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NEUROSCIENCE FOREFRONT REVIEW

THE NEUROPATHOLOGY OF SCHIZOPHRENIA: A SELECTIVE REVIEW OF PAST STUDIES AND EMERGING THEMES IN BRAIN STRUCTURE AND CYTOARCHITECTURE

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Abstract—Schizophrenia is a devastating mental illness. Although its etiology is still largely unknown, strides have been taken throughout the last several decades to elucidate the nature of the neuropathology behind this disorder. The advent of neuroimaging technologies such as computerized axial tomography and magnetic resonance imaging have progressed knowledge about the macroscopic brain changes that occur in schizophrenia, including the characteristic reduced ventricle size and reductions in gray matter volume, whole-brain volume, and white matter anisotropy. Although this review presents a broad outline of current and historical neuropathological research in research, the focus is primarily on the quantitative neuropathology of the cerebral cortex in schizophrenia, which may underlie many of the larger scale changes observed. The reduced neuropil hypothesis has been suggested as a microanatomical explanation to account for these macroscopic changes, although the present review finds that evidence does not always support this. A quantitative summary of these studies, focused on neuron density, provides support for the finding of increased neuron density in schizophrenia, with variation dependent on age. This is consistent with neuroimaging data and implicates an altered aging trajectory as a factor in the pathogenesis of schizophrenia. Combined with evidence from other neuroanatomical studies reviewed here, as well as studies in childhood-onset schizophrenia the evidence converges on a progressive neurodevelopmental model of schizophrenia related to altered neuroplasticity. The evidence also supports a particular vulnerability of inhibitory cortical circuits with markers of interneurons showing some of the more consistent reductions in schizophrenia.
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Key words: schizophrenia, neuropathology, neuron, neuroplasticity, aging, inhibition.

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Abbreviations: AP, antipsychotic; BA, Brodmann areas; CT, computerized axial tomography; GAD, glutamic acid decarboxylase; MRI, magnetic resonance imaging.

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Contents

BACKGROUND

Schizophrenia is a mental disorder that affects 1% of the population (Carpenter and Buchanan, 1994); however, its etiology still remains largely unknown. It is characterized by changes in behavior and cognition, and volumetric and histological studies have confirmed that there are multiple structural differences found in the brain in schizophrenia.

The publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders has brought to the forefront the controversy surrounding the definition of schizophrenia as a singular disease process. The conception of schizophrenia has changed drastically since its inception as a disorder of mental deterioration to its most recent categorization as a

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single disease with multiple subtypes. Although its newest definition has done away with the subtype categorization, which was widely recognized as unhelpful and flawed, debate as to how best to define schizophrenia continues. A single disease classification system, such as has been used in the past, would prove most functional and have greatest ease of use for diagnostic and research purposes. However, at this time, no signature pathognomic pattern of abnormalities has been identified as reliably characteristic of the disease (Moncrieff and Middleton, 2015). Although certain behavioral characteristics are often associated with schizophrenia, such as disordered thought processing or changes in affect, these do not reliably manifest the same way in every person who is diagnosed with schizophrenia. Therefore, until such time as a structural or behavioral characteristic can be confirmed to be a defining characteristic of schizophrenia, in order to move forward and make strides in learning more about this syndrome, we are forced to rely on past diagnostic measures that combine individuals with relevant characteristics into one heterogeneous group.

In the current review, we have adhered to the prevailing definition of schizophrenia, that of a heterogeneous pattern of abnormal behaviors and structural changes that causes significant disruption and impairment. Through use of an inclusive definition such as this, relevant past research can be identified that may inform future research to better subdivide and redefine the syndrome known as schizophrenia. Only with a thorough understanding of the mix of pathologies and behaviors that are classified as schizophrenia will it be possible to redefine the syndrome more appropriately.

As the schizophrenia literature is very large, the scope of this review is necessarily limited. The focus will be on quantitative changes in the cerebral cortex with an emphasis on cytoarchitectural changes, presented in the context of a general outline of brain structural changes. Specialized topics such as the involvement of the hippocampus and the genetic contribution to schizophrenia have their own sub-literature, and will not be focused on here. Historical perspectives of the neuropathology of schizophrenia will be acknowledged, and a discussion of current and emerging lines of enquiry will be presented. Section "A quantitative summary" presents a quantitative summary of studies of cell density in the cerebral cortex in schizophrenia. However, due to the size of the overall schizophrenia neuropathology literature from the last 40 years, the rest of this review takes a selective approach in order to present the broader context and does not reference all published studies.

INTRODUCTION

Emile Kreapelin originally described 'dementia praecox' as a process of ongoing deterioration. It was believed that Alzheimer's disease was more common in schizophrenia (Corsellis, 1962). However, the emphasis has since shifted away from the conception of schizophrenia as a degenerative condition, as meta-analysis indicates that progressive dementia is not more common in schizophrenia than in age-matched controls (Baldessarini et al., 1997). Neurodegenerative pathological features, including neurofibrillary tangles, plaques, astrocytes, and microglia appear to occur at the usual rate in schizophrenia (Arnold et al., 1998).

Although an early study reported a marked increase in fibrillary gliosis (Stevens, 1982) (which is a marker for neurodegeneration (Falkai et al., 1999) and a typical astrocytic brain response to neural injury resulting in scarring), subsequent studies suggested that this was only present in cases which had other (usually unrelated) pathologies (Bruton et al., 1990), and several studies did not find it in schizophrenia (Falkai et al., 1999; Falke et al., 2000). More recently, the number of astrocytes themselves has not been found to be increased (Falke et al., 2000), while findings on microglia have been variable (Bernstein et al., 2009) (for more on microglia, see section "Microglia and neuroinflammation"). One study found increased microglia in schizophrenia (Steiner et al., 2006), and it has been suggested that increased density of microglia (Steiner et al., 2008) and decreased oligodendrocytes (Honer et al., 1999) may be present in a subgroup of subjects defined by death by suicide. Rajkowska et al. (2002) reported a decrease in astroglia in several cortical layers in schizophrenia in the prefrontal cortex, indicating altered glia, and particularly astrocytes, although not in the form of gliosis (Schnieder and Dwork, 2011). One study looking at microglia in elderly schizophrenia patients did find higher densities of microglia compared with controls (Radewicz et al., 2000). The amount of amyloid plaques and neurofibrillary tangles was also noticeably higher in schizophrenia as compared to controls (Radewicz et al., 2000).

ALTERED MACROSCOPIC BRAIN STRUCTURE

In 1976, a computerized axial tomography (CT) study was the first imaging study to show that patients have larger ventricles than controls (Johnstone et al., 1976). Although it had been hypothesized that brain changes were a part of the disease, the advent of CT and magnetic resonance imaging (MRI) technology made it easier to visualize and quantify these changes.

Meta-analyses (Wright et al., 2000; Olabi et al., 2011) have confirmed that between patients and controls, there are often larger ventricles in schizophrenia (an increase of about 26%) and decreases in both gray matter and whole-brain volume or brain weight (estimated at 2% reduction) (Harrison et al., 2003). A recent meta-analysis looking at sub-region differences found that the insula, thalamus, and anterior cingulate cortex were the structures most commonly identified as different in schizophrenia (Crow et al., 2013). In general, among the most commonly identified regional structural effects are reduced volume of the medial temporal lobe, the superior temporal gyrus, and the insula cortex (Honea et al., 2005). Enlargement of the ventricles has been found to be correlated with reductions in some of these structures, including reduced superior temporal gyrus, parahippocampal gyrus and fusiform gyrus volumes (Chance et al., 2003), and one meta-

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analysis found that ventricular enlargement is progressive after the first episode (Kempton et al., 2010). Other reports have found that ventricular enlargement appears to be generalized (Sanfilipo et al., 2000), relatively constant (Owens et al., 1985; Harvey et al., 1990; Daniel et al., 1991; Vita et al., 2000), and not clearly linked to volume reduction in surrounding structures (Bogerts et al., 1990; Kawasaki et al., 1993).

By far the most intensively studied regions are the hippocampus and the frontal lobe. This emphasis reflects the frequently expressed view that limbic and frontal lobe malfunction can best explain the symptoms of schizophrenia. Reductions in volume have been found in the hippocampus (Nelson et al., 1998; Wright et al., 2000; Arnold et al., 2015), although inconsistent findings of no difference in regional size has been noted in the hippocampus (Heckers et al., 1990; Walker et al., 2002; Highley et al., 2003b), and in other structures, including the thalamus (Arnold and Trojanowski, 1996; Harrison, 1999; Cullen et al., 2003). In MRI studies, such contradictory findings may be due to the partial volume effect (Chance et al., 2002): one study found that when corrected for overall brain volume, there was no difference between schizophrenia and controls in hippocampal volume (Tanskanen et al., 2005). However, this is a decreasing confound in more recent MRI studies, as higher scan resolution continues to reduce the size of the error, and indeed recent MRI studies on the hippocampus have shown decreased subfield volumes in schizophrenia (Haukvik et al., 2015; Kawano et al., 2015).

