Section 1
Chapter 1

Schizophrenia

Structural imaging of schizophrenia

Thomas J. Whitford, Marek Kubicki and Martha E. Shenton

Introduction

Emil Kraepelin, one of the founding fathers of the diagnostic concept of schizophrenia, argued that the disorder was underpinned by abnormalities in brain structure. In his 1899 textbook, Kraepelin wrote: "in dementia praecox [schizophrenia], partial damage to, or destruction of, cells of the cerebral cortex must probably occur" (Kraepelin, 1907). Since that time, an enormous amount of research has been undertaken with an eye to determining whether or not Kraepelin was correct. Until recently, the question of whether patients with schizophrenia (SZ) exhibit abnormalities in brain structure was more or less synonymous with the question of whether they exhibit abnormalities in gray matter (GM). The GM, so-called because of its grayish appearance in post-mortem tissue sections, is thought to consist primarily of neuron bodies, dendrites, axon terminals and other synaptic infrastructure and certain classes of neuroglia. Until recently, the vast majority of research aimed at investigating the neuroanatomical underpinnings of SZ has focused on GM. This is perhaps understandable, given that GM comprises both the brain's fundamental units of information processing (neurons) and the sites-of-action for most psychotropic medications (synapses). In recent years, however, a growing proportion of contemporary research has begun to focus on the "other half of the brain" (as wryly denoted by Fields, 2004), i.e. the white matter. The white matter (WM) is primarily constituted of myelinated axon sheaths, which form the infrastructure for signal transmission between spatially discrete populations of neurons. By way of analogy, just as the Internet is comprised of spatially disparate computers connected via electrical cabling, the brain is comprised of spatially disparate neurons connected via myelinated axons. Despite the fact that the role of WM in facilitating and modulating communications between discrete brain structures makes it theoretically relevant with respect to the prevailing "connectivity" models of SZ (as discussed in the third section), it is only in the past decade that WM has become a major topic of interest in the SZ research community. A major factor underlying this increased interest has been the development of diffusion tensor imaging (DTI) as a mainstream neuroimaging technique. Unlike in conventional MRI, in which WM appears relatively homogeneous, DTI enables the visualization and quantification of fine WM structure. The development of DTI as a WM imaging technique, in combination with concurrent advances in the image quality afforded by conventional MRI, has meant that it has now become feasible to address the question of whether patients with SZ exhibit abnormalities in their GM, WM, or both (see Figure 1.1).

The primary aim of this chapter is to provide a review of the vast body of published research that has used either structural MRI or DTI to investigate for neuroanatomical abnormalities in SZ patients. The chapter also considers the implications of this research with respect to two fundamental questions relating to the neuropathology of SZ, namely: (1) what are the possible causes of the reported GM and WM abnormalities in patients with SZ, and (2) is there a causal relationship between these GM and WM abnormalities? The first section of this chapter provides a broad overview of the most consistent findings of the MRI studies that have investigated GM abnormalities in SZ patients. The second section provides a finer-grained analysis of the more than 50 published DTI studies that have investigated WM abnormalities in SZ.[1] This section also includes some discussion as to the physiological bases and clinical implications of

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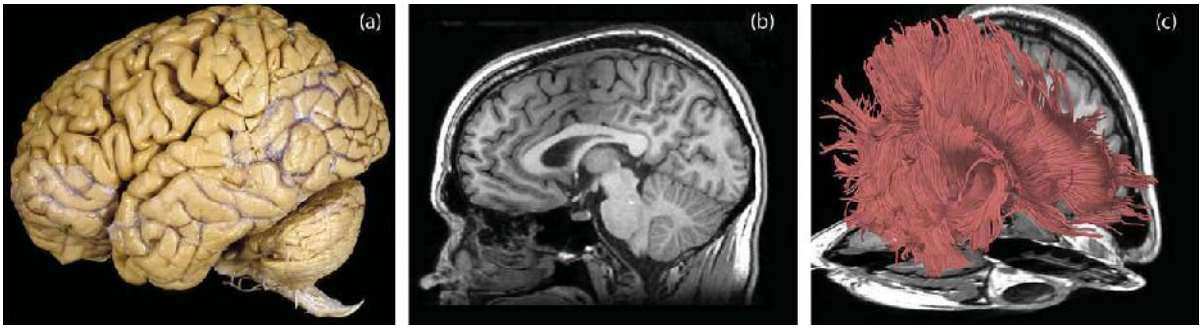

Figure 1.1 (a) A post-mortem specimen of the human brain. Image used with kind permission of Getty Images. (b) A structural magnetic resonance image (MRI) of the living human brain, showing a clear distinction between the gray and white matter. (c) Using diffusion tensor imaging (DTI) to image white matter in the living human brain. Note how that in contrast to panel (b) in which the WM appears largely featureless and homogeneous, DTI enables a far richer visualization of the macrostructural features of WM fiber bundles.

these WM abnormalities. Finally, in the third section, a speculative hypothesis is introduced which suggests how the GM abnormalities, WM abnormalities, hyperdopaminergia and clinical profile characteristic of SZ could potentially arise from a single neuropathological mechanism.

