The Neuropathology of Schizophrenia

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Foreword

In the summary to his chapter on the Neuropathology of Schizophrenia, in *the New Oxford Textbook of Psychiatry*, 2010, Paul Harrison said *…the neuropathology of schizophrenia has made significant advances as an integral part of the broader progress in understanding the neurobiology of the disorder*.

In the interim there has been a vast expansion of information on the neuropathology of the schizophrenic brain, due to the study of subcortical brain and advances in immune histochemistry, antibody generation, the use of digital microscopy which has yielded much finer, more accurate studies, and the elimination of demographic heterogeneity by better tissue collection from the Stanley consortium.

These advances are timely and important because of the vast expansion of structural and functional imaging, so that there is much more information about where the functional abnormalities arise and how they relate to symptoms and aetiology. Neuropathology is directed to answer the more fundamental question—what is the basis in brain which gives rise to these abnormalities?

Williams has organized this compendium by the brain's anatomy, identifying the structural and cellular abnormalities in the main brain regions affected, then considering intra-brain connections between regions and what these changes can tell us about function and the disease manifestations. For instance, the amygdala emerges as a key nucleus with signals coming into the basolateral area which is a focus of pathology. There are no reported abnormalities in the corticomedial area which provides the output from the amygdala to the fornix via hippocampal circuits, and to the orbital frontal area, but there are cellular and structural abnormalities in the basolateral area which are particularly important for explaining dysfunction in schizophrenia.

Thus the book provides a major change in focus to a more basic level in the chain of causality, moving from the prevailing knowledge of functional changes seen indirectly in imaging studies to examine the actual brain changes which give rise to them, and how the latter explains the former. It is a timely and welcome compendium of recent advances in the neuropathology of schizophrenia which is essential for every student of this most important subject in psychiatry.

May 2020

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Introduction

1

Matthew Williams

The neuropathology of schizophrenia has had a history full of promise and frustration. It has been an area of interest for well over a century, from Kraepelin's 1896 publication on dementia praecox to the modern day. Yet 40 years ago was pronounced virtually dead in [1] paper containing the now-infamous saying that schizophrenia was 'the graveyard of neuropathology' [1]. In the 1980s, there was a return to neuropathological examination of schizophrenia following the early imaging findings from the 1970s [2–7]. Since then, imaging techniques have encouraged a new generation of neuropathological research, and many papers have presented findings in schizophrenia across the brain. There have been a few findings generally agreed upon across multiple studies, such as increased ventricular size, decreased cortical volume, particularly in the frontotemporal regions, and a lack of brain torque. But the biological causes and importance of these changes have remained elusive.

In the years since Kraepelin first described the 'dementia praecox' that would become the collection of disorders now grouped under the term schizophrenia. Initially thought to be a progressive brain disorder much as we think of modern dementias, it was Alzheimer himself who began neuropathological investigation into the disorder. This started 80 years of study that ended in apparent failure, with Plum's famous comment in 1972 and the poor reviews of neuropathological findings in the field by Corsellis in 1976 [1, 8]. However, the first systematically repeatable findings in the 1970s using the new technology of brain imaging led to a resurgence of interest in neuropathological investigation; followed in the 1980s, new methods of stereology and computer-assisted counting were developed to allow better quality research to be performed. Since then, neuropathology in schizophrenia has continued as a research field, although not always easily. As

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some of the discussion below makes clear, research groups often find directly contradicting results, or promising findings that cannot be replicated. The consensus seems to be that there is pathological involvement in the schizophrenia syndrome, but it is limited to specific regions, is subtle and extremely hard to accurately describe, whilst issues of heterogeneity of sampling and methodology still loom large.

Neuropathology is still, by far, the best method to examine cytoarchitectural changes in the brains of schizophrenia [9], and the extensive developments in recent years in brain imaging in on the one hand and molecular biology on the other do not remove the need for expert pathological techniques, but indeed enhance it.

Complementary use of functional or structural imaging in concert with neuropathological techniques can yield more useful information than either discipline alone. Modern imaging techniques, whilst extremely advanced, still lack the resolution to examine changes in cell size or density. Structural imaging may inform us of areas of interest or change in the larger-scale changes in the brain, such as grey matter shrinkage, but cannot tell us the actual changes going on within the tissue to cause such change. The use of neuropathology to complement such as study in an identically selected cohort of cases can shed light on the possible or likely causes of the shrinkage, such as increased or decreased cell density. Similarly in functional studies, an imaging finding, such as a change in neurotransmitter quantities, can benefit from neuropathological research on the synapses, neurons or glia involved in these studies, as has been previously demonstrated by assessment of dopamine in the substantia nigra and striatum [10].

A more common but still often underused combination is the link between neuropathology and molecular biology. Partially this is due to the difficulty in using formalin-fixed tissue and paraffin-embedded tissue (FFPE) for molecular tasks, but studies using neuropathological tissue as a source for techniques such as protein estimations and DNA and RNA studies can give valuable insight as data on molecular and biochemical changes can be collected alongside neuropathological findings such as localization with specific cell types, associated cell numbers or densities and morphometric changes [11]. Although comparative analysis of DNA extraction quality from FFPE tissue varies depending on pathological fixation methods and still shows superior output using frozen tissue [12, 13], future research uptake and benefits are optimistic for continually improving use of FFPE tissue in molecular methods [14]. The future of neuropathological research likely lays in greater integration with these other methodologies and the application of these specific skills and techniques to complement other research types.

Recently, some laboratories have used proteomics and neuropathology to good effect. One study into the anterior cingulate cortex used neuropathological methods followed by application of mass spectrometric sequencing to identify schizophrenia-specific proteins, with 35 locations involving 19 proteins differentially expressed in various psychiatric disorders, schizophrenia prominent amongst them. All but three of these proteins have previously been associated with the major psychiatric disorders [15]. Clearly this is a crude analysis, but innovative, and demonstrates the clear potential for deeper study of tissues in schizophrenia and other neurological

disorders. Associated molecular analysis has also been proved useful, as demonstrated clearly by the prefrontal cortex GABA-AA receptor change presented with altered synapses from neuropathological investigation [16].

The field is still unable to identify a clear 'pathology of schizophrenia' in the way it is described in illnesses such as Parkinson's disease or glioma as discussed by Shapiro [17]. However, we can describe far better why we have not identified such a pathology but more importantly the biological reasons why such a clear pathology does not exist.

With the improvements of imaging technology and genetic techniques, most dramatically the development of sequencing, epigenetics and high-resolution brain scanning over the last 15 years, pathology seems to have been left further behind as a method for examining schizophrenia and associated psychiatric disorders. But improvements so far this century in tissue sourcing, digital pathology methods and antibody generation have recently yielded a marked increase in the quality of neuropathological research. As neuropathology is still the only way to look at the fine details of changes at the cellular level, a vital link between the worlds of molecular biology and imaging sciences and fundamentally the level at which much biology operates, it would be a great shame if the field and expertise therein were allowed to decline. Indeed a better way forward would be improved collaboration between molecular biologists and imaging scientists, utilizing the improved range of neuropathological techniques to consistently demonstrate findings across field to overcome the issues of replication which have been so common in schizophrenia research for so many years.

With these methods revealing more detail and giving us a wider range of tools than ever before, neuropathology can reveal even greater detail on the often-subtle changes in this disorder. Much as researchers in the 1970s and 1980s stood at a new era of neuropathological research with the inventions of structural brain imaging and immunohistochemistry, in 2020 we now stand at a similar point with the greater range of techniques available.

In this book, we hope to make clear that the challenges of the future likely lie in further development of better microscopy and staining, to widen the field as much as elucidate greater detail, and retain focus on the brain systems and circuits that still need the detailed focus from neuropathology to fundamentally advance our knowledge of this illness and bring the discipline into the twenty-first century.

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A Note on Neuroanatomy

2

Matthew Williams

2.1 Sectioning and Orientation

The orientation of a brain section may seem obvious to a neuroanatomist, but those without extensive experience in dissection may not find it so straightforward. The brain is, of course, an immensely complicated organ, and even with common terminology and cutting practices, there are still variable ways of sectioning and naming structures and regions. Here we describe the standard method we use for consistency through this text for clarity. The neuropathology of schizophrenia is difficult enough without us introducing more confusion!

In Fig. 2.1, we show the image of a human brain as seen from the left side in an undissected state. Around are the four primary directional terms used in neuroanatomy. The anterior of the brain is to the left of the page, which will be maintained throughout the text. Some texts and references use the terms rostral-caudal in place of anterior-posterior.

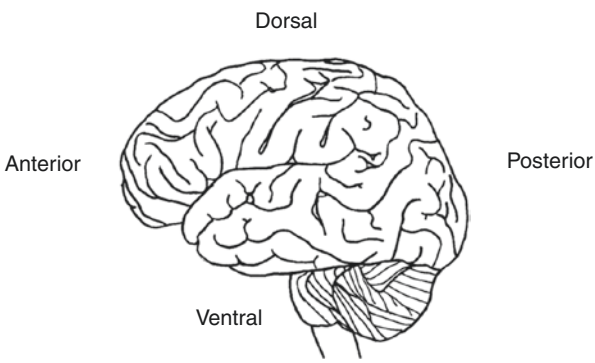

Fig. 2.1 Illustration of human brain viewing the left side in sagittal orientation. The anterior of the brain is to the left of the page, which will be maintained throughout the text

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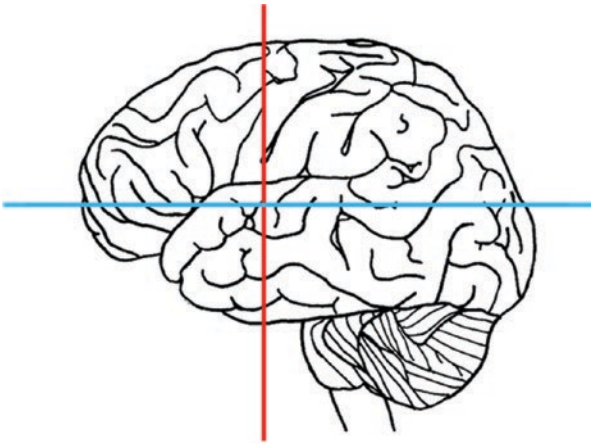

Fig. 2.2 Illustration of human brain viewing the left side in sagittal orientation. Red line indicates the direction and orientation of coronal section, whilst the blue line indicates the direction and orientation of axial section

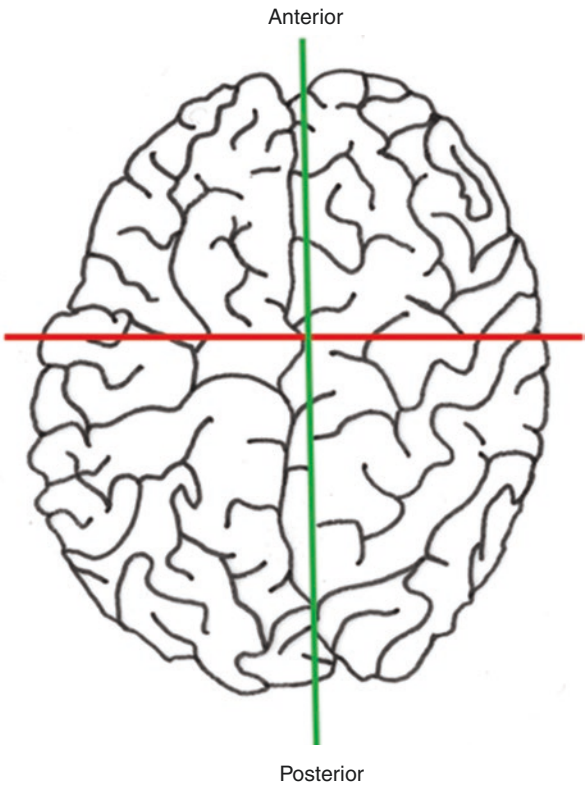

Fig. 2.3 Illustration of human brain viewing from above in axial orientation. Red line indicates the direction and orientation of coronal section, whilst the green line indicates the direction and orientation of a sagittal section. The anterior is towards the top of the image

Figure 2.2 shows how two of the common cuts are made from this perspective. The coronal cut, possibly the most common cut used in the field, runs across the brain from left to right and ventral to dorsal. The axial cut runs perpendicular to the ground when a person is standing, cutting from left to right and anterior to posterior.