Regional differences in sub-region shape have been found (Chance et al., 2003), including reductions in volume of the temporal lobe, superior temporal gyrus and parahippocampal gyrus; these reductions may be lateralized to the left hemisphere in posterior regions, and to the right hemisphere in anterior regions (Crow et al., 2013). In the healthy brain, it has been suggested that lateralization may have resulted in the capacity for language in humans (Crow, 2000) (see 'Hemispheric Asymmetry' section).

Diffusion tensor imaging is one modality that has been increasingly used to investigate white matter differences in schizophrenia, providing important information about tracts and connectivity (see 'Connectivity and myelination' section). These studies have reported decreases in anisotropy, particularly in the left frontal (Jeong et al., 2009; Mitelman et al., 2009; Spoletini et al., 2009; Walther et al., 2011; Henze et al., 2012; Nazeri et al., 2013; Quan et al., 2013) and temporal (Friedman et al., 2008; Hoptman et al., 2008; Rametti et al., 2009; Phillips et al., 2011; Kitis et al., 2012) lobes. DTI investigations in gray matter in schizophrenia have reported increased diffusivity in the superior temporal gyrus, parahippocampal gyrus and insula, but no change in anisotropy from controls (Lee et al., 2009; Moriya et al., 2010).

Hemispheric asymmetry

Differences in asymmetry have been found in schizophrenia. The healthy human brain is lateralized, often to the left, and it has been suggested that this is a defining human characteristic (Annett, 2002). It has been found that asymmetry of the brain is reduced in patients with earlier illness onset (arguably those with a more serious form of illness), compared to those with later onset and controls (Crow et al., 1989), and a reduction in width asymmetries has been found in patients with psychosis (Falkai et al., 1995; DeLisi, 1997). Functional asymmetry has also been found to be reduced in schizophrenia, and is related to illness duration (Ribolsi et al., 2014). Regional reductions in asymmetry have been found in pre-motor, prefrontal, temporal, sensori-motor, and occipito-parietal areas (Bilder et al., 1994). Again, these findings of asymmetry are not without their contradictions: no difference in volumetric asymmetry of the planum temporale has been found (Meisenzahl et al., 2002), although differences in length and width have been found (Harasty et al., 2003). These differences in shape may account for the negative findings of regional volumetric differences (Barta et al., 1997), as meta-analysis has shown that there is indeed a reduction in asymmetry in the planum temporale in schizophrenia (Shapleske et al., 1999). One study indicated a slight reduction in the hemispheric asymmetry of cortical depth and neuron density in the parietal lobe (Smiley et al., 2012), similar to findings of reduced cortical thickness asymmetry in *in vivo* imaging (Niznikiewicz et al., 2000) (although other studies have found no change in asymmetry in this region (Hamilton et al., 2007). Additionally, these changes in asymmetry may interact with sex, as volumetric and asymmetrical changes have been found in males but not females in some parts of the inferior parietal lobe (Frederikse et al., 2000). In some studies, the asymmetries appear to be reversed by gender: a reduction has been found in white matter parieto-occiptal volumes in females with schizophrenia, but an increase was found in males compared to controls (Highley et al., 2003b). As males generally experience earlier illness onset than females, this difference in asymmetry may be related to age at illness onset. Increased gyrification in schizophrenia has also been found selectively in males, lateralized to the right hemisphere (Vogeley et al., 2000; Harris et al., 2004), although other studies have not found this difference in gyrification (Highley et al., 2003b), or, conversely, found decreased gyrification in men with schizophrenia lateralized to the left hemisphere (Palaniyappan and Liddle, 2012). A recent mathematical approach to cortical gyrification has reported abnormal morphological relationships in gyrification in schizophrenia (Palaniyappan et al., 2014).

MICROANATOMICAL FINDINGS

Methods

Although neuropathological investigation via staining tissue in order to visualize it through the microscope has a long history, recent decades have seen a rapid increase in the number of antibodies available for immunohistochemistry, as well as the adoption of stereological methods and the development of proteomic, transcriptomic, and other new techniques. The focus of this review is on quantitative anatomy and therefore the methodological benefits of the introduction

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of stereology are relevant. Over the last 20 years, increasingly widespread use of stereological principles has led to advances in methodology, which have had the effect of reducing bias and improving reproducibility of findings. Stereology facilitates the practical application of a mathematically rigorous approach to unbiased sampling in order to estimate essential anatomical elements such as volume, density and surface area. Several methods have been developed to estimate these different elements. Of particular interest for quantitative histology is the optical fractionator method used to estimate the total number of cells in a structure. This is estimated from the number of cells sampled within a systematically randomly sampled set of unbiased counting spaces covering the entire region of interest with uniform distance between the counting spaces in directions X, Y and Z. However, it should be noted that some compromises are often necessary for working with human brain tissue. For example, sampling is often not truly random with respect to the axes of a brain structure of interest because a characteristic orientation is necessary for the definition of the structure. In addition, the entire region of interest is often difficult to define, or unavailable, due to the demands of brain banking and the necessity of sharing very rare human tissue among researchers. For this reason, an estimate of the total cell count is often not reported, and instead a density per unit volume is used for comparison. Furthermore, the limited tissue penetration of antibodies in immunohistochemistry (typically less than 5 μ) means that most immunohistochemical estimates of cell density are effectively 2-D. By contrast, histological tinctorial stains can be applied to thick sections and enable 3-D stereological sampling. This contrast is addressed in the quantitative analysis of cell density, below (section "A quantitative summary"). These compromises notwithstanding, stereological principles provide a rigorous approach emphasizing the need for unbiased comparability.

Neuronal cell size and number

Several brain structural components have been suggested as the basis for the large-scale differences between schizophrenia patients and controls. One of the more consistent findings to date is a modest and possibly fairly widespread reduction in neuronal size, accompanied by evidence of reduced dendritic and/or axonal arborizations (Eastwood and Harrison, 1995; Perrone-Bizzozero et al., 1996; Davidsson et al., 1999; Fatemi et al., 2001; Vawter et al., 2002). Smaller cell size may be a key change associated with decreased basilar dendritic spine density in schizophrenia, particularly in deep layer III pyramidal neurons (Lewis and Gonzalez-Burgos, 2008). This finding has been understood to indicate that a reduction in neuropil (the space between cells, including axons, dendrites, and synapses) surrounding a normal complement of neurons may be the explanation for the reduced brain volume documented at the macroscopic level (the 'reduced neuropil' hypothesis (Selemon and Goldman-Rakic, 1999)). The alternative view, that subtly decreased neuron number may be a contributing factor, has gained some support through slowly accumulating evidence, although coupled with evidence of longitudinal reductions at the macroscopic level, it appears to conflict with the prevailing absence of neurodegenerative markers.

In normal aging, it has been reported that mild cognitive effects are associated with increased cell density, whereas more severe cognitive impairment is associated with a lower cell density due to pathological cell loss in dementia (Chance et al., 2011). If cortical gray matter tissue volume is reduced in schizophrenia, without a concomitant increase in neuron density, then neuronal loss is implicated. Evidence from the limited number of studies that have attempted to assess total neuron number within the cerebral cortex supports this conclusion. A previous assessment of global cortical neuron number in schizophrenia indicated that this was within the normal range (Dorph-Petersen et al., 2009). However, a review of studies of neuron number in specific regions indicates a reduction in neuron number in schizophrenia: approximately 15% average reduction in neuron number was recorded in patients. Of these studies, the majority (seven out of eight) (Falkai et al., 1988; Pakkenberg, 1993; Krimer et al., 1997; Thune et al., 2001; Stark et al., 2004; Dorph-Petersen et al., 2007; Schmitt et al., 2009) recorded a reduction in mean neuron number in schizophrenia of more than 5%, although the effect did not reach statistical significance in the small samples of two studies (Krimer et al., 1997; Thune et al., 2001). However, studies of cell density are far more numerous than estimates of total number (Smiley et al., 2011). Total neuron number is essentially the product of a cell density estimate and a region size estimate, and a key challenge for estimating total neuron number in a cortical area is the precise definition of the cytoarchitectonic region boundary, in order to measure the region size.

Reduced neuropil hypothesis

The reduced neuropil hypothesis (Selemon and Goldman-Rakic, 1999) emphasizes the apparent consistency between findings of increased cell density and alterations of synaptic and dendritic architecture, and posits that over time in schizophrenia, the amount of neuropil decreases, mediated by changes in dendrites, axons, and terminals. Reduced neuropil may be a result of excessive synaptic pruning during development and maturation (Feinberg, 1983), or it is possible that the full complement of synapses fail to develop at this time. A misrouting of axons may also be possible, supported by evidence of altered asymmetry. Where synaptic changes have been found in schizophrenia, they have usually been in the direction of a reduction, particularly in glutamatergic synapses (Eastwood and Harrison, 1995; Perrone-Bizzozero et al., 1996; Garey et al., 1998; Davidsson et al., 1999; Glantz and Lewis, 2000). Where evidence has not been found for reductions in presynaptic terminals, it has been suggested that these changes may depend on post-synaptic dendritic morphology instead.