MRI studies of GM abnormality in patients with schizophrenia: a review

In 2001, Shenton *et al.* published an influential review of the 190+ studies published to that point which had used MRI to investigate for neuroanatomical abnormalities in SZ patients. On the basis of the reviewed literature, Shenton *et al.* (2001) concluded that SZ patients, as a group, exhibit subtle but incontrovertible volumetric reductions in a number of GM structures. Specifically, the review reported consistent volumetric reductions in GM of the temporal cortex (especially the superior temporal gyrus), and the GM structures of the medial temporal lobe (esp. hippocampus), and moderately consistent reductions in the frontal cortex (esp. orbitofrontal), parietal cortex (esp. inferior parietal lobule) and basal ganglia (esp. striatum). Since Shenton's review, there has been an exponential increase in the number of MRI studies in SZ, such that there are currently more than 800 studies published in the literature.[2] Given the large number of studies, it is clear that providing a comprehensive review of the current MRI literature in SZ (as per Shenton *et al.*, 2001) would require the writing of an entire book, and as such is outside the scope of this chapter. Thus instead of providing a comprehensive review, this section aims to summarize the most consistent findings in the MRI literature by considering a selection of particularly illustrative studies.

SZ is associated with widely distributed GM abnormalities, which are observable with MRI

The past decade has seen enormous developments in both MRI acquisition and analysis technologies, with the development of 3 T magnets for human research and the rise of voxel-based morphometry as cases in point. In terms of identifying GM abnormalities associated with SZ, however, the findings of contemporary MR studies have, by and large, been consistent with the conclusions drawn by Shenton *et al.* (2001) almost a decade ago. It is now clear that SZ patients, on average, show abnormal volumetric GM reductions, observable with MRI, throughout a substantial proportion of the brain.[3] And whilst it is true that some GM regions have been more consistently reported as being volumetrically abnormal compared to others – with the language centers of the temporal cortex, the ganglia of the limbic lobe and the association areas of the parietal cortex being especially strongly implicated (Honea *et al.*, 2005; Glahn *et al.*, 2008; Pearlson and Marsh, 1999) – it is also true that almost every square millimeter of GM has been reported as being volumetrically reduced in SZ patients in at least one study. Thus it appears as though the GM pathology experienced in SZ is either not spatially localized (in contrast, for example, to the localized atrophy of the motor neurons in Amyotrophic Lateral Sclerosis), or that it is initially localized but spreads with illness progression.

GM abnormalities are observable early in the illness, and ostensibly pre-morbidly

The question of whether GM abnormalities are present in SZ patients at the time of their first psychotic episode has been the focus of a great deal of recent research, which has been motivated by at least two factors. First, it is hoped that gaining a better understanding of the dynamics of neuropathology will shed light onto both the nature of SZ and its underlying causes. Second, studying patients suffering from their first episode of schizophrenia (FES) allows us to address the issue as to whether the neuroanatomical abnormalities so consistently reported in patients with chronic SZ (CSZ patients) actually result from the neuroleptic medications that patients are typically exposed to, as opposed to anything fundamental to the disease process itself. This issue is particularly problematic in light of studies which have indicated that: (1) exposure to antipsychotic medication can influence brain structure in and of itself (see Scherk and Falkai, 2006, for a review), and (2) different classes of antipsychotics have differential effects on brain structure (Konopaske *et al.*, 2008), making it difficult to covary for patients' neuroleptic exposure by converting the dosages of different medications into a common scale (such as the Chlorpromazine-Equivalent Scale). First-episode studies have attempted to address this issue by minimizing the confounding effects of medication exposure on brain structure by investigating patients who have had little or no exposure to neuroleptics.

Of the studies that have investigated for GM abnormalities in patients with FES, the majority have reported evidence of abnormal volumetric GM reductions. Furthermore, these reductions have, by and large, been observed in similar brain regions to those consistently identified as being structurally compromised in patients in the chronic phase of the illness (see reviews by Steen *et al.*, 2006; Vita *et al.*, 2006). However, on the whole, these studies have indicated that the neuroanatomical abnormalities exhibited by FES patients are both less severe and less widespread than the abnormalities exhibited by patients with chronic schizophrenia. Support for this point is provided by a recent meta-analysis by Ellison-Wright *et al.* (2008), who directly compared the extent of the GM reductions exhibited by CSZ patients in 20 voxel-based morphometry (VBM) studies to the reductions exhibited by FES patients in 9 VBM studies. The results of this meta-analysis indicated that the CSZ patients exhibited significantly more extensive GM reductions in the frontal cortex (esp. dorsolateral prefrontal cortex), temporal cortex (esp. superior temporal gyrus) and insular cortex, compared to the FES patients.