Figure 2.3 illustrates the brain as viewed from above, showing the outside of the brain in an axial orientation. Shown are the directions of a coronal and a sagittal cut,

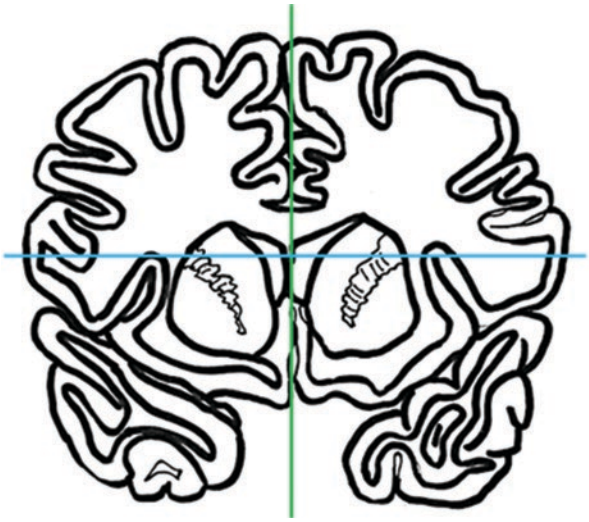

Fig. 2.4 Illustration of human brain cut in coronal section at the level of the anterior striatum. The blue line indicates the direction and orientation of axial section, whilst the green line indicates the direction and orientation of a sagittal section

the second of which runs the length of the brain from anterior to posterior and ventral to dorsal.

Likewise, Fig. 2.4 illustrates a coronal cut through the brain, at the level of the anterior part of the basal ganglia, through the striatum and more anterior parts of the temporal lobes. How the axial and sagittal cuts are orientated from this direction is shown in the image.

Whilst many of the definitions described here are arbitrary or at least contain reasonable variables, there is something in neuropathology that many of my colleagues and I find baffling. The definitions of coronal, axial and sagittal cuts are universally understood. They are 90° from an axis on the standard *xyz* arrangement based on the orientation of the human brain in its position in the skull. As a brain is taken for dissection, orientated in the same manner to the cutting surface as it is in the skull in life, the axial plane is parallel to the cutting surface, presenting a cut as if the brain is observed from above (or below of course). The sagittal cut is similar in principle, perpendicular to the cutting surface, running front to back and revealing the brain structure as observed from the side. Whilst it seems obvious to me and every neuroanatomist and neuropathologist I have ever worked with, the coronal cut should be made left to right across the brain, again perpendicular to the cutting surface as if viewing the brain from the front or back. Indeed, the angle of the coronal cut in other texts is not consistent, varying between 15° and 35°. Surely the human brain is a complex, folded and involuted enough structure not to wish for further confusion? Those of us who have delved into dissection and anatomy enough know that even the most expert individual can be disorientated with unconventional sections showing unexpected structures and anatomical arrangements. Unless specifically described otherwise, all diagrams in this text are drawn with the three sectioning directions 90° to one another as shown in Figs. 2.2, 2.3 and 2.4.

2.2 The Prefrontal Cortex

The prefrontal cortex (PFC) is a structure that has been the subject of considerable investigation but has differing definitions. Some reports and guides describe the PFC as a substantial part of the frontal lobe, consisting of the lobe anterior to the premotor cortex, possibly including the subgenual region (summarised in Fig. 2.5). However, other texts and guides use the PFC to refer only to the region around the frontal pole at the very anterior-most part of the frontal lobe, consisting only of the cortex around the frontal pole consisting of Brodmann area 10 the anterior part of Brodmann area 11 (shown in Fig. 2.6).

A third interpretation of the PFC refers to Brodmann areas 9 and 10 (shown in Fig. 2.7), with area 9 often being referred to in the literature as the dorsolateral PFC (dlPFC). In this text, we use the Brodmann-defined regions as shown in Fig. 2.7 when referring to the PFC.

2.3 A Note on Stereology

The issue of stereological methods in neuropathology is a fraught one, but perhaps nowhere more so than in schizophrenia research. The considerable feelings held by researchers who favour one of the two broad methods is evident to anyone who has even briefly viewed the relevant literature in this field or read the comments from a rejected paper from a reviewer who strongly believes in the 'other' method than the one the author used. These are design-based and model-based measures. Both of

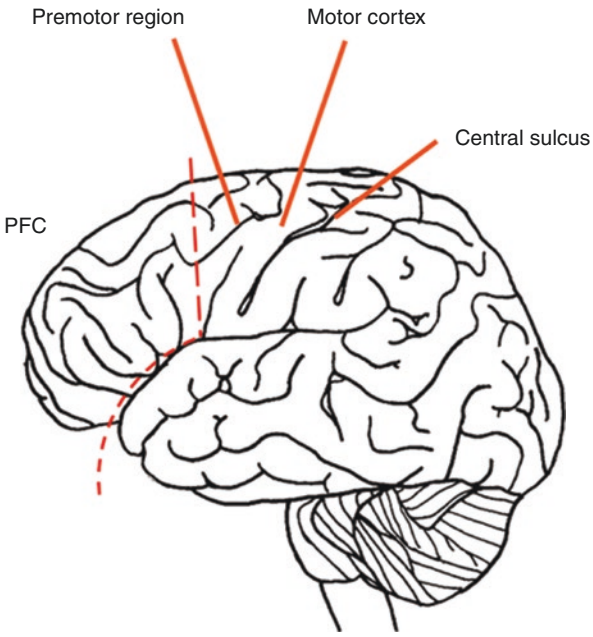

Fig. 2.5 Sagittal view of large PFC definition. Dotted line indicates the boundary of the PFC by this definition, anterior to the motor cortex and the central sulcus, marking the posterior end of the frontal lobe

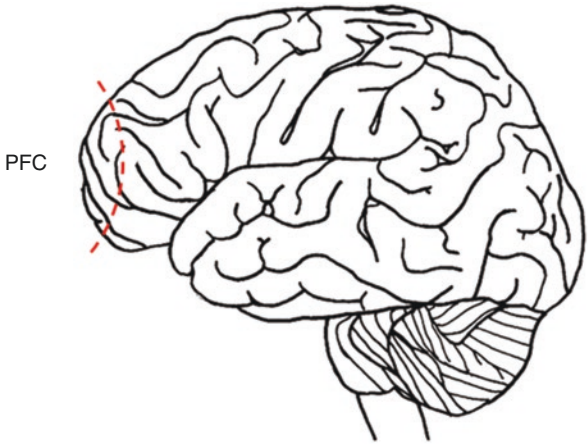

Fig. 2.6 Sagittal view of smaller PCF cortex definition. Dotted red line shows the area of the smaller PFC, only covering the cortical tissue in the area around the frontal pole

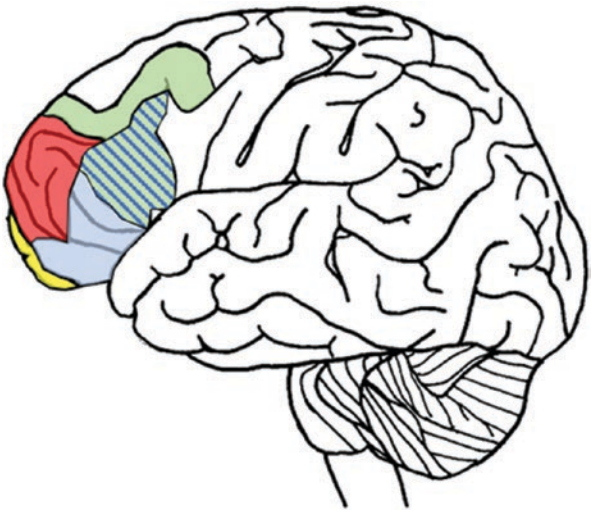

Fig. 2.7 The Brodmann areas of the anterior frontal lobe. Areas 9 (green), 10 (red), 11 (yellow), 46 (blue) and 9/46 (green/blue patterned)

these methods have their proponents [1–12], and as technology has advanced, this argument has moved to digital microscopy, with terms for these methods such as 'biased' and 'unbiased' having a more significance regarding marketing than real objectivity.

The relative advantages of design-based stereology, involving examination through the depth of thicker-cut sections known as the *z*-axis, have been reviewed in the references described above. The idea of looking 'through' the tissue in the *z*-axis is an appealing one, as thicker sections are more likely to yield accurate 3D information of cell organisation. However, a 3D section is only anchored on the slide in 2D, along the *x*- and *y*-axis, meaning that the chemical processing of tissue in fixation and staining has a disproportionate effect of shrinkage on the *z*-axis. This leads to a key downside of the design-based method being that this uneven and

disproportionate *z*-axis effect must be accounted for, typically involving extensive use of mathematical corrective factors to eliminate the errors caused by the shrinkage. These, of course, can only be estimates and introduce additional errors into the analysis. Also, given biological scientists' reputation for lower mathematical expertise than in other disciplines, this can introduce project-limiting complexity into such studies. Indeed some papers explicitly have to state that 'no mathematical equations or calculations are shown in this review' in order to put their argument across to their colleagues [7]!

This contrasts with older techniques grouped as model-based stereology, wherein more typical slides are sectioned thinly, often in the range of 5–15 μm, precluding the use of *z*-axis measures. Measured variables are then counted across this slide in a 2D fashion, in effect adding an additional error into the measures by potentially increasing the apparent numbers or densities of the count through a hypothetical *z*-axis. This method too contains a base error in that taking a very thin section through tissue, sometimes thinner than the cells being measured, can lead to biases artificially weighting the cell count numbers high or low based on the counting frame organisation.

As much as it will draw ire from some within the neuropathology community, experimental results have clearly demonstrated that the two methods are of roughly equal accuracy given the number of variables laboratory researchers in this field face. In fact, direct comparison between these two methods by measurement of the total number of dopaminergic neurons in the substantial nigra of the C57BL/6J mouse often used in Parkinson disease models is reported thus:

> Statistical analysis showed no significant difference between estimates generated using model- or design-based stereological methods compared to empirically-derived counts using serial reconstruction.
>
> (Baquet et al. [13])

The repeatability issues seen in the many papers in this field are suggested to be the results of heterogeneity of diagnosis and tissue source, variability in dissection and sectioning, staining methods and the definition of cells, counting techniques and frames rather than the stereology methods in a well-controlled experiment. Therefore, in this text, we discuss neuropathological results regardless of the method of stereological examination used.

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Gross Pathology in Schizophrenia

3

Matthew Williams

3.1 Overall Brain Size

Whilst schizophrenia was described by Kraepelin more than a century ago as a progressive disorder, showing continual worsening of cognitive state and organic brain anomalies, it is unclear as he based this conclusion on a direct study [1].

In a large-scale early study examining total brain size using pneumoencephalography in 1935, Moore et al. discussed findings suggesting decreasing cerebral volumes with the duration of 'mental disease' [2], consistent with the idea that psychiatric disorders represented a form of neurodegeneration. When studied in 1962 by using pneumoencephalogram, definite cerebral atrophy was diagnosed in 168 of 278 patients, most often as ventricular enlargement. With air filling of the outer cerebral spinal fluid spaces, cortical atrophy was reported in about one third of the cases, and although these were not correlated with neurological signs, the ventricular enlargement was found to be correlated with EEG abnormality [3].

Overall, the whole brain in schizophrenia shows little global change in volume measured by structural imaging and pathological methods. Some studies report no change at all [4, 5], whereas others have reported both regional and overall brain changes in schizophrenia, particularly with respect to illness duration (reviewed in [6, 7]).