A decrease in dendritic spines has been reported in both frontal and temporal association areas in patients

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(Garey et al., 1998; Glantz and Lewis, 2000). This decrease in spines seems to occur without a corresponding decrease in neuron number: it has been shown in both the prefrontal and occipital cortices that neuron number does not decrease over time in schizophrenia, and in fact density of neurons increases (Selemon, 2004), although these findings are not always consistent between studies (see section "Neuron density"). However, more recently Kreczmanski et al. (2007) found reduced neuron number in the caudate nucleus, the putamen, and the lateral nucleus of the amygdala, with no change in neuron density. This indicates that, in some areas, there is a decrease in neuron number accompanied by a decrease in volume of neuropil. These results suggest that the reduced neuropil hypothesis may not explain the full story in schizophrenia pathology. Similarly, Smiley et al. (2009, 2011) reported a decrease in cortical width in the planum temporale in schizophrenia but no associated increase in neuron density. Therefore, closer packing of neurons may not always underlie reduced cortical volume, and subtly decreased neuron number represents an alternative contributing factor (Smiley et al., 2011).

Other neuroanatomical investigations have also yielded results incompatible with the reduced neuropil hypothesis: Di Rosa et al. (2009) reported decreased cell density and wider minicolumns (a unit of microanatomical structure) in schizophrenia compared to controls. Wider minicolumns were interpreted to be a consequence of relatively great neuropil and not a decrease in neuron number. Minicolumns did not change with age in patients but they did become thinner with age in controls, indicating a normal age-associated reduction in neuropil in controls but not in patients. Previous studies (Chana et al., 2003; Chance et al., 2008; Di Rosa et al., 2009) have found that the contrast between patients and controls depends on when in adulthood the cell organization is measured. A suggested hypothesis is that, in normal adulthood, aging is associated with a restructuring of neuropil (the space between cells), such that the neurons are closer together in old age, whereas in schizophrenia the neurons do not become more closely packed. This is consistent with the interpretation that patients have altered neuroplasticity, although not necessarily reduced neuropil, which may manifest in different ways (see 'Neuroplasticity and cognitive reserve' section).

Immunohistochemistry

In 1990, Masliah et al. (1990) described a new method of measuring synaptic density by using immunohistochemistry to measure the density of synaptophysin, a protein present in presynaptic terminals. Using this marker, presynaptic terminal density has been found to be reduced in schizophrenia in the medial temporal lobe (Eastwood and Harrison, 1995), frontal and visual cortices (Honer et al., 1999; Perrone-Bizzozero et al., 1996), and the cingulate cortex (Davidsson et al., 1999). Additional presynaptic markers SNAP-25 (Fatemi et al., 2001) and synapsin (Vawter et al., 2002), as well as synaptophysin (Eastwood and Harrison, 1995) have also been found to be decreased in the hippocampus in schizophrenia, as has SNAP-25 in the frontal cortex (Honer et al., 2002). However, Glantz et al. (2000) and Eastwood et al. (2000) did not find a change in synaptophysin mRNA in the prefrontal cortex, suggesting the possibility that changes in patients in prefrontal cortex volume, measured by MRI (Honea et al., 2005), may relate to post-synaptic dendritic morphology, rather than pre-synaptic terminals. Abnormal axo-dendritic plasticity is most acute in those areas of the brain that go on developing for longer periods of time, i.e. asymmetric association cortex (Arendt, 2003). This may be linked to altered brain aging effects on microscopic neuroanatomy.

The use of specific immunohistochemical cell markers has helped to identify effects in sub-populations of neurons and some consistency has emerged from the use of markers which identify predominantly inhibitory interneurons in neocortex: seven studies have reported the density of this class of cells is reduced by over 10% (Beasley and Reynolds, 1997; Beasley et al., 2002; Woo et al., 2004; Chance et al., 2005; Todtenkopf et al., 2005; Wheeler et al., 2006; Pantazopoulos et al., 2007), compared to only three studies that reported the contradictory finding of an increase (Daviss and Lewis, 1995; Kalus et al., 1997; Tooney and Chahl, 2004). A few of these studies used the global marker glutamic acid decarboxylase (GAD), the enzyme primarily responsible for synthesizing GABA, but most used a mixture of markers for the calcium-binding proteins parvalbumin, calretinin and calbindin, each of which tends to identify a partially separate sub-population. The densities of interneurons identified by parvalbumin and somatostatin markers are reduced in schizophrenia in the hippocampus (Konradi et al., 2011; Zhang and Reynolds, 2002) and its neighbouring cortical region, the parahippocampal gyrus (Wang et al., 2011), although the density of GAD immunopositive neurons here has been found to be increased (Schreiber et al., 2011). A decrease in density of calbindin-immunoreactive neurons has been found in the planum temporale (Chance et al., 2005). Disruptions in the molecular building blocks of interneurons have also been reported (Woo et al., 2008; Marin, 2012; Nakazawa et al., 2012). However, these findings are not necessarily consistent between brain regions or between different classes of inhibitory interneurons (Raghanti et al., 2010). Parvalbumin neurons appear to show the most consistent changes, hypothesized to be linked to NMDA receptor hypofunction and electrophysiological Gamma-band disruption (Gonzalez-Burgos et al., 2010). The discrepancies between markers relate to the unresolved issue of whether the changes reflect the absence of cells, or the absence of protein expression in those cells. The absence of interneurons is likely to result in disinhibition of local pyramidal neurons. The alternative scenario, that the cells are still present but there is a loss of calcium-binding protein expression, would likely also indicate an altered electrophysiological phenotype, resulting in disrupted local inhibition.

The hypothesis of altered inhibition in schizophrenia is well established: Lewis et al. (2005) have been instrumental in suggesting that inhibitory cortical circuits are centrally involved in the pathology and resulting dysfunction in schizophrenia. Broadly, if GABA neurons and GAD

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are decreased in schizophrenia (Akbarian et al., 1995; Gonzalez-Burgos et al., 2010), excitatory neurons are disinhibited (Beneyto and Lewis, 2011), resulting in aberrant increased activity (Shah and Lodge, 2013). GABA neurons in prefrontal cortex have been shown to be critically important during tasks involving executive function (Lewis et al., 2005) and a reduction in these neurons is likely to lead to impairment on tasks of executive function (Beneyto and Lewis, 2011).

A recent area of inquiry in schizophrenia research is the topic of perineuronal nets; these are nets formed of chondroitin sulfate proteoglycans that surround some interneurons (Shah and Lodge, 2013). Perineuronal nets contribute to functions such as neuronal migration and circuit formation and synaptic plasticity, all of which may be disrupted in schizophrenia (Pantazopoulos et al., 2010). These have been shown to be disrupted in the hippocampus in an animal model of schizophrenia (Shah and Lodge, 2013), as well as in the medial temporal lobe in postmortem brain tissue (Pantazopoulos et al., 2010). It has been suggested that this loss of perineuronal nets further reduces inhibition from interneurons, producing increased aberrant activity from pyramidal neurons (Shah and Lodge, 2013).

Neuron density

The reduced neuropil hypothesis (Selemon and Goldman-Rakic, 1999) posits that over time in schizophrenia, the amount of neuropil decreases; this results in an increase in neuronal density, relative to healthy individuals, and may explain the reduced brain volume over time in schizophrenia. Consequently, the most common microscopic assessment conducted in order to shed light on the cellular basis of gray matter alterations in schizophrenia is the examination of neuron density. Studies of cell density in schizophrenia report contradictory findings, both positive (indicating either increased or decreased cell density) and negative (Esiri and Crow, 2008). Although estimations of neuron density cannot identify all of the neuronal changes in schizophrenia, estimations of density can provide useful information about where changes are occurring, relative to healthy individuals, and can provide some detail as to the scale of these changes. In the past, this has been the most common quantitative method of investigating differences in schizophrenia and therefore lays the groundwork for current and future work.

Most studies of neurons in the frontal cortex have been performed in Brodmann areas (BA) 9, 46, 4 and 10, and in the anterior cingulate cortex (BA 24). Studies of neuronal density have yielded inconsistent findings ranging from no change to increased or decreased neuronal densities. These findings mostly refer to pyramidal or non-pyramidal neurons or neurons immunoreactive for calcium-binding proteins. As has also been found for the hippocampus, the few studies of cell size have provided more consistency, with normal or slightly reduced neuron size being a common result (Rajkowska et al., 1998). In the prefrontal cortex, a selective reduction of large pyramidal neurons in schizophrenia was found by Rajkowska et al. (1998), indicating particular vulnerability among the magnopyramidal neurons. Studies have found increased density of interstitial white matter neurons in the prefrontal cortex, which is hypothesized to relate to the failure of inhibitory neurons to migrate appropriately in development (Beasley and Reynolds, 1997; Eastwood and Harrison, 2005; Joshi et al., 2012).