There is even some evidence suggesting that GM abnormalities may in fact precede the onset of psychotic symptoms in people who subsequently go on to develop schizophrenia. Pantelis *et al.* (2003), for example, compared the GM profiles of 23 people at "ultra-high risk" (UHR) for developing schizophrenia (based on genetic vulnerabilities, the presence of subclinical symptoms, and several other factors) who subsequently went on to develop psychosis (UHR-P) with 52 UHR people who subsequently did not go on to develop psychosis (UHR-NP). Pantelis *et al.* (2003) found that the UHR-P group exhibited lower GM volumes in hippocampal complex, superior temporal gyrus, inferior frontal cortex and cingulate gyrus compared to the UHR-NP group. Subsequent studies have also identified GM abnormalities in the paracingulate cortex (Yücel *et al.*, 2003), pituitary gland (Garner *et al.*, 2005) and insular cortex (Borgwardt *et al.*, 2007) in UHR groups (see Wood *et al.*, 2008 for a review).

GM reductions are due to neuropil elimination as opposed to neuron death

There is now considerable evidence indicating that the GM abnormalities characteristically observed in SZ patients are not the result of (any substantial degree of) neuron death. For example, the brains of SZ patients have consistently been observed *not* to exhibit gliosis. Gliosis, which refers to the proliferation of astrocytes in damaged regions of the central nervous system (CNS), is a general feature of the immune system's response to necrotic cell death in the CNS (Pekny and Nilsson, 2005). Hence, the fact that the brains of SZ patients have consistently been found not to exhibit gliosis (e.g. Roberts *et al.*, 1986) is evidence against the notion that SZ is associated with any substantial degree of neuron death via necrosis. However, the absence of gliosis does not exclude the possibility that SZ patients experience neuron death via apoptosis. Apoptosis, or programmed cell death, is not always associated with gliosis, as apoptotic cells typically alert immune cells prior to committing suicide, thus reducing the

non-specific immune response (Thompson, 1995). It is thus possible that the GM reductions characteristically exhibited by SZ patients are caused by increased levels of apoptosis. The empirical evidence does not, however, support this possibility. Pakkenberg (1993), for example, used optical microscopy to estimate the total number of neocortical neurons in the brains of 8 SZ patients and 16 controls. On the basis of this technique, Pakkenberg (1993) estimated that there was (on average) 22.06×10^9 neurons in the neocortex of the controls, and 22.12×10^9 neurons in the SZ patients – numbers that were essentially statistically identical ($p = 0.97$). The results of this study were subsequently replicated by Selemon and Goldman-Rakic (1999) in the prefrontal cortex. However, while Selemon and Goldman-Rakic (1999) did not find evidence of neuron death, they did find evidence of abnormally increased neuron density in SZ patients. They argued that since SZ patients typically show volumetric GM reductions compared to controls, the best explanation for this increase in neuron density was that "the distance between neurons diminished while the number of neurons is not changed" (p. 18). On the basis of this, they proposed the "reduced neuropil hypothesis", which argued that the increased neuron density and decreased GM volume exhibited by SZ patients resulted from the elimination of the neuropil (i.e. dendritic arbors and associated synaptic infrastructure) between neuron bodies. As will be discussed further, the idea that the volumetric GM reductions in SZ are caused by abnormal reductions in synaptic infrastructure has potential implications with respect to the WM abnormalities discussed later in the chapter.

GM abnormalities are likely progressive, at least over the initial years of illness

There is now a considerable amount of evidence to suggest that SZ patients experience progressive GM atrophy in the early stages of their illness (Whitford *et al.*, 2006; Sun *et al.*, 2009; Cahn *et al.*, 2002; Salisbury *et al.*, 2007; Kasai *et al.*, 2003). In contrast, a smaller proportion of the studies on chronic SZ patients have reported progressive GM reductions above those experienced by matched healthy controls. A study by Gur *et al.* (1998) directly compared the degree of GM volume reduction that occurred in the frontal and temporal lobes over a 2–4-year follow-up interval in FES patients, CSZ patients and healthy controls. The results showed that the FES patients experienced a significantly greater amount of progressive GM atrophy over the follow-up interval than did the CSZ patients, who on the whole did not experience more GM reductions than did the healthy controls. Similarly, Van Haren *et al.* (2008) compared the GM reductions over a 5-year period experienced by 96 SZ patients (aged between 16 and 56), and 113 matched controls. They reported that, over this 5-year interval, the most severe GM reductions were experienced by the youngest patients in the earliest stages of the illness, and that GM reductions experienced by the older patients were similar in degree to the reductions experienced by the healthy controls. Hence it appears that while SZ patients experience progressive GM reductions in the early stages of their illness, these reductions do not continue over patients' life spans, but rather decelerate with age to normal (or near-normal) levels. What factors might potentially underlie this curvilinear pattern of GM atrophy?