The magnetic resonance imaging (MRI) scans was first used across nine patients with schizophrenia and five control subjects, allowing multiple-plane views of the brains of schizophrenic patients, which demonstrated much greater detail of morphological structure than the standard CT scans of the time. Although this study, small sample size that it has, showed no significant differences in several quantitative measurements between groups, it did usher in a new method of examining the brain [8]. However, a 2012 meta-analysis covering over 18,000 subjects across over

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300 studies found a decrease in total brain volume in schizophrenia of around 2%, independent of medication. Within this grey matter, shrinkage was more pronounced with longer disease duration and higher antipsychotic doses, whereas white matter volume showed no difference between medicated and unmedicated patients [9]. Similarly, the total brain weight is reported to be decreased in schizophrenia by around 2% (meta-analysis in Harrison et al. [10]; Crow [11]).

Schizophrenic twins from concordant and discordant pairs have smaller whole-brain volumes than control twins, suggesting there may be a fundamental brain change in brain volume from early in development not wholly characterised by the presence of specific alleles, although the details of this finding requires significantly more study to elucidate [12–19].

Whilst the global brain change in schizophrenia is subtle, and in typical studies likely overwhelmed by the effects of sample heterogeneity, there does appear to be a small but persistently significant decrease in overall weight and size of the brain in schizophrenia.

3.2 Ventricle Enlargement

The introduction of computed tomography into psychiatric research led to the 'rediscovery' of the ventricular change in consistently reported schizophrenia patients studied by pneumoencephalography almost a century ago [20]. The enlargement of ventricles in schizophrenia, particularly the lateral ventricles, is perhaps the most consistently described pathological change in the illness. Ventricular enlargement in schizophrenia was first described in 1976 using early CT scans [21] and has been confirmed by many imaging studies since (reviewed in [5]), as well as post-mortem examination [22]. Four decades ago, a study of 44 chronic schizophrenic patients showed that they have larger ventricles than matched controls. Ventricular enlargement did not correlate significantly with cortical abnormalities, but even in studies where there was no observed correlation between lateral ventricular size and length of illness, a positive correlation between the size of the third ventricle and the duration of schizophrenia has still been reported [23–25], subsequently followed up by a substantial study of 166 schizophrenia cases where overall symptom severity was significantly correlated with larger ventricle volumes in the lateral, third, and temporal region [26].

More advanced imaging studies have reported this finding consistently, with ventricular measures more highly correlated in patients by age, diagnosis, duration and severity. The high correlation between lateral and third ventricular size in schizophrenic patients suggests a pathologic process affecting both the structures, as well as neuropathological correlation between ventricle size and corpus callosum and temporal lobe sizes. Enlargement of both third and lateral ventricles may be more specific to schizophrenic patients than enlargement of either structure alone, and along with the progression with age, these findings support the progression of ventricular enlargement [5, 12, 19, 26–37].

There have been sceptical voices on the enlargement of ventricles in schizophrenia. These have mainly focused on the problem of heterogeneity of sampling

introducing too much noise into measures when factors such as diagnosis, schizophrenia subtype, age, sex, body size and medication are considered, making the ventricular volume-to-brain ratio an artefact of standardisation of image processing. However, the overwhelming opinion is that this is a real phenomenon in a field in which heterogeneity of results is the norm.

3.3 Asymmetry and Brain Torque

A proposed link between brain symmetry and insanity has had a long history [38, 39]. Wigan [39] suggested the hemispheres were '*two perfect organs of thought and volition—each, so to speak, a sentinel and a check on the other*', with right-handedness indicating the dominance in 'power' of the left hemisphere. Consistent with this reasoning, Crichton-Browne [38] supposed '*the cortical centres which are last organised, which are the most highly evolved and voluntary, and which are supposed to be located on the left side of the brain, might suffer first in insanity*', being the first to link lateralisation with progressive brain change in forms of psychiatric illness.

Today we have observed that healthy brains naturally show a weighted bias from anterior to posterior when observed from above (Fig. 3.1). This is observed as the right frontal lobe being wider than the left frontal lobe, with this being reversed in

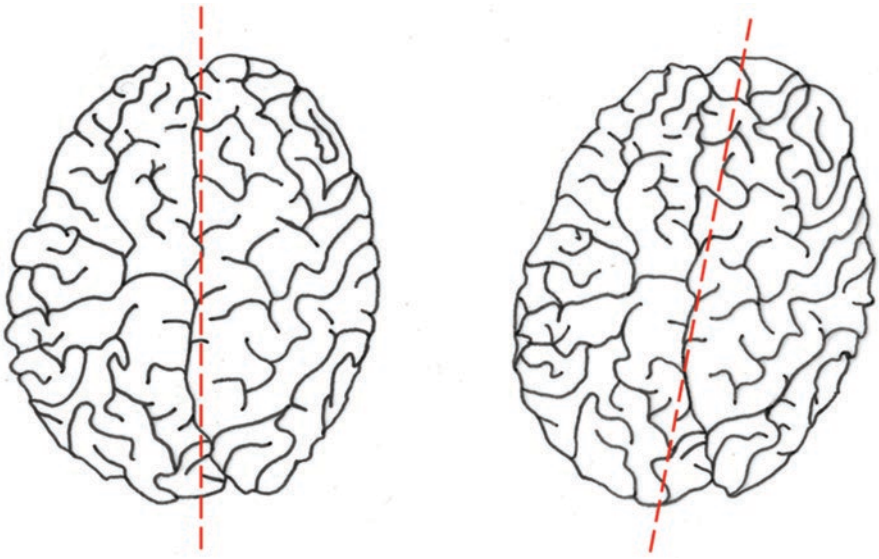

Fig. 3.1 Comparison of schizophrenia brain to control. Although intuitively the more 'normal' looking brain, the diagram on the left is illustrative of a schizophrenia case, whilst the brain on the right is a more typical orientation of a control brain. The red dotted lines indicate the centreline of each brain, clearly showing the loss of torque in schizophrenia. Brain anterior is at the top of the image and viewed from a dorsal perspective

the occipital lobes, giving the impression of a 'lean' or 'bulge' running from front-right to back-left, termed the brain 'torque' [24, 25, 40–43]. The model for this brain torque is suggested to produce an effect on the asymmetry of brain connectivity, as the torque drives the transmission within the system in the direction left occipito-temporo-parietal, right occipito-temporo-parietal, right dorsolateral prefrontal, left dorso-lateral prefrontal [44]. This torque has been reported to be absent in schizophrenia, giving the brain a more symmetrical look [45]. Whilst both neuropathological and imaging studies have reported different findings on the issue [40, 46, 47], the majority do seem to suggest a decrease in the extent of torque in the illness (discussed in [48]). Due to the lateralised nature of the change in cerebral asymmetry in schizophrenia, there have been two primary schools of thought regarding the cause. First, it is a marker for neurodevelopmental change [49–53], and second, it is a link between asymmetry and schizophrenia due to the evolution of language [54–59]. Whilst there have been reports and discussions of the role of language in the clinical manifestation and symptomatology of schizophrenia [60–63], it does not translate well into the pathological reports [64].

One recent intriguing connectome analysis reported reduced asymmetric nodal efficiency in several frontal regions and the hippocampus in schizophrenia, as well as abnormal hemispheric asymmetry of brain anatomical network topology associated with clinical features such as duration of illness and psychotic psychopathology in patients. The authors note the lateralised nature of hemispheric disconnectivity and highlight the potential for using brain network measures of hemispheric asymmetry as neural biomarkers for schizophrenia and its clinical features [65]. Whilst only an early investigation of the application of connectome analysis in schizophrenia research, new techniques may well reveal more beneath the apparent change in brain asymmetry and torque in the future as this is clearly an area requiring further investigation.

3.4 Occipital Bending

Occipital bending (OB) is a neurodevelopmental phenomenon, and it has been suggested that OB 'twist' creates a prominent shape difference between the left and right posterior temporal regions and a larger left planum temporale [66]. Occipital bending is more prevalent amongst schizophrenia patients than healthy subjects with a prevalence in schizophrenia patients of 13/37 (35.1%) than in control subjects of 6/44 (13.6%), illustrated in Fig. 3.2 [67]. This therefore supports a development underpinning to the development of schizophrenia with auditory–verbal hallucinations. With the addition of enlarged lateral ventricles, pressure may be applied to the surrounding structures, effectively displacing them in medial, anterior and posterior directions. Consistent with this hypothesis, Zhao et al. [48] reported 'interhemispheric fissure bending' to be more frequent in schizophrenia than in controls and the amount of OB to be more pronounced. Those findings suggested that torque occurs in various regions along the midline, not only in the occipital lobe. Furthermore, they recently reported occipital asymmetry in a group of medication-naive schizophrenia subjects [68]. There is also a reported increase in white matter volume in the left precalcerine region, consistent with this being the cause of the

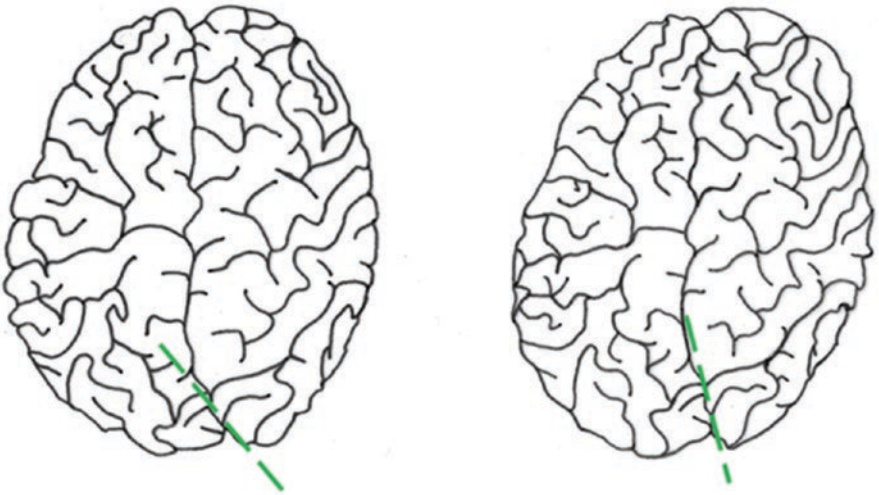

Fig. 3.2 Illustration of a schizophrenia brain from above, showing a dorsal view with the anterior at the top of the image. Left is illustrative of a schizophrenia case, whilst the brain on the right is a more typical control brain. The dashed green line shows the extent of occipital bending often observed in the illness

observed rightwards bending [67]. However, further examination is required to determine if this is the cause of occipital bending or a result of other factors distorting the shape of the occipital lobe during development. Also, we must bear in mind that whilst statistically more common in schizophrenia, occipital bending is observed in only 35% of cases reported.

3.5 Global Structural Imaging

Global grey changes are also well documented, and critically both global grey matter change and ventricular enlargement are key findings that are present before the onset of first-episode psychosis [69–74].

Whilst grey decrease can be detected as an overall loss across the entire brain, with a corresponding overall increase in cortical density in schizophrenia, it is a regional phenomenon, particularly focused in the frontotemporal regions [75–77] and the periaqueductal grey matter thickness around the third ventricle in schizophrenia [78, 79]. Imaging studies have not only suggested a decrease in overall cortical grey matter in schizophrenia generally that is also present before the first episode (reviewed in [77]). This has led to the proposal of the 'reduced neuropil hypothesis', suggesting reduction in inter-neuronal neuropil in the brain, focusing on the frontal, cingulate and temporal cortices, is a critical feature of cortical pathology in schizophrenia, representing a functional change in cortical circuit function [80].

