter changes. Nevertheless, recent findings using a PET tracer specific for a presynaptic protein (SV2A) provide in vivo evidence for lower synaptic terminal density in fronto-temporal regions in the disorder, consistent with, but do not prove, lower synaptic density in the brain. Questions remain regarding whether synaptic alterations are present at illness onset or develop later, and the relationship between them and the other neuroimaging findings we have reviewed.

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COMPETING INTERESTS
OH is a part-time employee of H Lundbeck A/s. He has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Angellini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Heptares, Global Medical Education, Invicro, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Recordati, Roche and Viatris/Mylan. Neither Dr Howes or his family have holdings/financial stake in any pharmaceutical company. Dr Howes has a patent for the use of dopaminergic imaging. ES, GC and CC have reported no biomedical financial interests or potential conflicts of interest. The views expressed are those of the authors and not necessarily those of H Lundbeck A/s, the NHS/NIHR or the Department of Health.

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