Please cite this article in press as: Bakhshi K, Chance SA. The neuropathology of schizophrenia: A selective review of past studies and emerging themes in brain structure and cytoarchitecture. Neuroscience (2015), http://dx.doi.org/10.1016/j.neuroscience.2015.06.028

Neuroscience xxx (2015) xxx–xxx

NEUROSCIENCE FOREFRONT REVIEW

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

K. BAKHSHI AND S. A. CHANCE *

Department of Clinical Neurosciences, University of Oxford, Oxford, UK

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.

Key words: schizophrenia, neuropathology, neuron, neuroplasticity, aging, inhibition.

*Corresponding author. Address: West Wing Level 1 Neuropathology, John Radcliffe Hospital, Headley Way, Headington, Oxford OX39DU, UK. Tel: +44-0-1865-234934.
E-mail address: steven.chance@ndcn.ox.ac.uk (S. A. Chance).
Abbreviations: AP, antipsychotic; BA, Brodmann areas; CT, computerized axial tomography; GAD, glutamic acid decarboxylase; MRI, magnetic resonance imaging.

http://dx.doi.org/10.1016/j.neuroscience.2015.06.028
0306-4522/

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

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-

Please cite this article in press as: Bakhshi K, Chance SA. The neuropathology of schizophrenia: A selective review of past studies and emerging themes in brain structure and cytoarchitecture. Neuroscience (2015), http://dx.doi.org/10.1016/j.neuroscience.2015.06.028