A link has been made between sulcal widening and ventricular size in monozygotic twins with schizophrenia [18, 81], suggesting that the increased ventricular

volume is the more visible part of a more global but more subtle change in brain surface shape. A more recent study has reinforced this notion, with 14 monozygotic twin-pairs concordant and ten monozygotic twin-pairs discordant for schizophrenia analysed alongside 17 twin-pairs of monozygotic controls, as well as 22 discordant sibling-pairs and 56 pairs of unrelated control subjects, assessing the extent of basic developmental and genetic variability on brain growth. Within-pair similarities for whole brain volume increased as pair members were more closely related genetically, with monozygotic twins showing greater similarity than siblings, siblings in turn showing more similarity than unrelated control subjects. Schizophrenic twins, from concordant and discordant pairs, had smaller whole brain volumes than control twins, and discordant pairs showed more abnormalities in the third and lateral ventricular volumes than concordant twins [12–17, 19].

Mathematical analysis of the overall surface of the brain in imaging studies has revealed a subtle, but significant, effect of cortical flattening where the overall surface of the brain shows significant flattening of the sulci and gyri using structural MRI [82, 83]. The subtle nature of this effect, detectable only by complex mathematical analysis of the entire brain surface, means that neuropathological detection of such a phenomenon is likely impossible, although in the anterior cingulate cortex, a single study has suggested a decrease in bifurcation frequency of the primary cingulate sulcus in schizophrenia but not bipolar disorder or major depressive disorder using pathological measures, offering possible confirmation of flattening [84].

Whole brain volume is under high genetic control and smaller whole brain volume is a reflection of the genetic liability to develop schizophrenia. The variation in hippocampal and ventricular volumes within discordant monozygotic pairs indicates a role for environmental factors in determining these volume abnormalities in schizophrenia. Such factors may also underlie the more extensive morphometric deviations in patients from monozygotic discordant twins than in their counterparts from concordant twins.

The suggested change in whole brain size is thought to be a consequence of the neurodevelopmental hypothesis of schizophrenia. This proposes an interaction between multiple susceptibility genes and environmental insults in pre- or postnatal development, resulting in altered brain development and the emergence of psychosis in early adulthood. It has been suggested that most neuropathological deficits observed in post-mortem and neuroimaging studies of schizophrenia are in fact lesions that originated in early life, leaving their marks on certain brain regions to be discovered later on, but recent longitudinal neuroimaging demonstrates a progressive component to the neuropathology of schizophrenia. This, at least, suggests the possibility that the progressive decline seen in the illness may be arrested in some fashion [85–89].

3.6 Serum Changes Related to Neuropathology.

For obvious reasons, there has been a desire to find a straightforward blood-based biomarker for schizophrenia. Attempts to identify one have not met with success in any to be used as a diagnostic method. However, some studies in this area have produced intriguing results.

Translocator protein (TSPO) was originally named the peripheral benzodiazepine receptor (PBR) and is found throughout the brain and in many parts of the body [90]. TPSO is located in the outer mitochondrial membrane and has a key role in the transport of cholesterol into the mitochondria as a rate-limiting step for steroid synthesis. This occurs particularly highly in microglia, and TSPO is a target for neuroimaging studies. As a consequence of this, microglia have been suggested to play a role in several psychiatric illnesses by way of inflammatory processes, discussed further in Chap. 12 [91–94].

Whilst research has not found platelet PBR binding to be diagnostic for schizophrenia, it has been suggested to have some interaction with certain symptoms. Significant negative correlations have been reported between PBR density and scores for aggressive behaviour, hostility and anxiety in schizophrenia patients, independent of illness subtype, homicidal and suicidal history and antipsychotic treatment [95]. Whilst TSPO/PBR may not be useful as a direct diagnostic biomarker, there may be more to the biology of this protein in the illness than previously suspected.

S100β is an astrocytic protein and an indicator of astroglial function which has been reported to have increased serum concentrations in schizophrenia, although whether this is linked to positive or negative symptom severity, medication or duration of illness is unclear [96–103]. Comparison of CSF S100β as well as serum S100β shows that elevated levels in unmedicated as well as medicated schizophrenic patients with S100β concentrations in serum were positively correlated with a more severe psychopathology [104] and correlated with the clinical courses of severe schizophrenia and major depression over time [105], further suggesting glial cell involvement in the illness progression.

Brain-derived neurotrophic factor (BDNF) is a protein first purified in 1982. It is a member of the neurotrophin family of growth factors along with nerve growth factor (NGF), which share roughly half their amino acid identity. It is formed from the *BDNF* gene found on chromosome 11 at location 11p14.1. Pro-BDNF originates in the endoplasmic reticulum and transported to the Golgi complex then to the trans-Golgi network, and by the action of carboxypeptidase E and convertase, the 13 kDa mature BDNF molecule is formed and released outside the plasma membrane. Due to the role of BDNF in neurodevelopment, learning, memory and cognition, it has received attention in psychiatric illness, including schizophrenia [106–111]. Two recent meta-analyses have examined BDNF findings in schizophrenia research. The first consists of blood BDNF levels in schizophrenia compared with healthy controls and examined potential effects of age, gender and medication. Included are individual studies of BDNF blood levels in schizophrenia, having a wider diagnostic inclusion by including schizoaffective disorder or first episode psychosis. Overall, it examined only 16 studies providing what the authors describe as ‘moderate quality evidence of reduced blood BDNF levels’ in schizophrenia. More detailed analysis showed reduced BDNF in drug-naïve and medicated patients as well as in males and females with schizophrenia but with considerable heterogeneity of results [112].

The second reviews 25 studies ranging from 2002 to 2011 including a total of 1663 schizophrenia cases and 1355 control cases. These groups both average around 38 years old and are 66% male. However, the authors report that 15 of the included

studies were rated as ‘poor quality’ or ‘very poor quality’ but despite this there was evidence of significant and robust statistical findings of lower serum BDNF in cases of schizophrenia, although the authors conclude that the low quality of the majority of the studies and significant sample heterogeneity means that this result is too weak to make firm conclusions [113–115].

Given the studies described and the lack of certain conclusions that have been drawn from larger analyses, it is too early to say whether BDNF is reduced in schizophrenia. But the body of evidence is substantial enough to encourage more rigorous examination of serum neurotrophic factors as a particular marker for schizophrenia.

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Frontal Cortex

4

Matthew Williams

4.1 Definition and Structure

The frontal lobe is a prominent, bilateral cortical structure extending from the anterior pole of the brain to the central sulcus. The central sulcus runs along the lateral surface of each hemisphere following an arch shape to separate the motor and sensory cortices and marks the posterior limit of the frontal lobe. On the lateral surface of each frontal lobe hemisphere, the lateral sulcus separates the frontal lobe from the temporal lobe. The hemispheres of the frontal lobes are separated by the longitudinal fissure, a substantial sagitally orientated cleft visible from dorsal and ventral views due to its complete separation of the frontal lobes around the margin of the genu of the corpus callous.

There are no neural structures either crossing or within the longitudinal fissure, although it does contain the falx cerebri, one of the three dural folds (along with the falx cerebelli and tentorium cerebelli) which prevents physical movement of the frontal lobes with head and body movements. From the ventral aspect, the most prominent structures are the orbitofrontal indents containing four gyri, the medial-, posterior-, anterior and lateral-orbitofrontal gyri.

The main anatomical structures of the frontal lobes are shown in Figs. 4.1 and 4.2.

4.2 Cortical Organisation

The cerebral cortex is what most people see when they visualise a brain. It is composed of a thin sheet of neurons, only a few millimetres thick, which coats the outside surface of the brain almost completely above the cerebellum and midbrain. Whilst a broadly consistent structure, although showing changes in the size and

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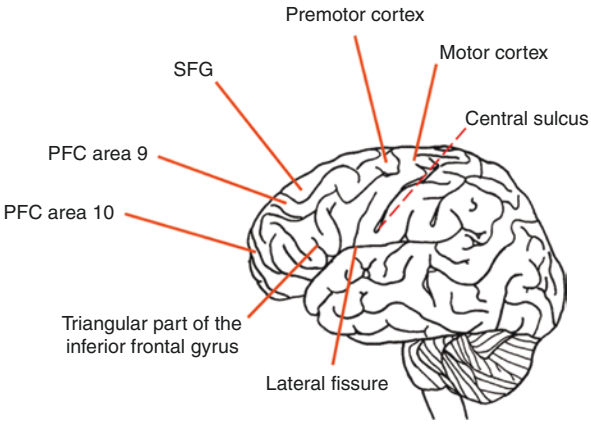

Fig. 4.1 Sagittal external view of the frontal lobe. *PFC* prefrontal cortex, *SFG* superior frontal gyrus

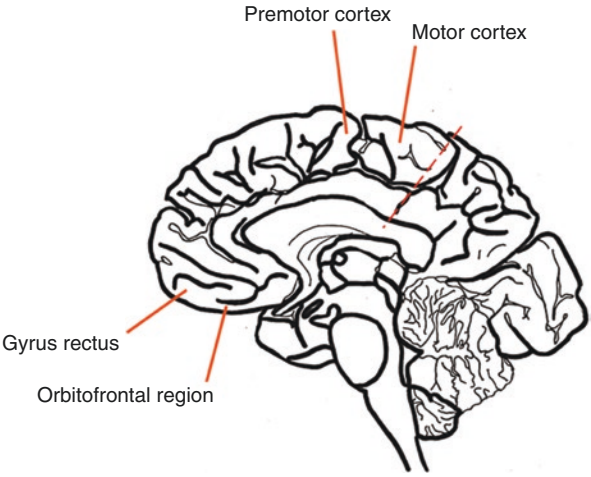

Fig. 4.2 Medial view of frontal lobe in sagittal cut. Dotted red line indicates posterior limit of frontal lobe

structure of the six cortical layers that make up the cortical sheet between different regions, the cerebral cortex is involved in the processing and regulation of language, abstract thought, motor control, sensory perception, vision, hearing, adaptive responses and emotional involvement.

Cortical structures have received extensive examination in schizophrenia. Indeed, due to the symptoms and commonly associated psychoses that have led some authors to suggest that schizophrenia is purely cortical disorder. However, due to the functions of the many cortical regions, neuropathological research has been highly focused on a few structures thought to be key in schizophrenia, leading to an uneven knowledge of possible neuropathological change across the cerebral cortex.

The neocortex has a distinct six-layered structure, more obvious is some brain regions than others.

The first layer, adjacent to the surface of the brain, is known as the molecular layer. This layer is cell poor, although glia have been observed with higher densities by neuropathological studies.

Layers II and IV, also known as the external and internal granular layers, respectively, are relatively thin cortical layers comprised primarily of smaller stellate or granule cells. Non-pyramidal cells are generally grouped together, making up around a quarter of all cortical neurons, are much smaller, typically having a diameter of under 10 μm. They have been described into groups by the fine anatomy of their projections as basket cells, chandelier cells, multipolar cells, bipolar cells and double bouquet cells. Overwhelmingly, these smaller cortical neurons have many projections which remain within the local cortex and have inhibitory GABA-mediated effects on their targets, although a few are excitatory by means of GLU connections.

In contrast, layers III and V are much larger and are composed primarily of pyramidal neurons. Pyramidal neurons are the most common type of cortical neuron, characterised by their distinct conical shape, but also by their pattern of spiny dendrites. They have a longer apical dendrite that projects from the peak, often thought of as the top, of the cell body, ascending vertically to the cortical surface. Pyramidal cells also have basal dendrites which project from around the base of the cell, projecting horizontally across the cortical layer.

The deepest layer, VI, is known as the multiform or polymorphic layer and is characterised by a large number of fusiform pyramidal cells.

4.3 Major Connections and Pathways

Overall, the cortical grey matter makes up a little under 40% of the frontal lobe by volume [1]. This cortical region forms part of an extensive connective network involved in socioemotional abilities and in the executive function of humans and other primates. Comparative studies suggest that the characteristic differentiation of the prefrontal lobe of humans compared to that of other primates lies more in circuit organisation than mere size of the structure, which has been implicated in the unique cognitive abilities of humans [2].