Most cytoarchitectural studies of the temporal lobe have focused on the superior temporal plane (the planum temporale and Heschl's gyrus) and the medial temporal lobe (the parahippocampal gyrus and entorhinal cortex). Altered clustering (Beasley et al., 2005) and reduced volume of layer III pyramidal neurons (Sweet et al., 2003) have been found in the planum temporale, and a size reduction of the largest pyramidal neurons has been found in the left hemisphere but not the right (Simper et al., 2011). It has been suggested that these findings implicate impaired feed-forward connections (Sweet et al., 2003) and altered interhemispheric connections (Simper et al., 2011) in schizophrenia. The balance of findings (both increased and decreased neuron densities) is consistently mixed, as with the literature on the frontal lobe. The studies of temporal lobe neocortex contribute to an overall age-dependent contrast between patients and controls (Chana et al., 2003; Chance et al., 2008; Di Rosa et al., 2009), which may implicate altered neuroplasticity in schizophrenia.

Studies of the visual cortex also find a mix of increased and decreased neuron density, while reports of reduced total neuron number appear to be largely dependent on reduced regional volume (Dorph-Petersen et al., 2007). Alternative groupings of cortical regions (for example, 'limbic cortex', including cingulate cortex and entorhinal cortex) similarly reveal mixed results.

Of the other regions of the brain, the thalamus has been the most studied brain area; its clear structural boundaries have resulted in more studies of total neuron number than in the cortex. Overall, these studies show that altered total neuron number tends to be found as a result of gray matter volume reduction, and not a decrease in cell density (Pakkenberg, 1990; Popken et al., 2000; Young et al., 2000; Danos et al., 2002). The alterations of neuron density (both increases and decreases) are relatively small: at least seven studies (Danos et al., 2002; Cullen et al., 2003; Highley et al., 2003a; Dixon and Harper, 2004; Young et al., 2004; Danos et al., 2005; Byne et al., 2007) report less than 5% change, and the larger effects that may be reported for total number are usually due to the reductions in thalamic nuclear volumes. Studies of the basal ganglia are fewer but again show inconsistency of findings with regard to neuron number and density. Kreczmanski et al. (2007) found reduced neuron number in the caudate nucleus, the putamen, and the lateral nucleus of the amygdala, with no change in neuron density. This indicates that in subcortical gray matter, decreased neuron number is an effect associated with a reduction in the size of the region, and is accompanied by a lesser effect on cell density.

The instances of reduced density in several studies are unlikely to be due to an increase in reference

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volume (i.e. overall size of the region), as gray matter volume is generally found to be reduced in schizophrenia in both imaging and post-mortem studies (Levitt et al., 2010). However, the substantial number of studies that find decreased cell density in schizophrenia (Beasley et al., 2002; Zhang and Reynolds, 2002; Chance et al., 2005; Cullen et al., 2006; Wang et al., 2011; Smiley et al., 2012) are in conflict with the reduced neuropil interpretation. A unifying interpretation may be indicated by some individual studies (Chana et al., 2003; Chance et al., 2008), which show that the contrast between patients and controls depends on when in adulthood the cell organization is measured. It has been reported that normal neuron density in the auditory cortex increased with age in controls, whereas it was unchanged with age in patients: patients less than 50 years of age therefore had increased density (reduced spacing) relative to controls, while patients greater than 60 years had reduced density (increased spacing) compared to controls (Chance et al., 2008).

In the schizophrenia literature, findings of increased neuron density appear to be mainly the result of studies with patients at the younger end of the age range (although, note that the age range of subjects in post-mortem studies is generally older than most *in vivo* imaging studies). Therefore, it is possible that reduced neuropil characterizes patients in young-to-middle adulthood who do not typically achieve peak average developmental expansion of neuropil during adolescence and early adulthood. The deficient synaptic connectivity that could cause this lack of development may be the same process that underlies the failure to undergo normal aging changes. Less change in neuropil is a plausible consequence of deficient synapse formation and reduced neuroplasticity, as is the initial lack of expansion of neuropil in early life.

Microglia and neuroinflammation

A specific interest has arisen in microglia, due to evidence of disordered microglia and a posited link to the neuroinflammatory response in schizophrenia (Najjar and Pearlman, 2015). Microglia are the macrophages of the brain and have a mesodermal origin, unlike other neuroglia such as astrocytes, oligodendrocytes and ependymal cells. They are the main source of pro-inflammatory cytokines such as tumor necrosis factor α and interleukin-6 in the central nervous system (Monji et al., 2013). Inflammatory processes in schizophrenia likely play a role in the high incidence of metabolic syndrome in schizophrenia (Na et al., 2014). Increased microglial cell density has been found in the prefrontal cortex (Fillman et al., 2013; Radewicz et al., 2000) and in the auditory association cortex (Radewicz et al., 2000). Increased microglial cells have also been found in the anterior cingulate cortex and mediodorsal thalamus of patients with schizophrenia who had committed suicide during acute psychosis (Steiner et al., 2006). As evidence of increased pro-inflammatory cytokines has been found in schizophrenia (Miller et al., 2011), it has been suggested that increased long-term activation of microglia populations, possibly due to early-life exposure to a pathogen, has a detrimental, and perhaps apoptotic, effect on neural architecture (Monji et al., 2013). However, it is unclear if the inflammatory markers constitute a healthy response or detrimental contributor to pathology (Graeber and Streit, 2010), as pro-inflammatory cytokines also have roles in neurogenesis and synaptic transmission, among others (Na et al., 2014). Activated microglia and pro-inflammatory cytokines, especially interleukin-6, play a crucial role in neurogenesis, alterations of which may underlie neuronal disturbances in schizophrenia (Na et al., 2014).

Fung et al. (2014) found increased presence of neurons in subcortical white matter associated with elevated cortical cytokine mRNA. These neurons may be the consequence of disrupted neuronal migration associated with the condition. These changes in gray and white matter are also reflected in changes in other glial cell populations: Hof et al. (2003) found reduced density of oligodendrocytes in the prefrontal cortex and in underlying white matter. In general, the neuroglia have been reported to be reduced in density with sometimes altered morphology – Williams et al. (2013) found reduced density of astrocytes in the cingulate cortex in schizophrenia, and Uranova et al. (2004) found reduced density of oligodendroglia in the prefrontal cortex in schizophrenia. Nevertheless, most, if not all, neuropathologies (i.e. Alzheimer's disease, Parkinson's disease) are to a various extent associated with activation of microglia and astrocytes (Deverman and Patterson, 2009; Hanisch, 2002), making the specificity of these findings to schizophrenia less certain. Furthermore, negative findings indicating no alteration have also been reported (e.g. Falkai et al., 1999), particularly for astrocytes, even in the presence of microglial changes (Radewicz et al., 2000).

A quantitative summary

A meta-analytical summary is presented in order to synthesize previous literature on neuron density. This meta-analysis was performed in early 2013, and was intended to investigate changes with age in neuron density in schizophrenia.

Employing a strategy similar to neuropsychological and brain imaging literature, where meta-analysis of a mixture of studies employing similar methods is often used to reveal previously undetected irregularities in the data, an inclusive approach was taken toward studies of the cortex using neuropathological methods. In the neuropathology literature, there is apprehension about the meta-analytic approach based on *a priori* assumptions about the different roles and presumed differences in disease effects on different cell populations. However, these assumptions remain unproven, as it has not yet been convincingly demonstrated that there are distinct cell populations that are affected more than others. On the basis of this, as summarized by this review, and following the principle of Occam's razor, we adopted an agnostic view of the mixed reports of disease effects on cell populations in schizophrenia. Here we treated all cell measurements as examples of a generic principle of particle distribution within the defined space of the human cerebral cortex.

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A literature search was performed up to and including February 2013, using the online search engine ''PubMed'' and two previous comprehensive reviews on cell density in schizophrenia (Harrison, 1999; Esiri and Crow, 2008). The analysis included all studies of neuron density in regions conforming to the usual six-layered cortical structure; the most intensively studied regions included the frontal lobe and temporal lobe. It should be noted that the selection of regions included the cingulate cortex, primary visual cortex and parahippocampal cortex, but excluded the hippocampus and subcortical gray matter, as these regions have their own idiosyncratic structure. The resulting studies measured neuron density in various cell populations; some of the different cell types were identified by immunostaining. Although immunostaining has limitations related to antibody detection, which may influence density estimation, these issues are well known. Such published studies require adequate optimization, including case–control comparisons, so a systematic confounding effect would not be expected due to methodology alone.

An initial 69 papers resulted from the online search and references from the previous reviews; 30 were eventually selected for inclusion in the meta-analysis, based on the following criteria: (1) they were published in English; (2) they were accessible online; (3) mean measurements of density were reported for both patients and controls; (4) measurements were for neurons, not glia; and (5) measures were taken from the cortex and not white matter. Due to the statistical methods used in the analysis, papers were only included in the model if they reported an estimation of the standard deviation or standard error, and if data were available on all of the variables included in the statistical model (gender, age, duration of illness, type of cell measured). Based on cell type, the studies were grouped into two broad categories, 'inhibitory' and 'other'. Although the cells grouped as 'inhibitory' (calbindin, GAD, parvalbumin, and somatostatin) may not be conclusively determined to be inhibitory cells, this broad approximation made use of the inhibitory cortical circuits hypothesis (Lewis et al., 2005) and provided a framework for classifying the cell types in a concise way (see section ''Nuron density'' for further comments on the inhibitory cortical circuits hypothesis). See Table 1 for a complete listing of the studies included in the analysis.