It has previously been suggested that the answer to this question might lie in the normative period of brain development that typically occurs during late adolescence to early adulthood (Feinberg, 1982; Keshavan *et al.*, 1994), which is an age that corresponds to the typical age of onset for schizophrenia. Adolescence is a period of enormous structural change in the healthy human brain. In an influential study, Bourgeois and Rakic (1993) used electron microscopy to count the number of synapses in the visual cortex of macaque monkeys aged between 2.7 and 5 years (i.e. the period corresponding to their adolescence). Over this period, they observed the monkeys to lose approximately 5000 synapses per minute in the visual cortex alone. This staggering number could well have been even higher in the association cortices of these monkeys, given that the association cortices are among the last brain regions to mature (Yakovlev *et al.*, 1967). The sheer scale of this "synaptic prune" (as it has been dubbed) suggests that its effects might be visible in humans with MRI. And indeed, a number of MRI studies have reported a period of accelerated GM volume loss in healthy people, beginning around 16 years of age and continuing until around 25–30 years of age (Whitford *et al.*, 2007b; Pfefferbaum *et al.*, 1994; Steen *et al.*, 1997).

Given the sheer number of synapses thought to be eliminated in this periadolescent "synaptic prune", it seems reasonable to assume that even a minor

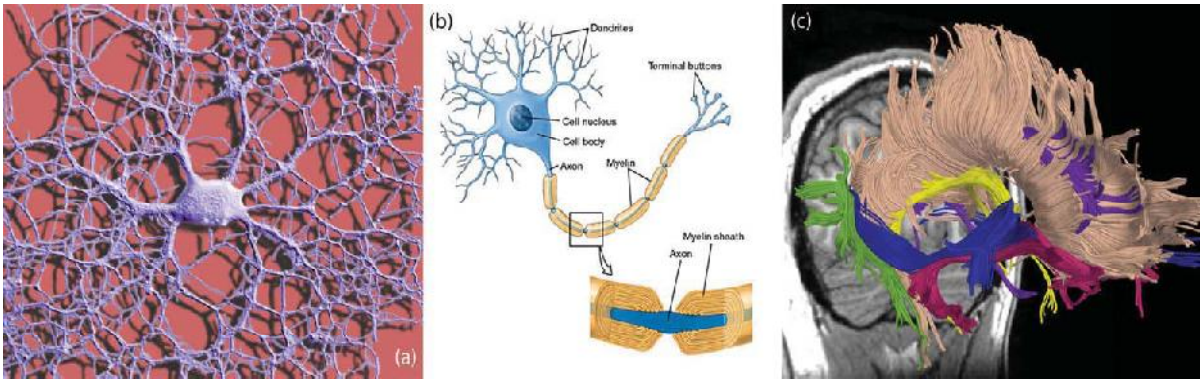

Figure 1.2 (a) An electron microscope image of an oligodendrocyte in rat optic nerve. Note the cell processes branching from the soma: these processes go on to form the myelin sheaths that insulate the axons of neighboring neurons. A single oligodendrocyte is capable of myelinating a single axon segment of up to 50 neurons. Image used with kind permission of Dr. Kachar at the Laboratory of Cell Structure and Dynamics at the National Institutes of Heath, and Dr. Wagner at the Department of Biology at the University of Delaware. (b) A schematic of the cellular features of a myelinated neuron. The primary purpose of myelin is thought to electrically insulate the axons and thus increase the transmission velocity of the action potential. Image used with kind permission of Prentice Hall. (c) Using DTI tractography to image the primary white matter fiber bundles of the brain. Myelinated axons connecting spatially disparate populations of neurons typically cluster together into large fiber bundles known as fascicles. This image illustrates the shape and trajectories of some of the major WM fiber bundles in the brain, including the corpus callosum (brown), cingulum bundle (purple), fornix (yellow), uncinate fasciculus (pink) inferior longitudinal fasciculus (green) and inferior fronto-occipital fasciculus (blue).

abnormality in the mechanisms underlying this process could potentially result in catastrophic consequences. Following this line of reasoning, Feinberg (1982) suggested that schizophrenia could arise because of an abnormality in this period of periadolescent brain maturation. A strength of Feinberg's (1982) theory is that it is able to explain why SZ patients only seem to exhibit progressive GM atrophy in the early stages of their illness. Specifically, if the GM atrophy exhibited by SZ patients is caused by an overly aggressive maturational period of synaptic pruning, then the end of this maturational period might be expected to result in an end to the progressive GM atrophy. The mechanisms underlying the synaptic "hyper-prune" hypothesized by Feinberg (1982) have implications with respect to the WM abnormalities reported in SZ patients (and summarized in the following section), and these implications are discussed further in the final section.