Three different circuits originating from the anterior frontal grey matter are considered of major importance for the functioning of the PFC, namely the dorsolateral circuit, orbitofrontal circuit and the circuit involving the anterior cingulate portions of the frontal lobe.

The dorsolateral circuit promotes organisation ability, planning and attention. From a clinical point of view, damage to these pathways can cause perseveration, reduced ability for abstraction, organisation and planning, loss of decorum, impaired verbal fluency, poor performance on complex figure copying and difficulty in sequencing motor acts [3].

Brodmann area 9 contains neuron cellular bodies defined as at the beginning and end of the dorsolateral circuit. These neurons project to the dorsolateral portion of the caudate nucleus, from which juncture they develop direct and indirect pathways which appear to have a reciprocal modulation mechanism via excitatory and inhibitory stimuli. The direct pathway enters the dorsolateral region of the external and internal globus pallidus and the rostrolateral portion of the pars reticulata of the

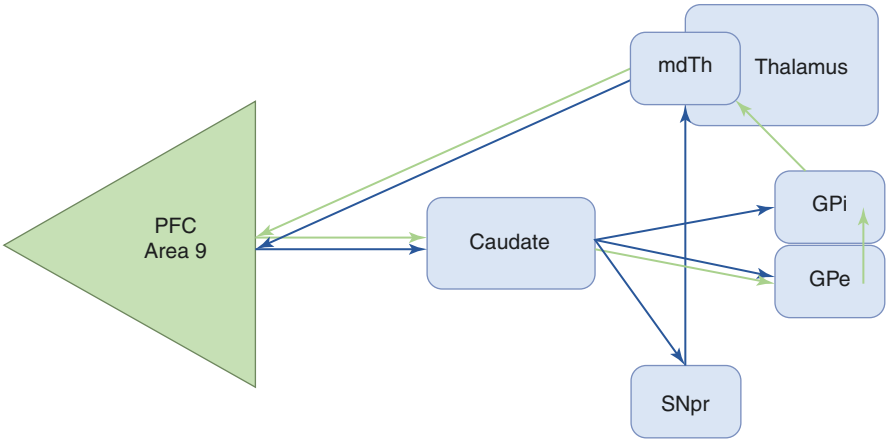

Fig. 4.3 A summary of the dorsolateral circuit. Blue arrows indicate the 'direct' pathway, whilst the green arrows represent the 'indirect' pathway. *PFC* prefrontal cortex, *mdTh* mediodorsal thalamus, *GPi* globus pallidus internal, *GPe* globus pallidus external, *SNpr* substantia nigra pars reticularis

substantia nigra. The indirect pathway connects to the dorsal portion of the globus pallidus external. In the anterior ventral and dorsomedial thalamus portion, there is an input of fibres from the internal globus pallidus and the substantia nigra pars reticulata where the direct and indirect pathways join. From the mediodorsal thalamus, the circuit returns to the Brodmann area 9, completing the circuits (summarised in Fig. 4.3), although tract tracing studies in other primate species have suggested the dorsolateral circuit may be more complex than currently described [3–5].

The orbitofrontal cortex is distinguished by its unique pattern of connections with crucial subcortical associative learning nodes, such as basolateral amygdala and nucleus accumbens. By virtue of these connections, the orbitofrontal cortex is uniquely positioned to use associative information to project into the future and to use the value of perceived or expected outcomes to guide decisions [6]. A summary of the orbitofrontal circuit is shown in Fig. 4.4.

As with the other circuits, much of our knowledge of the frontal-anterior cingulate circuit comes from primate research. The PFC-ACC circuits are complex and comprised of multiple closed and open loops. Figure 4.5 describes a simplified circuit describing the primary relevant projections to the PFC. Input from orbitofrontal and entorhinal areas provides the anterior cingulate circuit with information from the internal and external environment, respectively. From this, the individual is able to initiate motor activity that is based on the emotional relevance of external stimuli. Damage to this circuit would disrupt the integration of emotional information with motivational mechanisms and produce unmotivated, apathetic behaviour [7–14].

Besides the three main circuits of the frontal subcortical neuronal network, some authors have cited further two circuits, the inferior temporal cortical circuit and a circuit between Brodmann area 7 in the posterior parietal region and Brodmann area 46. Lesions involving the inferior temporal cortical circuit have been linked with

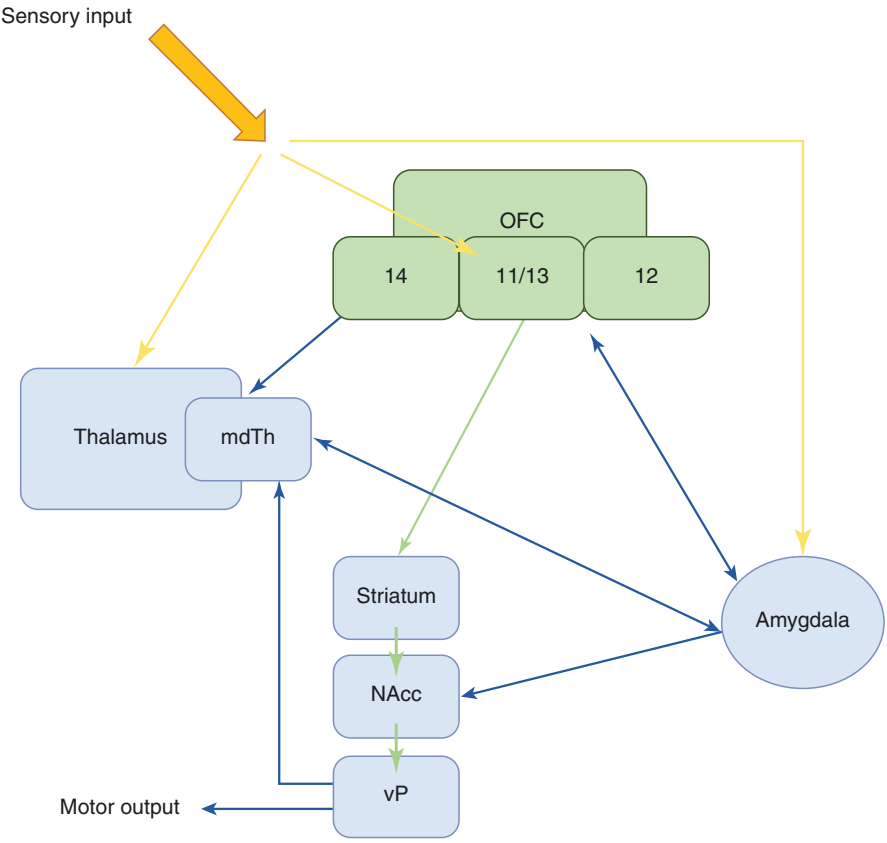

Fig. 4.4 A summary of the orbitofrontal circuit. Orange pathways describe sensory inputs, blue and green pathways are separated for clarity. *OFC* orbitofrontal cortex, *mdTh* mediodorsal thalamus, *NAcc* nucleus accumbens, *vP* ventral pallidum. Numbers refer to Brodmann areas

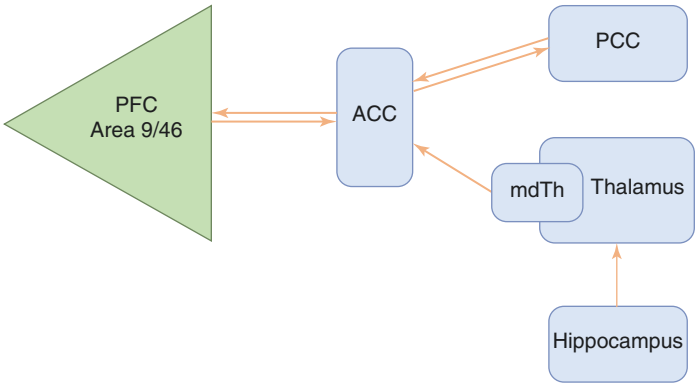

Fig. 4.5 A simplified model of the main constituents of the frontal-anterior cingulate circuit. *PFC* prefrontal cortex, *mdTh* mediodorsal thalamus, *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex

psychosis, deficits in visual discrimination and visual hallucinations, suggesting that damage to the circuit between Brodmann areas 7 and 46 is associated with impaired interpretation of visuospatial stimuli [1].

4.4 Frontal Lobe Changes in Schizophrenia

Whilst cortical grey matter loss, and corresponding cortical cell density, can be detected as an overall loss across the entire brain, it is largely a regional phenomenon, particularly focused on the frontotemporal regions [15–17] and the periaqueductal grey matter thickness around the third ventricle in schizophrenia [18, 19]. Imaging studies have not only suggested a decrease in overall cortical grey matter in schizophrenia but that is also present before the first episode (reviewed in [15]). Whilst white matter dysfunction in schizophrenia is discussed in detail in Chap. 11, the whole brain tractography shown in Fig. 4.6 illustrates vividly the role connections of the frontal lobe play in schizophrenia.

Neuropathological examination across the frontal lobes has suggested that overall grey matter is not changed, implying that the imaging findings of decreased grey matter are a subtle process occurring over a wide area. Higley et al. have suggested that these may include changes in shape and the pattern of gyral folding, although their subsequent investigation revealed no effect of schizophrenia on the gyrification of the brain [22, 23]. There are several comprehensive reviews of structural imaging in the frontal lobes in schizophrenia [24–27].

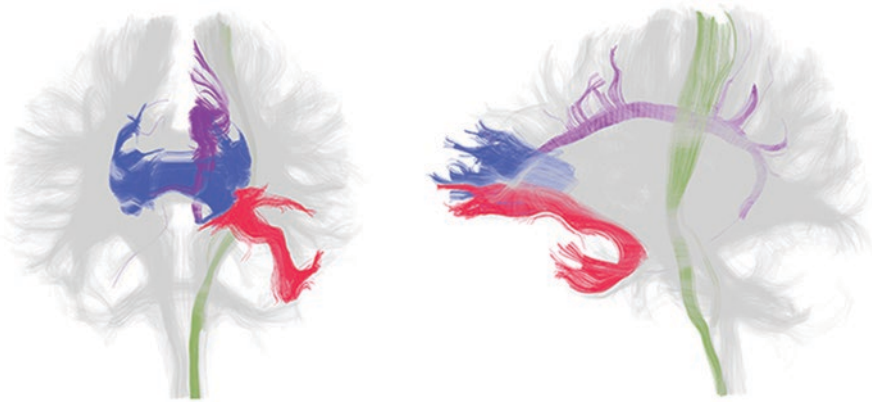

Fig. 4.6 White matter tracts most frequently identified as disrupted in patients with chronic schizophrenia. Lateral (right) and frontal (left) view of whole brain tractography. The uncinate fasciculus (red), cingulum bundle (purple), corpus callosum (blue, only the genu is shown) and internal capsule (green, only a portion spanning from the corticospinal tract is shown) are displayed in colour and the rest of the tracts are grey. Note that disruption in these tracts has been shown bilaterally but association and projection tracts are only coloured in the right hemisphere for clarity [20, 21]