A multilevel regression model was fitted to the data on neuron density. Type of measurement (2D or 3D) was

Table 1. Demographic details for studies included in quantitative summary

Study	Author(s)	*n*		Age		Density		Type of cell	Method
		Con	SZ	Con	SZ	Con	SZ		
1	Pakkenberg (1993)	16	8	59.7	60.3	38200	43200	Giemsa-stained	3D
2	Akbarian et al. (1995)	10	10	64.2	63.4	109.86	108.79	GAD	2D
3	Daviss and Lewis (1995)	5	5	53.4	52.0	73.7	123.5	Calbindin	2D
4	Selemon et al. (1995)	19	16	43.7	40.1	1.88E + 10	5.57E + 10	Nissl-stained	3D
5	Kalus et al. (1997)	5	5	66.0	60.2	1342	1434	Nissl-stained	2D
6	Woo et al. (1997)	10	10	53.9	53.6	60.3	61.2	Parvalbumin	2D
7	Selemon et al. (1998)	10	9	47.5	44.4	51627	62714	Nissl-stained	3D
8	Volk et al. (2000)	10	10	46.6	45.2	167.38	126.20	GAD mRNA	2D
9	Thune et al. (2001)	10	8	67	67.4	50200	47500	Giemsa-stained	3D
10	Beasley et al. (2002)	15	15	48.1	44.2	32.85	28.11	Parvalbumin	2D
11	Chana et al. (2003)	15	15	48.1	44.5	95.32	93.06	Nissl-stained	2D
12	Hashimoto et al. (2003)	15	15	43.3	43	24.1	20.8	Parvalbumin mRNA	2D
13	Law and Harrison (2003)	15	15	46.6	44.5	86.32	98.80	SMI32	2D
14	Pierri et al. (2003)	13	13	53.1	53.2	17468	17232	SMI32	3D
15	Selemon et al. (2003)	9	6	50.2	56.3	46400	52090	Nissl-stained	3D
16	Tooney and Chahl (2004)	6	6	43.0	44.0	41.87	45.31	Parvalbumin	2D
17	Woo et al. (2004)	17	17	58.1	58.4	191.67	166.67	GAD	2D
18	Chance et al. (2005)	12	12	65.5	67.8	57.29	46.75	Calbindin	2D
19	Miguel-Hidalgo et al. (2005)	13	11	46.8	46.0	8385.23	7655.18	NF200	3D
20	Cullen et al. (2006)	10	10	60.0	60.0	40000	33000	Nissl-stained	3D
21	Garey et al. (2006)	8	9	63.9	74.7	1036.06	1135.33	Nissl-stained	2D
22	Dorph-Petersen et al. (2007)	10	10	50.8	46.4	70500	67400	Nissl-stained	3D
23	Pantazopoulos et al. (2007)	16	10	64.1	62.4	3.87	3.04	Parvalbumin	3D
24	Morris et al. (2008)	23	23	48	47.9	67.7	52.5	Somatostatin	2D
25	Di Rosa et al. (2009)	13	11	68.3	65.5	1612.73	1228.00	Nissl-stained	3D
26	Dorph-Petersen et al. (2009)	12	12	45.2	47.3	20700	28600	Nissl-stained	3D
27	Brune et al. (2010)	22	20	44.1	44.7	58.47	54.45	VEN	3D
28	Simper et al. (2011)	16	16	66.3	66.9	4.02E + 10	3.47E + 10	Nissl-stained	3D
29	Smiley et al. (2011)	11	9	54.0	49.5	38350	37250	Nissl-stained	3D
30	Smiley et al. (2012)	24	24	44.3	39.8	26690.02	26628.81	Nissl-stained	3D

*Age and density are mean values.
*n = sample size; Con = controls.
*Age is measured in years; density is neurons/mm^2 (2D) or neurons/mm^3 (3D).
*'Method' refers to whether neurons were measured in two-dimensional space or three-dimensional space.
**Abbreviations:* GAD = glutamic acid decarboxylase; SMI32 = non-phosphorylated neurofilament protein; NF200 = phosphorylated and non-phosphorylated neurofilament protein; VEN = von Economo neurons; MAP2 = microtubule-associated protein 2.

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included as a covariate to adjust for the differences between two-dimensional and three-dimensional methods of cell counting, and acted as a multiplicative conversion factor on the two-dimensional values, so as to allow for comparison between two-dimensional and three-dimensional methods. Within-study and within-brain collection correlations were taken into account using these two variables as different levels in the model. Brain region measured did not significantly explain changes in neuron density, and so was not included in the model ($t = -0.218272$, df = 26, $p = 0.8289$). A weighted model was used in the analysis to account for the differences in sample size and provide the necessary homoscedasticity; there were 30 studies and 361 data-points included in the final model, including 326 individual data-points and 35 average data-points.

The meta-analysis revealed that baseline neuron density was significantly different between patients and controls as a main effect ($t = 4.4756$, df = 324, $p = 0.0000$), and was higher in patients. Below the age of 60, patients had a greater density of neurons compared to controls; this speaks to an overall increase in neuron density across cortical regions in schizophrenia. Neuron density increased with age in both schizophrenia and controls; however, the increase with age in controls was significant ($t = 4.2032$, df = 324, $p = 0.0000$), whereas the neuron density increase was much smaller and increased at a lower, non-significant rate with age in patients ($t = 0.4540$, df = 324, $p = 0.6502$) (Fig. 1A). The difference in rates between schizophrenia and controls was significant ($t = 3.1818$, df = 324, $p = 0.0016$). This effect was similar in patients with varying durations of illness (Fig. 1B). This resulted in different age trajectories of neuron density in patients versus controls (Fig. 1).

There was a statistically significant interaction between diagnosis and type of cell measured. Neurons were classified as either 'inhibitory' or 'other' (predominantly based on cell staining method); the density of inhibitory cells was different between patients and controls. The following markers were classified as 'inhibitory': calbindin, GAD, parvalbumin, and somatostatin. The following were classified as 'other': SMI32 neurons, NNFP neurons, NF200 neurons, and neurons labeled with a Nissl or Giemsa stain. In general, there was a lower density of 'inhibitory' neurons compared to other neurons, and this effect was significantly greater in patients than in controls ($t = -4.6849$, df = 324, $p = 0.0000$), constituting relatively reduced 'inhibitory' neurons in schizophrenia (Fig. 2). The overall trend across the age range for all neuron density showed that patients had a higher density than controls; however, with increased aging, controls overtook patients, achieving a higher density than patients at around age 70. This is in contrast to the aging trajectory of 'inhibitory' neuron density, where patients still started out with a higher density, but around the age of 40 controls overtook patients.

The findings support the hypothesis of increased neuron density in schizophrenia, and a differing trajectory of change with age in patients and controls. These effects in the microanatomy provide support for altered aging trajectories in macroscopic volumetric analyses in schizophrenia. The finding of decreased density of inhibitory neurons in schizophrenia lends support to the idea that there is dysfunction of inhibitory cortical circuits in the disease, particularly in the prefrontal cortex, which contributes to the altered cognition that is a hallmark of schizophrenia. Although this is a heterogeneous mix of brain regions, an analysis addressing all of these areas was deemed appropriate

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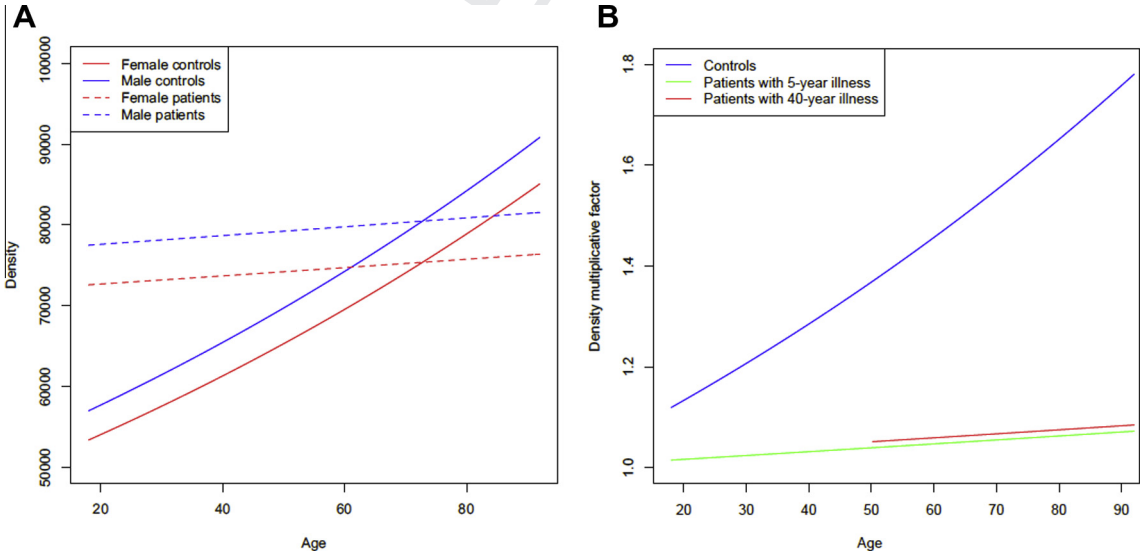

Fig. 1. Relationship of density with increasing age in patients and controls. A: As age increases, the density of both controls (solid lines) and patients (dotted lines) increases. However, this increase is at a different rate in controls vs. patients: controls have a density increase that occurs at a much faster rate than patients. B: Density is shown here as a multiplicative factor: the rate of density increase with age in controls (blue line) is higher than the rate in patients (red and green lines); the rate is similar in patients with both shorter (5 years: green line) and longer (40 years: red line) lengths of illness. *Density is estimated neurons/mm^3; age in years.