DTI studies of GM abnormality in patients with schizophrenia: a more detailed review

To reiterate from the first section, GM is thought to be constituted primarily of neuron bodies, dendrites, synaptic infrastructure and certain classes of neuroglia (e.g. astrocytes). In contrast, white matter (the subject of this section) is thought to be primarily constituted of myelinated axon sheaths. More precisely, WM is thought to be constituted of the compacted cell membranes of a specialized class of neuroglia named oligodendrocytes (see Figure 1.2a). The processes of these oligodendrocytes (known as myelin) can ensheath short segments of the axons of several neighboring neurons (see Figure 1.2b), with a single oligodendrocyte (OL) capable of providing myelin sheaths for up to 50 axons. The hydrophobic phospholipid bilayer provides electrical insulation for the axon, which reduces ion leakage across the axon membrane, thus preserving the amplitude of the action potential and increasing the conduction velocity of the action potential as it travels along the myelinated axon segment (Baumann and Pham-Dinh, 2001). Thus it is clear that WM in the brain plays a crucial role in modulating the speed of communication between spatially disparate populations of neurons.

Axons with similar destinations often form large fiber bundles. These fiber bundles represent the "information highways" of the brain, along which travels the bulk of communication between populations of neurons separated by more than a few centimeters. Some of the most prominent fiber bundles in the brain include the corpus callosum (connecting the

cortices of the two cerebral hemispheres), the superior longitudinal fasciculus (connecting the parietal and temporal cortices with the prefrontal cortex), the inferior longitudinal fasciculus (connecting the temporal and occipital lobes), and the uncinate fasciculus (connecting the frontal and anterior temporal lobes) (see Figure 1.2c). Although WM constitutes approximately 40% of the total mass of the brain, it has only recently become the topic of much empirical investigation. One of the reasons for the recent increased interest in WM has been the advent of Diffusion Tensor Imaging (DTI), which enables a more precise visualization of the WM than afforded by conventional MRI. A second reason lies in the growing popularity of "connectivity" models of SZ, as discussed below.

SZ as a disorder of neural integration

The conceptualization of schizophrenia as a disorder defined by abnormal cognitive integration dates back at least as far as Bleuler (1911). Bleuler described the cardinal symptoms of schizophrenia (the name he coined to describe Kraepelin's "dementia praecox") as a "loosening of normal associations" between thoughts. In his 1911 treatise, Bleuler commented:

> Often ideas are only partially worked out, and fragments of ideas are connected in an illogical way to constitute a new idea … This results in associations which normal individuals will regard as incorrect, bizarre, and utterly unpredictable.

Bleuler's conceptualization of schizophrenia as a disorder of cognitive integration has heavily influenced the contemporary "connectivity" theories of schizophrenia, which have sought to describe the neural underpinnings of this cognitive disintegration.

The unifying tenet of "connectivity" theories of schizophrenia is the proposal that rather than being caused by normal interactions between pathological GM structures, schizophrenia instead arises from pathological interactions between pathological GM structures (Friston, 1999). The various connectivity theories differ, however, in terms of the specific mechanisms they propose as underlying this "pathological interaction". Feinberg (1982), as previously discussed, has suggested that this pathological interaction could arise from an abnormality in periadolescent brain development. Specifically, Feinberg (1982) suggested that in schizophrenia: "too many, too few or the wrong synapses are eliminated", leading to "defects of neuronal integration" (p. 331). In a similar vein, Friston (1999) has argued that the fundamental neuropathology of schizophrenia lies in abnormal synaptic plasticity; that is, in the abnormal strengthening (and/or creation) and weakening (and/or elimination) of synapses in response to experience and development. Friston (1999) has argued that abnormalities in the processes underpinning the modulation of synaptic strength could lead to abnormal interactions between functionally specialized populations of neurons in SZ patients. In contrast, Crow (1998) has suggested that the aberrant neural interaction underlying schizophrenia is due to the fact that SZ patients do not exhibit the normative hemispheric specialization of the language centers. Specifically, Crow (1998) has suggested that the interhemispheric transmission delays associated with using both hemispheres to process language-related information could lead to abnormalities in neural timing and hence cognitive disintegration. And finally, Andreasen (1999) has emphasized the role of the thalamus and cerebellum in coordinating the development and maintenance of normative associations between cognitions originating in the prefrontal cortex. She has suggested that an abnormality in this coordination (or a "cognitive dysmetria", in her words) could cause SZ patients to "make abnormal associations between mental representations" (p. 785).

SZ as a disorder of neural integration arising from WM abnormalities

Bartzokis (2002) has offered a novel suggestion as to the underlying cause of the neural disintegration that is proposed to exist in patients with schizophrenia. Specifically, Bartzokis (2002) suggested that neural disintegration could arise from abnormalities in the periadolescent process of myelination. It has long been known that the normative developmental process of myelination continues well into the second decade of life, and that myelination of the association cortices are not complete until at least 30 years of age (Yakovlev *et al.*, 1967). Given the aforementioned role that myelin plays in increasing the transmission velocity of neural signaling, Bartzokis (2002) proposed that an abnormality in the periadolescent process of myelination (particularly in the late-developing association cortices) could result in transmission delays, causing "a loss of the brain's ability to function

normally by reducing its ability to maintain synchronous communication across functional neural networks" (p. 678). In other words, Bartzokis suggested that abnormalities in the normative maturational processes of myelination could cause a breakdown in the synchronicity of neural activity between spatially disparate brain regions. This basic argument has also been proposed independently by other researchers (Fields, 2008; Walterfang *et al.*, 2005).