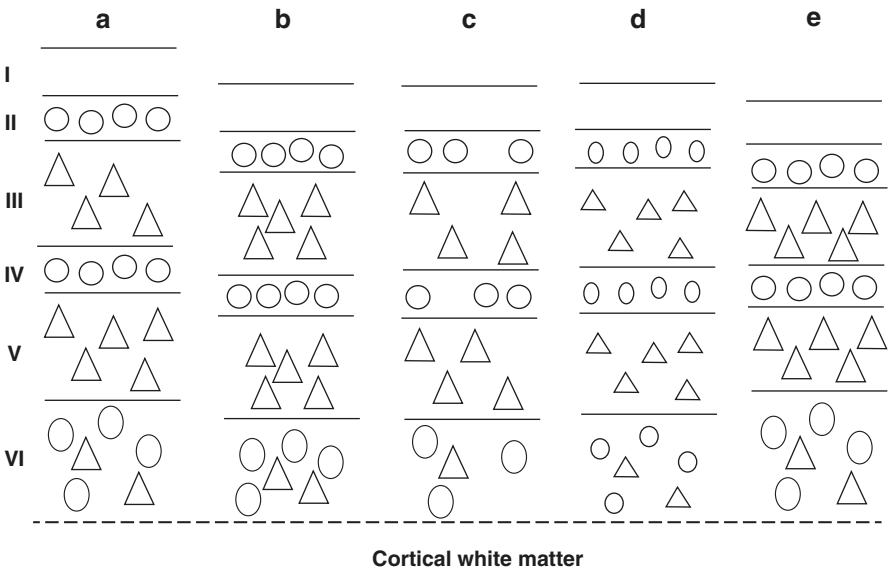

Fig. 4.7 Schematic demonstration of the different proposed reasons for cortical shrinkage in schizophrenia as discussed in text (b–e) compared to normal controls (a). (a) Cortex of normal controls showing the six cortical layers. (b) Increased packing density. (c) Decreased neuron number. (d) Decreased somal size. (e) Specific shrinking of pyramidal layers. I–VI represent the six neocortical layers

There is still no universally agreed cause of the reported cortical volume and thickness changes reported in schizophrenia. Several models have been proposed, summarised in Fig. 4.7. Some of these are plastic changes, such as neuron death, whilst some are elastic, such as glial cell density. Medication also affects the volume of brain regions as well as the illness itself, the progressive nature of which can complicate these measures further [28–33]. This has led to the proposal of the 'reduced neuropil hypothesis', suggesting reduction in inter-neuronal neuropil in the brain, focused on the frontal, cingulate and temporal cortices, is a critical feature of cortical pathology in schizophrenia, representing a functional change in cortical circuit function [34].

4.5 Prefrontal Cortex

Various definitions of the PFC have been discussed in Chap. 2, although various publications have inconsistent uses of the term. For clarity, the Brodmann areas are referred to where relevant in the text and are shown in Fig. 4.8.

The higher cognitive functions related to the functioning of the PFC can be subdivided into executive function, where this is more specifically linked to the dorsolateral portions of the frontal lobe (Brodmann areas 9, 10, and 46), language

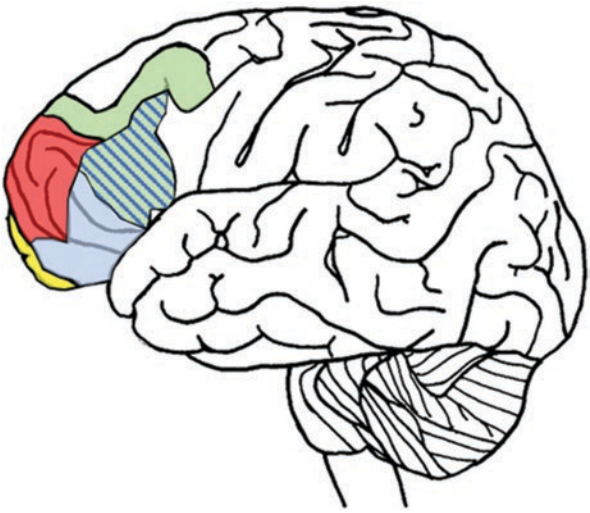

Fig. 4.8 The Brodmann areas of the anterior frontal lobe. Areas 9 (green), 10 (red), 11 (yellow), 46 (blue) and 9/46 (green/blue patterned). Terminology here is as described in Chap. 2

(Brodmann areas 44 and 45), emotional processing and sociability related to the orbitofrontal cortex (Brodmann areas 10, 11, 13, and 47) [2, 35, 36].

The PFC is one of the regions of the brain that shows pathological change in relation to clinical symptoms. Much like area 9, Brodmann area 46 has a key role in working memory [37–42], which shows deficits in schizophrenia [43–45]. Symptoms such as delusion, flat affect and asociality have been associated with cortical thinness in the dlPFC, areas 9 and 46 [46], whilst patients with prominent negative symptoms have greater regional alterations in the left dlPFC, whilst the pattern of functional alterations was unrelated to severity of negative symptoms [42]. These reports of cortical grey matter thinning in the PFC are primarily from structural imaging studies, although neuropathological examination has not shown changes in grey matter thickness [23, 47].

A key early study to estimate the total number of neurons in eight brains from chronic schizophrenic men and compared with 16 age-matched controls did not indicate that a major cell loss in the neocortex of schizophrenics is part of the disease [48]. However, within control cases, neuron density has been found to be higher in the left PFC than right, a finding that is reversed in schizophrenia. This is most prominent in layer III, with pyramidal cells were in this layer significantly large, whereas other studies have found that neuron decreases the PFC in schizophrenia [49]. Other studies of the PFC have shown to have increased overall neurons but decreased neuronal sizes with a substantial increase of small interneurons 70–140%. These pyramidal cells had decreased somal volumes by up to 14% when directly measured using histological methods, and layer V has been shown to have higher densities [50]. In layer III, this decrease in mean neuronal size was associated with a significant decrease in the density of large pyramidal neurons, and no change in glial size was reported. Consistent with this finding, another study conducted in the dlPFC by design-based methodology reported no change in neuron or

glial density in schizophrenia [51–53]. Whilst no altered density or number of neurons in the PFC may be a common finding in schizophrenia, examination of PFC cortical mini-columns has shown subtle alterations in the columnar cell spacing in PFC [54].

Perineuronal nets (PNNs) are extracellular matrix structures that enwrap many neurons in the brain. They regulate the postnatal experience-dependent maturation of brain circuits and maintain their functional integrity in the mature brain by stabilising their synaptic architecture. The investigation of PNNs by histology has revealed that densities of PNNs were decreased by 70–76% in layers III and V of the PFC in schizophrenia, compared with the normal control subjects, consistent with several studies showing pyramidal cell disruption in the PFC and across the frontal lobe more generally. That the timing of PNN development overlaps with the period when schizophrenia symptomatology gradually emerges raises the possibility that aberrant PNN formation might contribute to the onset of illness [55].

When PFC neurons are immunohistochemically labelled, a more complex patterns of change occurs. The density of calbindin-labelled neurons was 50–70% greater in schizophrenic cases, with cortical layers III and V/VI more seriously affected, consistent with the models of increasing neuronal density in these layers. In contrast, calretinin-labelled neurons did not differ significantly between schizophrenia and control cases, suggesting a selective increase in the density of a subpopulation of GABA-ergic local-circuit neurons [56–58]. Neurofilament200-labelled pyramidal cells show no change in packing density or somal size in layer III in the PFC in schizophrenia, although changes have been observed in depression [59, 60], whilst examination of TH-labelled neurons show no change in the PFC at all [61].

Neuropathological examination of the density of dendritic spines on the basilar dendrites of Golgi-impregnated pyramidal neurons in layer III in the dlPFC showed a significant effect of diagnosis but no change in layers V or VI. In the schizophrenic subjects, spine density on these neurons was decreased by 23% and 16% compared with the normal control and psychiatric subjects, respectively. In contrast, spine density on neurons in superficial layer III did not significantly differ across the three subject groups. Furthermore, spine density on deep layer III neurons in area 46 did not significantly ($P = 0.81$) differ between psychiatric subjects treated with antipsychotic agents and normal controls. Samples were obtained from 25 post-mortem schizophrenic brains and 31 non-schizophrenic controls [62–64].

There was a significant effect of diagnosis on spine density only for deep layer III pyramidal neurons in area 46. In the schizophrenic subjects, spine density on these neurons was decreased by 23% and 16% compared with the normal control and psychiatric subjects. In contrast, spine density on neurons in layer III in area 46 did not significantly differ across the three subject groups. Spine density on deep layer III neurons in area 46 did not significantly differ between psychiatric subjects treated with antipsychotic agents and normal controls. This region- and disease-specific decrease in dendritic spine density on dlPFC layer III pyramidal cells is consistent with the hypothesis that the number of cortical and/or thalamic excitatory inputs to these neurons is altered in patients with schizophrenia [62].

Whilst early measurement of glia in the PFC found no overall change in schizophrenia [29], more recent studies of glia sub-types has revealed differences in the disorder.

The PFC has seen considerable neuropathological focus on oligodendrocytes. A 25% reduction in oligodendrocyte numbers was found in PFC layer VI in schizophrenia, with a significant reduction in the number of perineuronal oligodendrocytes in the sublayers IIIa, IIIb and IIIc in schizophrenia compared to controls, as well as ultrastructural dystrophic and degenerative alterations of oligodendrocytes in layer V of Brodmann area 10 in schizophrenia. The numerical density of oligodendrocytes was significantly lower in the schizophrenia group compared to the control group. Young controls (age <50 years old) showed significantly higher numerical density of oligodendrocytes as compared to elderly controls (age >50 years old). Young and elderly schizophrenia subgroups did not differ significantly, but both the control subgroups have significantly higher numerical density of oligodendrocytes compared to the schizophrenia subgroups [65–71].

A recent transmission electron microscopy and morphometry investigation of microglia and adjacent oligodendrocytes were performed in layer V of Brodmann area 10 in 12 schizophrenia subjects displaying predominantly positive symptoms and nine with predominantly negative symptoms against 20 healthy controls yielded considerable insight into the interaction and function of these glial types in the PFC. Qualitative study showed microglial activation and dystrophic alterations of microglia and oligodendrocytes adjacent to each other in both the subgroups as compared to controls. A significant reduction in volume density and the number of mitochondria and an increase in lipofuscin granules were found in oligodendrocytes and adjacent microglia in both the subgroups. Density of lipofuscin granules and density and number of vacuoles of endoplasmic reticulum in microglia are increased significantly in the schizophrenia subjects displaying predominantly positive symptoms compared to controls (see Fig. 4.9). In the schizophrenia subjects displaying predominantly positive symptoms, density and number of mitochondria in microglia were correlated with number of vacuoles in microglia and with density and number of mitochondria in oligodendrocytes (see Fig. 4.10). Density of mitochondria in microglia was also correlated with density and number of vacuoles in oligodendrocytes in the schizophrenia subjects displaying predominantly positive symptoms.

Area of nucleus of microglial cells was correlated negatively with age and age at illness onset in the schizophrenia subjects displaying predominantly positive symptoms. In the schizophrenia subjects with predominantly negative symptoms, the number of mitochondria in microglia was correlated with the density of lipofuscin granules in oligodendrocytes, with no significant correlations between these parameters in the control group [72].