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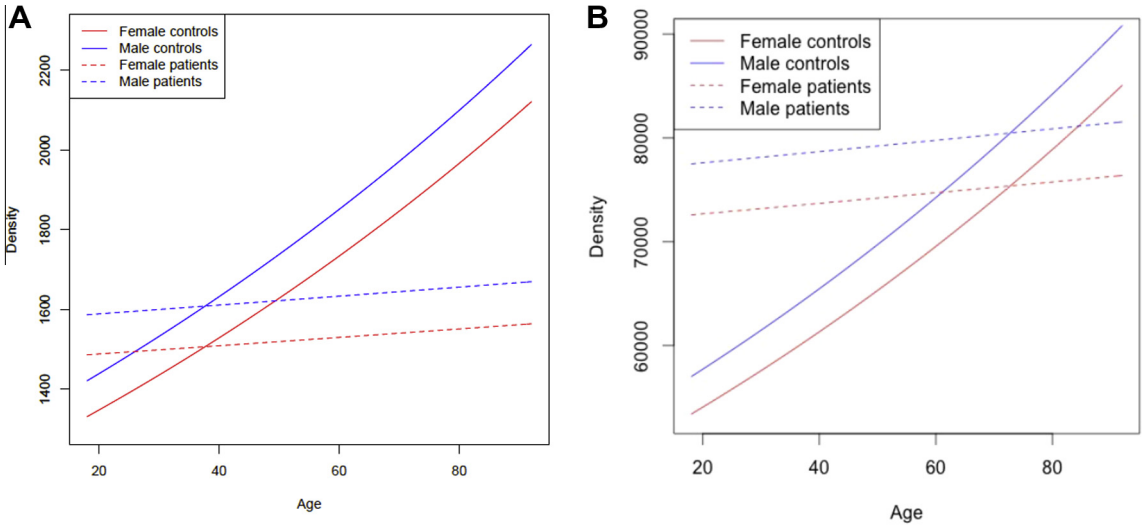

Fig. 2. Density of inhibitory (left) and 'other' (right) neurons in patients and controls. A: The density of inhibitory neurons is greater in patients (dotted lines) compared to controls (solid lines) before the age of 40, but after this time, the density in controls overtakes that in patients. The density in patients is almost the same from age 20 to age 80, while the density in controls almost linearly increases with age. B: The density of 'other' neurons (predominantly excitatory) in patients (dotted lines) is greater than that of controls (solid lines) before the age of about 70; after this time, the density in controls overtakes that in patients. The increase in density in controls occurs at a much higher rate than that in patients. *Density is estimated neurons/mm^3; age in years.

for this review given the current lack of certainty regarding the nature of different pathology in each region, as well as the absence of a unifying picture of this subject area. The information gleaned from such an analysis, although preliminary, can further inform future studies on neuron density, and can provide a basic framework for conceptualizing changes in microstructure in schizophrenia.

THE CASE FOR PROGRESSIVE CHANGE

Studies of longitudinal change in structures in schizophrenia have found that changes in the frontal and temporal lobes can often be noticed before changes in ventricular volume; they may even be detectable before symptom onset (DeLisi, 2008). Before the first psychotic episode, brain structure and size in patients at high risk of developing schizophrenia or in the prodromal phase may be distinguished from controls, and this difference persists after onset as the disease progresses (Harrison, 1999). DeLisi (1999) has suggested that this results from an underlying disease that first causes changes in brain structure, and then leads to progressive changes with age, in a manner that is different from healthy aging. Evidence of this comes from a recent review that reported that in both childhood- and adult-onset schizophrenia, the characteristic gray matter loss that is a hallmark of schizophrenia proceeds in a similar way in both groups, starting in posterior parietal regions and extending to frontal regions (Rapoport and Gogtay, 2011). It has been suggested that these brain changes are due to underlying abnormalities in the microstructure that are only revealed at symptom onset (Fatemi and Folsom, 2009). As patients age, this altered underlying structure is then hypothesized to interact with normal aging processes in an abnormal way, producing the progressive losses of gray matter that have been reported (van Haren et al., 2008a).

It is known from studies of healthy aging that there is a normal loss of synapses and dendrites, which leads to brain-wide decreases in volume (Morrison and Hof, 1997). Along with other microstructural changes, such as slight neuronal dysfunction, this has been posited to be the underlying cause behind the minor difficulties in memory retrieval and attention that occur in healthy aging (van Veluw et al., 2012). Although mildly dysfunctional, the losses during aging do not appear to be due to an entirely stochastic process and are moderated by ongoing neuroplasticity and cognitive reserve (Esiri and Chance, 2012).

A recent meta-analysis (van Haren et al., 2008b) provided evidence for a progressive loss of gray matter in schizophrenia that contributes to a different aging trajectory in patients compared to controls: cerebral volume in controls showed a curved trajectory with time, while patients had a linear decrease in cerebral volume with time. This study found that the most significant decreases in whole-brain and gray matter volumes and increases in ventricular volumes occurred before the age of 42 in patients. After this time, the rate of change was similar to that of controls. This age is notable as a fulcrum point in the lifespan contrasting controls with schizophrenia, as age 45 is often used as a cutoff for late onset schizophrenia, after which the incidence is notably lower (Jeste et al., 1995).

NEURODEVELOPMENTAL AND PROGRESSIVE NEURODEVELOPMENTAL THEORIES

Neurodevelopmental theories have flourished since Weinberger observed that such a theory could account for the timing of illness onset and might also explain the

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structural changes in the brain (Weinberger, 1987). The hypothesis that schizophrenia has an origin in the mechanisms that control brain development is at first thought surprising, especially since schizophrenia first occurs in early or middle adult life, and may occasionally have an onset even later than this. However, recent perspectives (Benes, 2004) suggest that some aspects of development (e.g. myelination) are extended and merge with ongoing plasticity in the mature brain, resulting in a trajectory of change that unfolds across the lifespan. One consequence of this is that the detection of a pathognomic abnormality against a dynamic background of lifetime variation is challenging. Although some brain changes are present at the onset of illness (DeLisi, 2008), the contrast between patients and controls may depend on the age at which measurements are taken (Chana et al., 2003; Chance et al., 2008). Strong evidence for ongoing brain structural changes in adulthood has emerged from longitudinal neuroimaging studies (van Haren et al., 2008b). Whereas the original neurodevelopmental hypothesis proposed that "a fixed lesion early in life interacts with normal brain maturational events that occur much later" (Weinberger, 1987), it now appears that the neurodevelopmental concept must be extended to encompass altered aging associated with ongoing abnormal neuroplasticity (Harrison and Weinberger, 2005; Chance et al., 2008; Kirkpatrick et al., 2008). A unifying hypothesis has emerged that rectifies these seemingly contradictory views: the progressive neurodevelopmental model suggests that onset of schizophrenia might be preceded by an alteration in neurodevelopment that is affected by maturational processes, and later interacts with neuroplastic processes in a way that is different from healthy aging (DeLisi, 1997; Woods, 1998; de Haan and Bakker, 2004; Selemon, 2004).

NEUROPLASTICITY AND COGNITIVE RESERVE

Altered neuroplasticity has been hypothesized to account for the different aging trajectory between patients and healthy controls (van Haren et al., 2008b). Abnormal neurodevelopment may cause the initial changes that lead to the development of schizophrenia; the effect of these changes is manifested at puberty, which coincides with the average age of onset (Pantelis et al., 2005). The prevailing conception of neuroplasticity is largely concerned with the development of brain networks before maturity. However, its role beyond that point should not be overlooked, when the emphasis of neuroplasticity shifts to the maintenance and modulation of the established networks. The marked brain structural changes occurring early in schizophrenia may reflect this shift: later in life, a departure from the usual neuroplastic processes causes further progressive brain changes in schizophrenia (Olabi et al., 2011). These changes with age are hypothesized to occur within the brain's broader neuroplastic repertoire, often based around synaptic integrity, which allows for restructuring in the brain and decreases and increases connections as necessary. Greater regional plasticity is a characteristic of associative regions, and is linked to higher rates of age-related change in association cortex (Arendt, 2003). The brain's adaptive plasticity contributes to its cognitive reserve (Barnett et al., 2006), which is instrumental in compensatory recovery mechanisms in aging and dementia (Bartres-Faz and Arenaza-Urquijo, 2011). A breakdown of the neuroplastic processes that contribute to cognitive reserve has been implicated as a potential reason for the progressive changes with age that are seen in schizophrenia (Ho et al., 2003). Although there is a multitude of evidence for progressive anatomical changes, a related progressive worsening of symptoms or functioning has not always been found (Holthausen et al., 2002). Where this is the case, a greater amount of cognitive reserve may be acting as a 'cushion' to prevent the additional brain changes from having an effect. The cognitive reserve hypothesis suggests that cognitive deficit due to accretion of pathology may be partly offset by a 'neural reserve', wherein brain networks can absorb a degree of damage without noticeable effects on cognition (Stern, 2009). The reduced peak expansion and less plastic neuropil structure proposed in schizophrenia may indicate an inherently reduced and less plastic neural reserve.