Given the length of time that schizophrenia has been thought of as a disorder of neural integration, and given that WM constitutes the anatomical infrastructure for long-distance communication in the brain, it is in some ways surprising how little attention WM has, until recently, received in the neuroimaging literature. In another sense, however, this is perhaps understandable, given the aforementioned difficulties associated with studying WM via conventional imaging techniques such as structural MRI. The few studies which have used conventional MRI to investigate WM abnormalities in patients with SZ have produced equivocal results. Some studies have reported volumetric and/or morphometric WM abnormalities in patients with schizophrenia, including in the corpus callosum (Rotarska-Jagiela and Linden, 2008), inferior longitudinal fasciculus (O'Daly *et al.*, 2007), and uncinate fasciculus (Park *et al.*, 2004). Other studies have reported volumetric abnormalities in FES patients (e.g. Price *et al.*, 2006), and at least one study has reported progressive volumetric WM atrophy over the first few years of illness in patients with FES (Whitford *et al.*, 2007a). In contrast, however, several other published studies have failed to find evidence of volumetric or morphometric WM abnormalities in SZ patients (Cahn *et al.*, 2002; Zahajszky *et al.*, 2001; Hirayasu *et al.*, 2001).

The development of DTI in the 1980s opened up new possibilities for the empirical investigation of WM in vivo. DTI differs from conventional MRI in that it is sensitive to spin dephasing associated with molecular movement. Specifically, DTI is sensitive to the random movement of water molecules that result from unpredictable thermal collisions, i.e. diffusion. DTI is based on the fact that the direction and extent of water diffusion in a given region of the brain provides clues as to the microstructure of the underlying tissue.

In brain tissue, the diffusion of water molecules is restricted by obstacles in the local environment, such as phospholipid membranes, myelin sheaths, macromolecules, etc. DTI relies on the fact that the extent to which diffusion is restricted differs between the different tissues of the brain. In the ventricular cerebrospinal fluid (CSF), for example, there are relatively few obstacles to diffusion. As a result of this, water diffusion in the CSF is relatively unrestricted, and is consequently isotropic (i.e. spherical). In contrast, in a WM fiber bundle, the dense and coherently aligned myelinated axons provide a considerable barrier to water diffusion, with water being more likely to diffuse parallel to the fiber bundle as opposed to perpendicular to it. By calculating the distance over which water diffuses from a given point in a given amount of time in a number of independent directions, it is possible to construct a three-dimensional shape that best describes the shape of the water diffusion. The shape describing this diffusion is conventionally modeled as an ellipsoid (see Figure 1.3).

The assumption in DTI is that the shape and size of this ellipsoid provide information about the diffusivity of the underlying tissue. There are various ways in which the "shape" and "size" of a diffusion ellipsoid can be quantified, but the two indices most commonly used in the literature are Fractional Anisotropy (FA) for shape, and Mean Diffusivity (MD) for size.

FA is a measure of the anisotropy (i.e. nonsphericity) of the diffusion ellipsoid. FA is generally calculated with the following formula:

$$\mathrm{FA} = \sqrt{\left((\lambda 1 - \lambda 2)^2 + (\lambda 2 - \lambda 3)^2 + (\lambda 1 - \lambda 3)^2\right)} \Big/ \sqrt{2} \cdot \sqrt{\left(\lambda 1^2 + \lambda 2^2 + \lambda 3^2\right)}$$

FA can vary between values of zero and one, with isotropic (spherical; Figure 1.3a) diffusion having a value of zero and completely anisotropic (aspherical; i.e. planar (Figure 1.3b) or linear (Figure 1.3c)) diffusion having a value of 1 (see Figure 1.3b). In a WM fiber bundle, reduced FA is generally assumed to reflect damage to the myelin or axon membrane, reduced axonal packing density, and/or reduced axonal coherence (Kubicki *et al.*, 2007).

MD, in contrast, is a measure of the size of the diffusion ellipsoid, i.e. the average displacement of water molecules as a result of diffusion in a given amount of time. MD is generally calculated with the following formula:

$$\mathrm{MD} = (\lambda 1 + \lambda 2 + \lambda 3)/3 = \mathrm{Trace}/3$$

MD is highest in tissues where there are few impediments to water diffusion (e.g. CSF), and lowest