Immunohistochemistry examining astroglia and microglia in the PFC schizophrenic and control brains by GFAP and HLA-DR has shown significant increases in microglial numerical density in schizophrenia compared with controls in Brodmann area 9 (115 cells/mm^{-2} compared with 89 cells/mm^2), although astrocytes showed no similar change, and GFAP immunoblotting in the PFC was unchanged in schizophrenia [73–75]. However, a similar study in Brodmann area 9

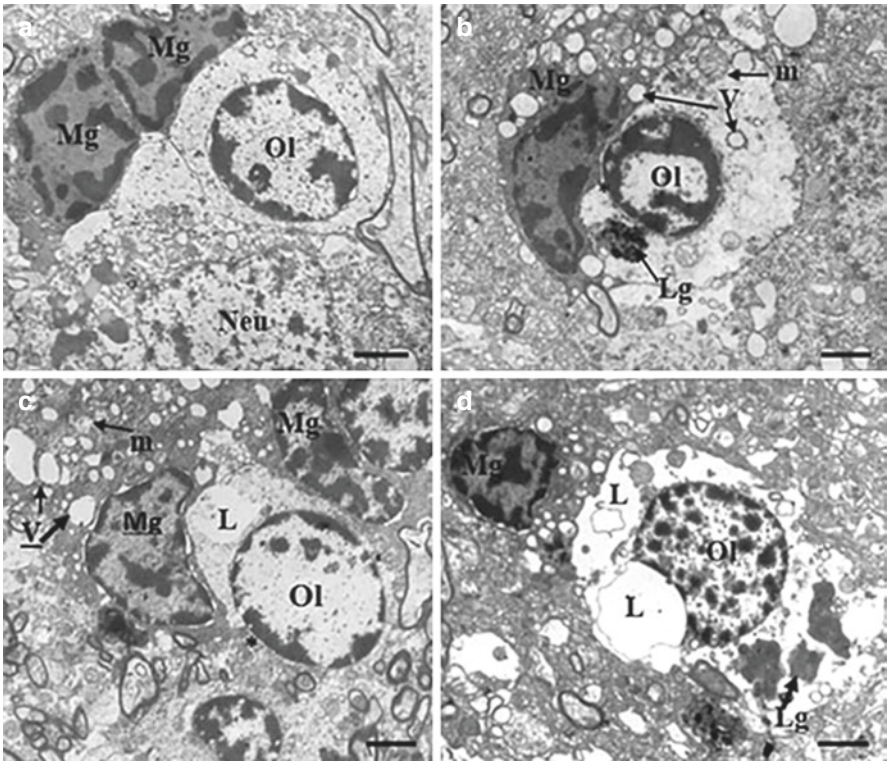

Fig. 4.9 These micrographs from layer V of the prefrontal cortex show microglia adjacent to oligodendrocytes from control brain (**a**) and from the schizophrenia-positive symptoms subgroup (**b**–**d**). 'Resting' microglia (**a**). Ameboid (activated) microglia (**b**). Dystrophic changes in microglia and oligodendrocytes: cytoplasm vacuolation, damaged mitochondria, accumulation of lipofuscin granules (**c**, **d**). Microglial cytoplasm contacts with oligodendrocyte nucleus (**b**, **c**, *). Focal lysis (L) of cytoplasm of oligodendrocytes adjacent to microglia (**c**, **d**). *Mg* microglia, *Ol* oligodendrocyte, *m* mitochondria (arrows); *V* vacuole (arrows), *Lg* lipofuscin granule (arrows) (scale bars = 1 μm) [72]

using GFAP immunohistochemistry examining GFAP-area fraction and astrocyte spatial distribution did show decreased area fraction and increased cell clustering in schizophrenia samples [76], and another study of astrocytes showed that astrocytic end-feet were deformed and swollen at a significantly higher rate in the PFC in schizophrenia compared to controls [70]. These results suggest that pathological change is likely occurring in regions of interest beyond that of simple numbers or density.

Two studies have now reported that in Brodmann area 9 and 10, there were no differences in mean capillary length, diameter or density in schizophrenia [47, 70]. Cerebral blood flow (CRB) has had a slightly more varied pattern of results. Schizophrenia cases with negative symptoms show a significantly lower resting CBF change rate in the PFC during cognitive tasks than normal controls, leading

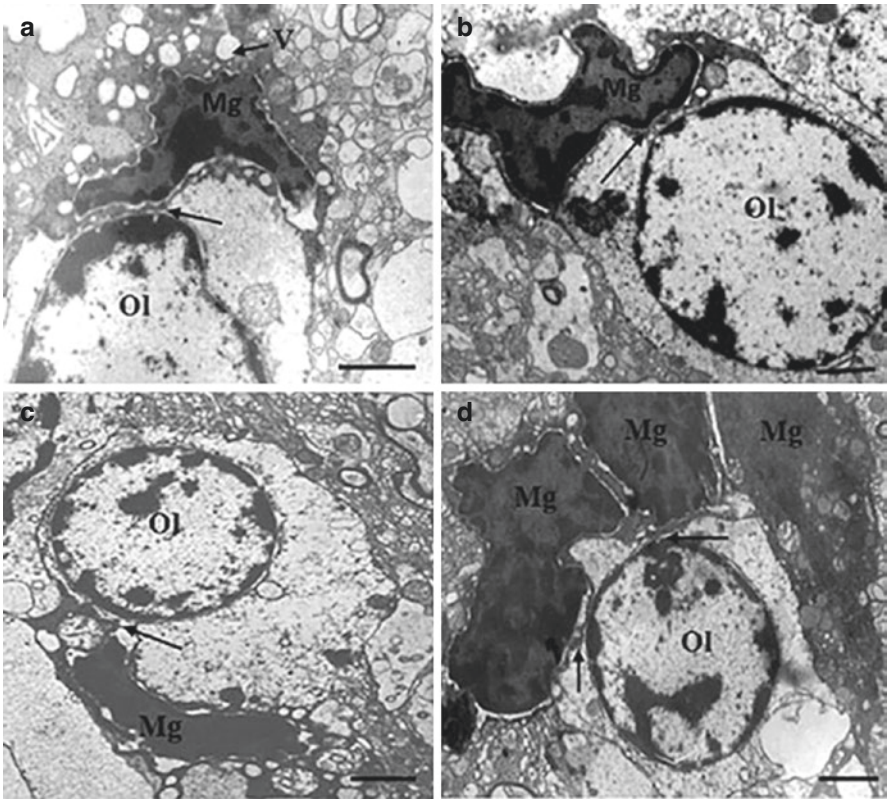

Fig. 4.10 These micrographs from layer V of the prefrontal cortex show microglia adjacent to oligodendrocytes from the schizophrenia-negative symptoms subgroup. Dark dystrophic microglia (**a**). Ameboid microglia (**b**), signs of apoptosis (dark nucleus and small rim of dark shrunken cytoplasm) (**c**, **d**). All microglia showed contacts with the nuclei of oligodendrocytes (**a**–**d**, arrows). A group (cluster) of three microglia surrounding dystrophic oligodendrocyte (**d**). *Ol* oligodendrocyte, *Mg* microglia. Scale bar = 1 μm [72]

Liu et al. to suggest that the negative schizophrenic patients have executive function deficits and lower resting CBF perfusion in left PFC [77], although other studies have suggested no change in the illness [78, 79]. Whilst rCBF is coupled to cerebral glucose metabolism, a possible link to the suggested metabolic changes in schizophrenia pathology, recent investigation has determined there is no specific PFC involvement [80].

There is good evidence now that dysfunction of the dlPFC in schizophrenia is associated with lamina-specific alterations in particular subpopulations of interneurons. In pyramidal cells, postsynaptic GABAA receptors containing different α-subunits are inserted preferentially in distinct subcellular locations targeted by inputs from specific interneuron subpopulations.

Changes in GABAA receptors or GABAA receptor subunit assembly or structure in schizophrenia have been suggested to contribute to the symptoms of

schizophrenia for almost 30 years [81]. Altered communication between GLU-pyramidal and GABAergic local circuit neurons would result in a loss of inhibitory tone, with consequent disinhibition of excitatory pyramidal cells, leading to increased excitatory output to other areas of the brain. An upregulation of post-synaptic GABA receptors may compensate for reduced inhibition to some extent [82, 83]. Alternately, the interaction between DA and GABA may be compromised by a loss of inhibitory tone in schizophrenia. It has been suggested that decreased GABAergic function may lead to increased DA activity. DA receptors are localised to GABAergic interneurons in rat and primate brain [84, 85], and DA afferents also terminate on cortical GABA interneurons to exert an inhibitory effect, thus exacerbating a deficiency in GABAergic neurotransmission [86].

Binding studies have shown increased binding of high affinity [^{3}H]muscimol or [^{3}H]GABA to the total population of GABAA receptors in the dlPFC of post-mortem schizophrenic brains compared with controls [82, 83, 87–90]. This has been supported by findings of increased GABAA receptor α1, α2, α3 and α5 subunit mRNAs, and α1 and β2/3 subunit proteins, in the schizophrenic PFC [91–95]. An increase in binding on GABAA receptors signifies elevated total GABAA receptor number in the regions examined in the schizophrenic brain. Specifically, the α1- and α2-containing GABAA receptors are preferentially localized to pyramidal cells in the cortex [92]. This may reflect a compensatory upregulation of GABA receptors in response to defective inhibitory modulation and input to pyramidal cells, caused by a reduced number of inhibitory interneurons, or deficient transport or release of GABA in these regions [61, 83, 86, 92, 96]. Older studies of the sub-populations of GABAA receptors that bind benzodiazepines have found no change in benzodiazepine binding [61, 97–99]. Decreased mRNA GABAA receptors and schizophrenia and protein expression of the γ2 subunit, required for high-affinity benzodiazepine binding [100], has been found in post-mortem schizophrenic brain compared to control cases [101, 102], although no change in γ1 or γ3 subunit proteins was observed in prefrontal cortex of schizophrenic compared to control brains [92, 103]. In subjects with schizophrenia, mean GABAA α1 mRNA expression was 17% lower in layers III and IV, α2 expression has been reported as 14% higher in layer II and α5 expression 15% lower in layer IV with α3 expression unchanged relative to controls. The mRNA expression of β2, which preferentially assembles with α1 subunits, is 20% lower in layers III and IV, whilst β1 and β3 mRNA levels were unchanged in schizophrenia. These expression differences were not attributable to medication effects [104, 105].

In cortical axons, α2-labelled Axon Initial Segments (AIS) in schizophrenia are increased by 113% compared to control subjects, and the density of α2-labelled AIS was negatively correlated with the density of chandelier axon terminals immunoreactive for the GABA membrane transporter, suggesting that GABAA receptors are upregulated at pyramidal neuron AIS in response to deficient GABA neurotransmission at chandelier axon terminals in schizophrenia. This implicates disturbances in inhibition at the chandelier neuron-pyramidal neuron synapse as a critical component of PFC dysfunction in schizophrenia [95].

A major problem with studies of post-mortem human brain is the probable influence of antipsychotic drugs on receptor expression. When schizophrenic patients are analysed as antipsychotic-medicated or antipsychotic-free, those that were medicated showed significantly lower [^{3}H]flumazenil binding to benzodiazepine sites compared to medication-free patients and normal controls [99]. A number of animal studies have therefore been conducted to examine whether the receptor alterations observed in schizophrenia are due to drug therapy. Investigations have shown that in the same animals, longer-term antipsychotic treatment does not alter the total population of GABAA receptors as determined by [^{3}H]muscimol binding, but it does increase the density of benzodiazepine-sensitive receptors [106, 107]. This suggests that antipsychotic administration results in a reshuffling of GABAA receptor subunits, leading to a greater proportion of receptors available for benzodiazepine binding.

Glutamic acid decarboxylase (GAD) is an enzyme that converts GLU into GABA (see Fig. 4.11). It is responsible for around 90% of the GABA in the brain, with GAD67 composed of around 80% of total GAD. GAD67 mRNA-labelled neurons are reported to be decreased through the cortical layers, but most prominently decreased by an average of 30% in PFC cortical layers III-V, whilst the mean GAD67 density for each labelled neuron was unchanged from controls in schizophrenia, suggesting that whilst the cell organisation may have changed, the cells themselves have not [56, 108]. The GAD67 transcript has been reported to be downregulated in several cortical regions of a significant portion of schizophrenia patients, and in a similar manner to GABAA receptor, changes may contribute to desynchronisation of cortical networks and cognitive dysfunction due to defective GABAergic inhibition [56, 109–115]. In fact, one study examining decreased GAD67 mRNA expression and decreased α5 mRNA expression in the dlPFC with

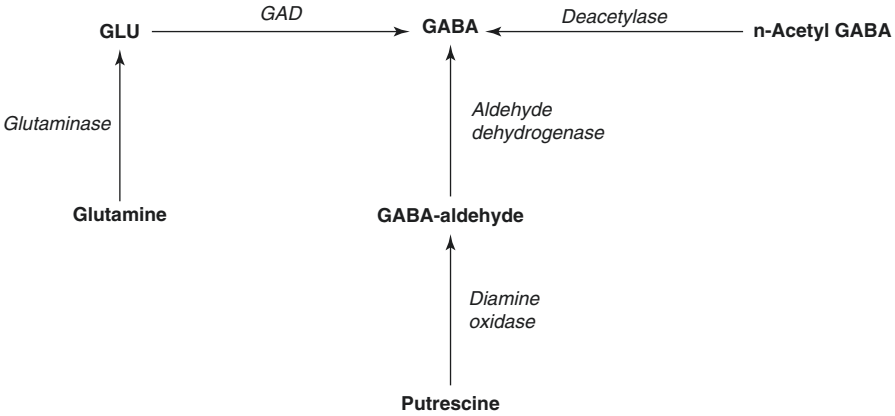

Fig. 4.11 Summary of primary GABA-synthesis pathways. GABA is synthesised from three main sources. Aldehyde dehydrogenase also catalyses the synthesis of GLU from glutamic semialdehyde. *GABA* γ-amino-butyric-acid, *GLU* glutamate, *GAD* glutamic acid decarboxylase

no significant change of other α-subunits confirms that GABA deficits and reduced GAD67 are consistent features of schizophrenia post-mortem brain studies. This does not confirm alterations in cortical α1 or α2 mRNA levels in the schizophrenic dlPFC, but suggests that downregulation of the α5 subunit mRNA suggesting that post-synaptic alterations of inhibitory receptors are an important feature of schizophrenia but may vary between cohorts [105].