Differences in both cellular development and age-related changes in the surrounding neuropil volume can combine with abnormal ongoing neuroplasticity in schizophrenia to create apparent inconsistencies in the effect of schizophrenia depending on age and sex. The integration of data on the dynamics of brain structure in schizophrenia relaxes the requirement for a "one-size-fits-all" hypothesis of the structural changes. For example, while altered neuropil may still form a key component of pathophysiology, the literature indicates that, in many studies, evidence of reduced neuropil may not be found. While this does not mean that the disorder cannot be due to a single process, the manifestation of that process may be detected differently across the lifespan when compared with the normal trajectory of development, maturation, and aging.

This interpretation is based on that of previous authors who have suggested altered neuropil (Selemon and Goldman-Rakic, 1999) and disrupted synaptic structure (Harrison and Weinberger, 2005), as well as altered axo-dendritic connectivity (Crow et al., 2007). At first glance the idiosyncratic behavior in psychosis does not seem to be the obvious manifestation of reduced plasticity. However, negative symptoms and cognitive deficits seen in schizophrenia are consistent with such a scenario. Furthermore, normal adult neuroplasticity does not appear to support highly labile behavior but is more likely to be a mechanism for behavioral and cognitive fine-tuning, something that may be lacking in psychosis. The contrast between patients and controls will be better understood with increased understanding of the normal trajectory of age-associated brain changes.

CONNECTIVITY AND MYELINATION

The altered trajectory of change in neuron density and gray matter volume with age in schizophrenia may be continuous (van Haren et al., 2008b), or phasic (Garver, 1997) and two factors that can influence the timing and

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pattern of these changes are brain connectivity and myelination. The timing of these changes may emerge when misconnectivity exceeds a given threshold, with a cumulative effect on brain areas and processes that go on developing longest (e.g. asymmetric association cortex) (Arendt, 2003). Few developmental processes continue into adult life, although myelination is a notable exception: expansion of the corpus callosum continues through the third decade of life, and it completes later in females than in males (Cowell et al., 1992; Pujol et al., 1993). There is a similar sex difference in the timing of illness onset (Crow et al., 2007) and, in view of this, it has been suggested that illness onset reflects the maturation of myelinated tracts (Crow et al., 2007), at which time the consequences of misconnected networks are exposed. Microarray studies have found alterations in myelin-related gene expression in schizophrenia (Tkachev et al., 2003); this supports findings of decreased oligodendrocytes in the superior frontal cortex (Hof et al., 2002) and abnormal myelination (Uranova et al., 2007). DTI studies have noted alterations in the white matter, specifically decreased anisotropy and reduced myelin content (Buchsbaum et al., 1998; Lim et al., 1999; Foong et al., 2000).

Modern microscopy indicates alterations in the numbers of glia (Cotter et al., 2001; Cotter et al., 2002; Segal et al., 2007; Vostrikov et al., 2007; Uranova et al., 2011; Vostrikov and Uranova, 2011), and accumulating molecular studies find changed gene expression associated with the late maturing process of myelination (Hakak et al., 2001; Tkachev et al., 2003; Sugai et al., 2004; Katsel et al., 2005). Consequently, interest has switched from astrocytes to oligodendrocytes, as oligodendrocytes are involved in myelination. The oligodendrocyte changes thought to be accompanied by altered gene expression and abnormal myelination (Uranova et al., 2011) are a possible source of the white matter alterations detected by DTI studies (Whitford et al., 2011; Nakamura et al., 2012; Nazeri et al., 2013). Since oligodendrocytes are known to express excitatory glutamate receptors, the putative deficits in glutamatergic neurotransmission in schizophrenia (see Harrison and Weinberger, 2005 for review) may reflect oligodendroglial changes. Disruption of the glutamate–glutamine cycle, or changes in perineuronal nets in late development, or altered myelination, are all likely to have ongoing effects beyond early development that may be detected in glial cell components (Beasley et al., 2009).

AGE OF ONSET AND ILLNESS DURATION

Some brain regional volumetric studies have found interactions between reduced cortical gray matter and age of onset in a sex-dependent manner (Highley et al., 1998; McDonald et al., 2000). Cellular changes in these regions were related to white matter connections (Chance et al., 2008; Simper et al., 2011), which also showed sex-dependent effects (Highley et al., 1998). It has been suggested that age of illness onset and its difference between the sexes may be related to the timing of maturation of myelinated white matter tracts, particularly the corpus callosum (Crow et al., 2007).

Age of onset and illness length are also linked to measures of disease severity (Remschmidt et al., 2007), and a difference in neuron density has been noted between early- and late-onset patients, as well as in relation to duration of illness (Brune et al., 2010; Olabi et al., 2011), although anatomical differences between early- and late-onset schizophrenia have been inconsistent (Rivkin et al., 2000). There have been findings of increased and more prominent brain changes in schizophrenia associated with a longer duration of illness, including more pronounced decreases in gray matter and total brain volume (Kasai et al., 2003; Burke et al., 2008; van Haren et al., 2008b; Tanskanen et al., 2010; Olabi et al., 2011). Reductions in volume of the hippocampus (Murakami et al., 2011) and primary auditory cortex (Crespo-Facorro et al., 2004) have also been shown to correlate with illness duration. MRI studies have found that decreases in gray and white matter in schizophrenia correlate with earlier age of onset and longer illness duration (Burke et al., 2008; Tanskanen et al., 2010), as well as with poor outcome and more severe symptoms later in the illness (van Haren et al., 2007; van Haren et al., 2008b).

GENDER

Brain structural differences between males and females are observed in schizophrenia. To avoid bias, many studies opt to only include males; this may also result from the fact that many brain collections only include male specimens. However, this trend toward using a more homogenous cohort has resulted in a lack of research on gender differences in measures of density and volume (Chance et al., 2008). Without adequate data on both genders, it is difficult to present a view on brain changes in schizophrenia as a whole. Many studies that have included both genders in their subject populations have found differences between males and females on measures of neuron density (Chana et al., 2003) and other neuroanatomical correlates (Di Rosa et al., 2009), in addition to differences between patients and controls. It has been reported that there are sex differences in proteome regulation and protein expression in the anterior cingulate cortex in schizophrenia (Martins-de-Souza et al., 2010), particularly involving proteins that regulate glutamate production.

Gender differences have been noted for several variables that influence or are affected by schizophrenia, such as cognitive functioning (Han et al., 2012), severity of illness (Hafner, 2003), type of symptoms (Ochoa et al., 2012), social functioning (Vila-Rodriguez et al., 2011), and substance use (Zhang et al., 2012). A meta-analysis reviewing the gender difference in schizophrenia indicated earlier age of onset in males as well as poorer social functioning and more severe negative symptoms than females (Hafner, 2003; Vila-Rodriguez et al., 2011; Ochoa et al., 2012). Therefore it is clear that studies that do not include female subjects are missing potentially informative data that may lead to greater characterization of the disease process.

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MEDICATION

Studies investigating brain changes over time are complicated by the fact that patients are usually taking varying doses of antipsychotic (AP) medication. It has been suggested that the action of APs on neurotransmission may result in changes in brain structure (Dazzan et al., 2005): a meta-analysis of the literature has found that, in general, APs serve to reduce brain volume and increase ventricular volume (Moncrieff and Leo, 2010). While first-episode studies provide a cross-sectional view of brain changes without the influence of medication, longitudinal studies of patients who continue to be AP-naïve are difficult to justify ethically. A group of first-episode patients has been reported that showed no difference in brain volumes at baseline, but that had significant reductions after one year; higher medication correlated with a greater decrease in volume (Cahn et al., 2002). However, several studies have indicated that medication does not affect measures of neuron density (Law and Harrison, 2003; Vogeley et al., 2003; Woo et al., 2004; Pantazopoulos et al., 2007; Maloku et al., 2010). A recent study on MAP2 expression in schizophrenia and Huntington's chorea patients showed that there were different levels of expression between the two groups (Somenarain and Jones, 2010); because both groups of patients received similar AP treatment, changes seen in schizophrenia may not be entirely due to the effect of medication. Clearly, the causal links between illness severity and length, degree of structural change, and medication dose are difficult to disentangle.