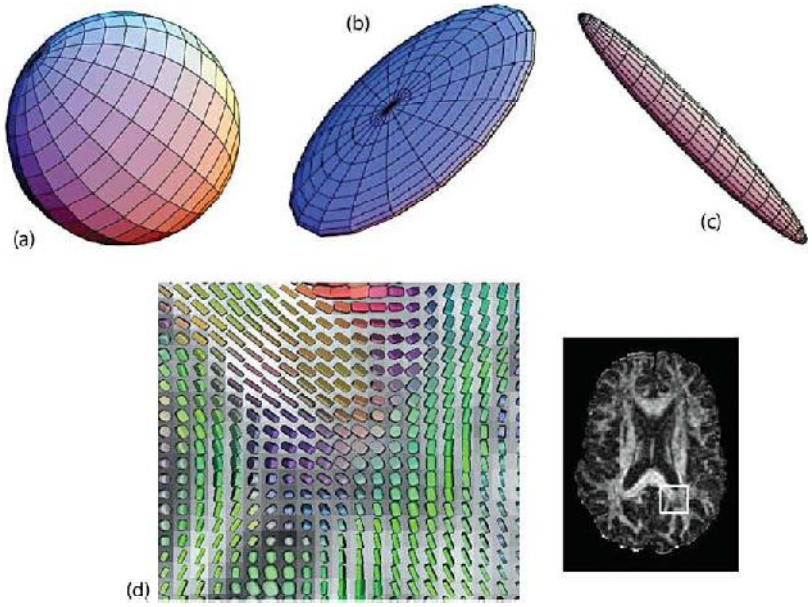

Figure 1.3 Diffusion ellipsoids come in many different shapes and sizes. Panel (a) illustrates the shape of the diffusion ellipsoid resulting from unrestricted water diffusion (i.e. isotropic). Isotropic diffusion is approximately what occurs in the fluid-filled ventricles where there are few obstacles to the diffusion of water. In the case of a WM fiber bundle, in contrast, the coherently aligned axon membranes and myelin sheaths constitute a significant obstacle to the diffusion of water. In this case, water will more readily diffuse parallel to the fiber bundle as opposed to perpendicular to it, and hence the resultant diffusion ellipsoid will be aspherical (i.e. anisotropic). An anisotropic diffusion ellipsoid can show either planar anisotropy (i.e. shaped like a disk as in panel (b)) or linear anisotropy (i.e. shaped like a cigar as in panel (c)). Mode is a measure of the linearity versus planarity of a diffusion ellipsoid. Panel (d) shows the variability in Mode between diffusion ellipsoids in the inferior fronto-occipital fasciculus of a healthy volunteer. Compare, for example, the "cigar-shaped" ellipsoids at the top left of the panel with the "disk-shaped" ellipsoids near the bottom left. Images used with the kind permission of Drs. Westin (panels a–c) and Kindlmann (panel d) at the Surgical Planning Laboratory, Department of Radiology, Brigham and Women's Hospital, and Harvard Medical School.

in tissues where diffusion is restricted at least one direction (e.g. WM). Although FA and MD are almost mathematically independent, they are often found to be inversely related in the brain (such that tissue showing high FA is generally found to show low MD), as the microstructural impediments that give rise to anisotropic diffusion also limit the maximal volume of the diffusion ellipsoid. Whilst FA and MD are the two indices that have been most commonly employed in the literature, a number of other indices – such as Mode (Ennis and Kindlmann, 2006), Inter-Voxel Coherence (Federspiel *et al.*, 2006), and Axial/Radial diffusivity (Song *et al.*, 2002) – have also been developed. As will be discussed further below, these novel indices are likely to play an important role in determining the microstructural underpinnings of the reported between-group differences in diffusivity.

Since 1998, when the first DTI study that investigated for WM abnormalities in SZ patients was published (Buchsbaum *et al.*, 1998), over 50 DTI studies have been published in the SZ literature. The methodologies and results of the DTI studies published to date are presented in Table 1.1. The remainder of this section summarizes the results of these studies, and discusses their implications with respect to the prevailing "connectivity" models of schizophrenia. This review aims to build on previously published reviews of the DTI literature, such as by Kubicki *et al.* (2007) and Kanaan *et al.* (2005).

Consistent findings in the DTI literature on SZ

As can be seen in Table 1.1, there have already been over 50 studies that have used DTI to investigate WM abnormalities in SZ patients, and this number is likely to increase dramatically in the next few years if recent publication trends are any guide. Some consistent results are already emerging, and these are summarized on a point-by-point basis in the following section. The following section also attempts to draw

Table 1.1 A summary of the studies published to date that have used DTI to investigate for white matter abnormalities in patients with schizophrenia. Acronyms: CSZ, chronic schizophrenia; FES, first-episode schizophrenia; EOS, early-onset schizophrenia; SPD, schizotypal personality disorder; nn, neuroleptic naive; hall, with hallucinations; nonhall, without auditory hallucinations; CON, controls; EPI, echo-planar imaging; LSDI, line-scan diffusion imaging; FSE, fast spin-echo; ROI, region of interest; VBM, voxel-based morphometry; WM, white matter; FA, fractional anisotropy; MD, mean diffusivity; ADC, apparent diffusion coefficient; MTR, magnetization transfer ratio; IC, inter-voxel coherence; CC, corpus callosum; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; FOF, frontal-occipital fasciculus; SFOF, superior frontal-occipital fasciculus; IFOF, inferior frontal-occipital fasciculus RA, relative anisotropy