Several studies have reported reductions in cortical gray matter volume that may be related to level of AP medication (Lieberman et al., 2005; Ho et al., 2011). At the same time, these appear to reveal enlargements in basal ganglia structures: one study found that patients on typical APs presented with increased size of the putamen at the same time as a decrease in the size of several cortical areas, including the insula, paracentral lobule, and the precuneus, compared with AP-naïve patients, while patients on atypical APs presented with an increase in the size of the thalami (Dazzan et al., 2005). Attempts to model treatment effects in rodents have revealed similar patterns of change, including enlargement of the corpus striatum and reduction of cortical gray matter (Vernon et al., 2012). A study of medication effects in primates reported increased neuron density in the cortex without reduction of total neuron number, implicating neuropil loss; this study also identified a reduction of glial cells as an effect of medication (Konopaske et al., 2007).

Recent studies have indicated that medication may be a substantial contributor to the trajectory of brain changes in patients. The microstructural effects of medication may be a non-specific side effect, or they may reveal a meaningful interaction with the disease. In the process of retrieving a better inhibitory balance in brain networks, medication could facilitate the loss of neuropil around misconnected or misfiring neurons. Haloperidol, in particular, has been shown to cause reduced neurites, reduced cell somal size, and neuronal apoptosis (Ukai et al., 2004), which presumably should contribute to eventual cell loss. Furthermore, studies of white matter have found that AP treatment appears to inhibit the normal age-related white matter volume expansion during early to mid-adulthood (Ho et al., 2011). This is around the time that evidence suggests the role of neuroplasticity shifts. The timing of brain changes, the age of illness onset, the pattern of connectivity and neuroplasticity, and the effects of medication therefore may be interlinked and, most notably, their interaction is seen in early-mid adulthood. The complexity of this interaction and its unexpectedly protracted time course make it perhaps less surprising that the literature on neuron density has offered inconsistent findings.

CRITICAL INTERPRETATIONS, CONCLUSIONS, AND FUTURE DIRECTIONS

Critical interpretation of findings

Methods for quantifying neuropathology have necessarily changed with advances in technology and understanding of the disease process. Current research in neuropathology involves the use of stereological techniques such as total volume measurements, cell number estimates, and cell density calculations. Morphological studies such as investigations of cell size and shape have also been conducted. Although these techniques do provide useful and relevant information, it is important to be aware of their limitations in order to accurately assess findings. For example, measurements of neuronal cell size that are extrapolated to represent total neuron number are confounded by the fact that pyramidal cells can have varying and irregular shapes (large, small) that are not necessarily appreciated by the automated cell counting methods, although some studies do take this into account by measuring cells in regions that have different-sized cells (Sweet et al., 2004). Volume measurements must accurately define regional borders, and often use the Cavalieri method, which describes the systematic sampling of a region of interest into blocks, slabs, and sections of standard height and area (Gundersen and Jensen, 1987; Dorph-Petersen and Lewis, 2011). Measurements of volume, number, and density and necessarily interrelated, with a density estimate coming from measurements of total neuron number within a given volume; however, this means that a change in density could be due either to a change in neuron number or to a change in region volume, or both. This uncertainty can be reduced by also reporting volume measurements. Other challenges in using postmortem tissue for neuropathological investigations include the risk of tissue shrinkage, which must be taken into account. Additionally, there are methodological challenges to overcome when using immunohistochemistry, such as ensuring that antigen binding is specific and accurate, and that labeling has penetrated throughout the section (Dorph-Petersen and Lewis, 2011).

In quantitatively summarizing data in neuropathology, as was done here with neuron density, it is important to keep in mind that methodology has changed with time. Techniques that were considered state-of-the-art in 1980 may no longer be as such, and it is likely that methods that are used currently are only more accurate

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and precise than those used previously. As published studies are held to high standards of protocol optimization and study design, an overview of the current and past literature is deemed appropriate; however, it is important to interpret findings as a stepping-stone for future work, rather than as an infallible benchmark. Quantitative summaries such as these can inform future directions of research by synthesizing previous knowledge and providing a useful framework for new lines of inquiry.

Conclusions

Schizophrenia is a heterogeneous syndrome, and recent care has been devoted to the categorization scheme for what is posited to be a multitude of disease states under the umbrella category of 'schizophrenia'. To maintain continuity with the past literature, it was felt to be appropriate to conform to the existing–definition of schizophrenia. Although there is a hetereogeneous mix of behaviors and structural and functional differences encompassed within schizophrenia, much can be learned from synthesizing this past knowledge.

Imaging studies in schizophrenia have revealed differences in schizophrenia that are well-established today: larger ventricles (Olabi et al., 2011), decreased gray matter (Harrison et al., 2003), and smaller hippocampi (Arnold et al., 2015) seem to be characteristic of the schizophrenia pathology, if not pathognomic. Two other macroscopic trends are worth noting, as they occur in multiple studies: decreased asymmetry in schizophrenia (Crow et al., 1989), along with altered gyrificaton (Palaniyappan et al., 2014). Differences in volumes of various forebrain subregions have also been reported, but with less consistent results. This lack of consistency appears to be a hallmark of schizophrenia neuropathology: it may be that schizophrenia involves a spectrum of brain network changes that are only unified in the extent to which they are all deviations from the healthy equilibrium.

Much attention has been focused on the microanatomy in schizophrenia, looking at neuropil, synapses, neurons, dendrites and synaptic proteins. The cytoarchitecture appears to be disturbed in schizophrenia, with decreased neuron number being a possible cause or consequence. The reduced neuropil hypothesis, an influential theory, posited that reduced spacing of cells and reduced neurites and synapses were the causes of change in schizophrenia, leading to increased cell density (Selemon and Goldman-Rakic, 1999). Although this has garnered support, findings of no change in or decreased density are prevalent. Evidence from different points in the lifespan suggests that the differences may be due to interactions with age (Chana et al., 2003; Di Rosa et al., 2009). A quantitative summary, presented here, provides further evidence for this, and suggests that neuron density is increased in patients compared to controls, and that the trajectory of change with age is significantly different in patients: density increased at a significant rate with age in controls, whereas in patients it did so at a much slower, non-significant rate. This summary also provided evidence of decreased density of inhibitory neurons in schizophrenia. The study of inhibitory interneurons has shown that these are also reduced in schizophrenia, providing support for the involvement of inhibitory cortical circuits in the development and maintenance of the disorder (Lewis et al., 2005). A lack of inhibitory interneurons could lead to disinhibition of excitatory pyramidal networks (Beneyto and Lewis, 2011). An interesting conclusion, then, is that the neuropathological picture of schizophrenia is not static but changes over time, and indicates that age and length of illness are relevant variables in any analysis. This is also supported by studies in childhood-onset schizophrenia (Rapoport and Gogtay, 2011), in the prodromal period (Harrison, 1999), and longitudinal studies (van Haren et al., 2008a). An interaction between such a dynamic view and the neurodevelopmental hypothesis of schizophrenia has produced the progressive neurodevelopmental model of schizophrenia onset (de Haan and Bakker, 2004). The analysis presented here suggests such an approach should be extended to encompass the evidence of altered plasticity throughout the life span, and may underlie changes seen in synaptic processes, neuron density, and volume.

Future directions

Evidence of altered oligodendrocytes (Uranova et al., 2011) and myelination (Hakak et al., 2001) in schizophrenia offer promising avenues for future research, and data from proteome and transcriptome analyses supports the role of oligodendrocyte dysfunction in schizophrenia pathogenesis (Martins-de-Souza, 2010). As with many psychiatric disorders, an equal emphasis on both genders is important for future studies, as the limited number of studies looking at sex interactions have shown notable differences between males and females. Evidence from animal models showing brain effects due to AP medication provides a stepping stone for ongoing research into medication effects, and whether the putative deficits attributed to schizophrenia are in fact due to the disease and not to medication. New developments in the field of proteomics suggest that, in the future, a panel of biomarkers may be able to aid classification of patients into diagnostic categories (Martins-de-Souza, 2013), as well as provide "proteomic profiles" of treatment response (Guest et al., 2013).

FINAL COMMENTS

Although the field of schizophrenia neuropathology contains many contradictory findings, some of the emerging themes address this challenge by acknowledging the dynamic nature of the disorder. A single, fixed pathological description may no longer be expected to reflect the complex nature of changes in development, adult plasticity and aging. Indeed, the diversity of phenotype may be considered a characteristic of the disorder that recognizes the evidence for multi-factorial genetic heritability.

The presence of some reasonably consistent changes in inhibitory neuron populations (also indicated by meta-analysis) and the focus on synaptic pathology appear

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promising, as does the posited role of oligodendrocytes and proteomic biomarkers. Although the interaction with medication has not been resolved, this provides further directions for future research. New techniques and more detailed pre-mortem phenotypic assessments (symptoms, cognitive abilities and brain imaging), as well as assessment across the full human age range, will continue to offer greater insight, and make the neuropathology of schizophrenia an increasingly understandable problem.

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Chance et al. (2006).

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