Study	Subjects	Acquisition details	Analysis method	Index	Significant groupwise differences (SZ relative to CON)	Significant clinical correlations
VOXEL-WISE/ MASS-ROI ANALYSIS						
Buchsbaum *et al.*, 1998	5 CSZ, 6 CON	1.5T, LSDI, 7 directions, 7.3×2.7×1.8 mm, 6 slices	VBM (whole brain WM, $p < 0.05$ uncorrected, $k = 116$ voxels)	RA	Reduced RA in frontal WM and temporal WM, especially WM adjacent to putamen	–
Agartz *et al.*, 2001	20 CSZ, 24 CON	1.5T, EPI, 20 directions, 1.8×1.8×4 mm, 22 slices	VBM (whole brain WM, $p < 0.21$ corrected, p(cluster) < 0.002)	FA	Reduced FA in splenium and forceps major	–
Foong *et al.*, 2002	14 CSZ, 19 CON	1.5T, EPI, 7 directions, 2.5×2.5×5 mm, 12 slices	VBM (whole brain WM, $p < 0.001$ uncorrected, p(cluster) < 0.05 corrected)	FA, MD	No significant group-wise differences in FA or MD	–
Ardekani *et al.*, 2003	14 CSZ, 14 CON	1.5T, EPI, 6 directions, 1.9×1.9×5 mm, 20 slices	VBM (whole brain WM, $p < 0.01$ uncorrected, $k = 200$ voxels)	FA	Widespread reductions in FA including in genu, midbody, splenium, inferior parietal lobule WM, superior and middle frontal gyrus WM, parahippocampal gyrus WM	–
Burns *et al.*, 2003	30 CSZ, 30 CON	1.5T, EPI, 6 directions, 1.9×1.9×5 mm, 31 slices	VBM (ROIs in uncinate, arcuate and cingulum, $p < 0.05$ corrected)	FA	Reduced FA in arcuate fasciculus	–
Sun *et al.*, 2003	30 CSZ, 19 CON	1.5T, EPI, 25 directions, 1.9×1.9×5 mm	ROIs in frontal, parietal, temporal and occipital WM, internal capsule, genu, splenium, and cingulum	FA	FA reductions in cingulum	–

Table 1.1 (cont.)

Study	Subjects	Acquisition details	Analysis method	Index	Significant groupwise differences (SZ relative to CON)	Significant clinical correlations
Hubl *et al.*, 2004	13 CSZhall, 13 CSZnonhall, 13 CON	1.5T, LSDI, 6 directions, 1.8×1.7×5 mm, 12 slices	VBM (whole brain WM, $p < 0.05$ uncorrected, $k = 99$ voxels), and ROI analysis of significant clusters	FA	Widespread reductions in FA including in CC, arcuate fasciculus, uncinate fasciculus, ILF	CSZhall showed reduced FA relative to CON in the arcuate, uncinate and ILF. CSZhall showed increased FA relative to CSZnonhall in the arcuate, uncinate, ILF and CC
Park *et al.*, 2004	23 CSZ, 32 CON	1.5T, LSDI, 6 directions, 1.7×1.3×4 mm, 31–35 slices	VBM (whole brain WM, $p < 0.005$ uncorrected, $k = 60$ voxels)	FA asymmetry	CSZ patients exhibited abnormally symmetrical FA in the cingulum, genu, internal capsule, uncinate and cerebral peduncle	–
Kubicki *et al.*, 2005	21 CSZ, 26 CON	1.5T, LSDI, 6 directions, 1.7×1.3×4 mm, 31–35 slices	VBM (whole brain WM, $p < 0.005$ uncorrected, $k = 50$ voxels)	FA, MTR	Reduced FA in CC, cingulum, SFOF, IFOF, arcuate, internal capsule, fornix; Reduced MTR in CC, fornix, internal capsule, SFOF	–
Kumra *et al.*, 2005	26 EOS, 34 CON	1.5T, EPI, 25 directions, 1.7×1.7×5 mm, 23 slices	VBM (whole brain WM, $p < 0.001$ uncorrected, $k = 100$ voxels)	FA	FA reductions in the cingulum	–
Buchsbaum *et al.*, 2006	64 CSZ, 55 CON	3T, FSE, 12 directions, 1.6×1.6×3 mm, 28 slices	VBM (whole-brain WM, $p < 0.05$ (replication) and $p < 0.005$ (exploration))	FA	Widespread reductions in FA including in genu, SLF, cingulum, internal capsule, frontal WM, temporal WM	–
Federspiel *et al.*, 2006	12 FES, 12 CON	1.5T, EPI, 6 directions, 3.8×3.8×5 mm, 12 slices	VBM (whole brain WM, $p < 0.02$ uncorrected, $k = 6$ voxels)	IC	Widespread reductions in IC including in CC, cingulum, SLF, internal	–