The *GAD1* promoter, located on chromosome 2q31, regulates GAD67 GABA synthesis enzyme expression. It has been reported that disease-associated changes in local chromatin templates at specific gene promoters apparently are accompanied by additional alterations in higher order chromatin structures, because decreased *GAD1/GAD67* expression in PFC is accompanied by a weakening of a long-range promoter-enhancer loop that normally interconnects regulatory sequences positioned up to 50 kb upstream of *GAD1* with the gene's transcription start site and proximal promoter [116]. Therefore, some of the risk-associated DNA polymorphisms at regulatory noncoding sequences could impact not only the epigenetic status of local chromatin structures, but could exert effects and impact epigenetic regulation of sequences that are positioned many kb's further up- or downstream. Larger-scale genome sequencing from post-mortem brain tissue should be conducted with the aim of studying epigenetic changes at locations affected by underlying genetic variation related to disease risk [117], working memory and other cognitive functions often compromised in psychosis [118, 119] (Fig. 4.12).

In the postsynaptic density fraction obtained from human post-mortem dlPFC tissue, there is a reduction in the activity of signalling cascades downstream of the NMDAR in schizophrenia, despite an apparent increase in NMDAR density and GluN1 expression [120]. Alterations in the molecules critical for NMDA-receptor-mediated neural transmission has been implicated in the dlPFC NMDAR in the

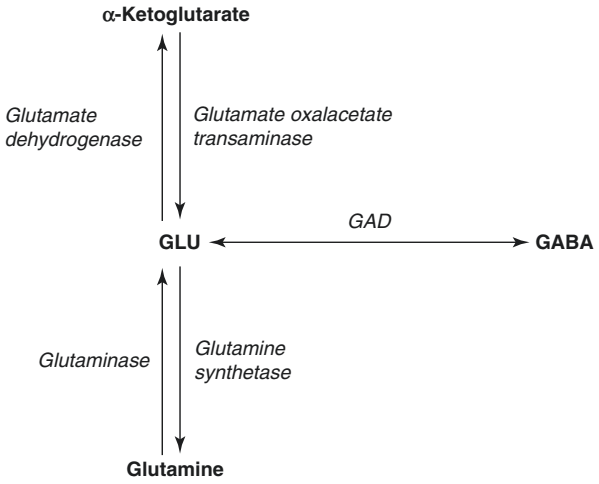

Fig. 4.12 Summary of primary GLU synthesis pathways. GLU is synthesised from three main sources. Aldehyde dehydrogenase also catalyses the synthesis of GLU from glutamic semialdehyde. The α-ketoglutarate–GLU reactions are both reversible. *GABA* γ-amino-butyric-acid, *GAD* glutamic acid decarboxylase, *GLU* glutamate

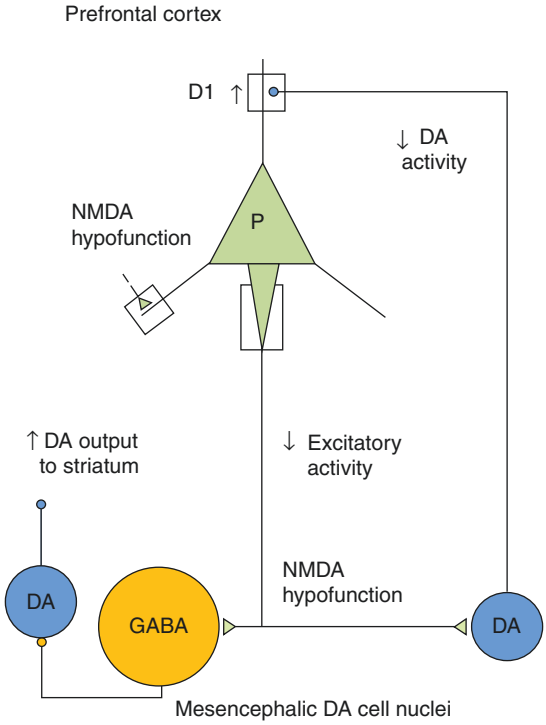

Fig. 4.13 Example for consequences of NMDA receptor hypofunction in glutamatergic–dopaminergic circuits. Hypofunction of NMDA receptors mediating excitatory inputs to prefrontal pyramidal cells in schizophrenia leads to decreased activity in cortical excitatory projections to mesencephalic DA cell nuclei. This results in decreased activity of DA neurons projecting to the DLPFC and increased activity of DA cells projecting to the striatum, as a consequence of decreased stimulation of GABA interneurons. Reduced DA levels in dlPFC lead to compensatory, but functionally insufficient, upregulation of D1 receptors [122]

pathophysiology of schizophrenia, being positionally important in the underlying abnormal cortical connections and altered neurotransmitters in the PFC circuits, explaining some of the prominent frontal cognitive disruptions observed in schizophrenia [121]. A model for NMDAR hypofunction on DA-GLU circuits is shown in Fig. 4.13. A meta-analysis examining in vivo GLU concentrations in schizophrenia measured by proton magnetic resonance spectroscopy has reported lower GLU concentrations that progressively decreased with age in frontal brain regions [123].

Members of the microtubule-associated protein (MAP) family are best known for their microtubule-stabilising activity and for roles regulating microtubule networks in the axons and dendrites of neurons. Further evidence suggests a much broader range of functions, such as binding to filamentous actin, recruitment of signalling proteins, and regulation of microtubule-mediated transport [124]. Immunocytochemical studies in Brodmann area 9 have shown a dramatic decrease in MAP2 and neurogranin in PFC layers III and V in schizophrenia [125].

Examination of the expression of the active form of calmodulin, critical as a calcium-binding protein in neurons, has been examined in layers III and V of Brodmann area 9 in six controls and six schizophrenia cases. Area fraction analysis has shown that in the schizophrenia cases there was a significant decrease in immunostaining in Brodmann area 9 layers III (58%) and V (44%), and a significant reduction in the density of immunopositive pyramidal cells in Brodmann area 9 (11%) layer III, (20%) layer V, with no difference in immunopositive interneurons. These data suggest a loss of the active form of calmodulin with pyramidal cells once again being preferentially affected [126]. In contrast calbindin (Cb), a protein mediating calcium absorption, shows the opposite effect in Brodmann area 9, with Cb-labelled neurons 50–70% greater in density schizophrenic subjects compared with control subjects, and consistent with calmodulin and other neuropathological findings shows cortical layers III and V/VI being preferentially affected [57, 127].

Almost half the altered proteins identified by proteomics were associated with mitochondrial function and oxidative stress responses. This was mirrored by transcriptional and metabolite perturbations. Cluster analysis of transcriptional alterations showed that genes related to energy metabolism and oxidative stress differentiated almost 90% of schizophrenia patients from controls [128].

In the mature human brain, GAP-43 marks circuits involved in the acquisition, processing, and/or storage of new information. Quantitative immunoblots revealed that the expression of GAP-43 is increased preferentially in frontal cortical grey matter of schizophrenia, a finding that was not observed in similar examination of GAP-43 mRNA by in situ hybridisation. These changes are not present in other neuropsychiatric conditions requiring similar treatments, potentially affecting the regional levels of both GLU and GABA. Examination of the levels of additional markers reveal that levels of synaptophysin are reduced in the PFC, possibly suggesting another mechanism of disorder in frontal lobe circuitry [129].

Other proteins such as SNAP-25 (synaptosomal-associated protein 25 kDa which directly executes membrane fusion by bringing the synaptic vesicle and plasma membranes together), SYN3 (Synapsin III which encodes a neuronal phosphoprotein associated with the cytoplasmic surface of synaptic vesicles) and Clusterin (associated with apoptosis) have all been shown to be disrupted in the PFC in schizophrenia, illustrating the wide-ranging disruption in basic biology in this disorder and the importance of greater investigation into proteins in future research neuropathology [64, 130, 131].

Wnt proteins are secreted, cysteine-rich glycolipoproteins that function as paracrine signalling molecules to affect target cells [132–134], and the Wnt-signalling pathway, important for cortical development and plasticity, and therefore, a potentially critical pathway in this structure in schizophrenia has been examined by means of GSK-3beta, beta-catenin and dishevelled-2 proteins. The results have been contradictory, with papers reporting changes and unchanged levels of these proteins in different studies, with a consensus not yet reached [135, 136].

Use of chip arrays has detected several protein peaks whose intensities differed between the schizophrenia and control groups to a highly significant degree, an analysis of which is capable of distinguishing between schizophrenia and controls

with a sensitivity and specificity of around 70%, further suggesting a distinct 'molecular/biochemical profile' of the illness [137]. Global proteomic analysis of post-mortem dlPFC tissue from schizophrenia patients and controls has resulted in the identification of 1261 proteins, 84 of which showed statistically significant differential expression. These reinforce the profile of disruption in the immune system, calcium homeostasis, cytoskeleton assembly and energy metabolism in schizophrenia [138].

Where there are protein changes, there will inevitably be changes in gene expression. The genetics of schizophrenia is an entire field in itself, and there are several comprehensive discussions of the possible interpretations of these functional changes in neural PFC circuits [53, 139, 140].

However, relative to the reported neurotransmitter changes is that a group of neighbouring SNPs are in linkage disequilibrium with each other within few kb from the *GAD1* transcription start site confers genetic risk for accelerated loss of frontal lobe grey matter [141, 142] and, via epistatic interaction with catechol-o-methyl-transferase alleles regulating synaptic DA, modulate PFC GABA levels [143]. Subjects with schizophrenia who are bi-allelic for this *GAD1* promoter-associated risk haplotype, in striking contrast to cases with the protective alleles, show a significant deficit in prefrontal *GAD67* transcript together with a shift in the epigenetic decoration of the surrounding chromatin, with loss of a facilitative histone methylation marking and excess of a repressive mark, histone 113 trimethyl-lysine 27 [144].

Multi-stage genome-wide association studies for schizophrenia with both examination of a Swedish national sample 5001 cases and 6243 controls followed by meta-analysis of previous studies consisting of 8832 cases and 12,067 controls, and finally by replication of SNPs in 168 genomic regions in independent samples 7413 cases, 19,762 controls and 581 parent–offspring trios, have revealed specific loci of interest in schizophrenia. These results in an estimate of 8300 independent, mostly common, SNPs contribute to schizophrenia risk and that these collectively account for at least 32% of the variance in liability. Examination of candidate genes at these loci suggests the involvement of neuronal calcium signalling [117]. More comprehensive reviews of the genetics of schizophrenia can be found in Kahn et al. [145] and Coelewij and Curtis [146].

At the gene level, there may be more impact from common environmental exposures mediated by influential epigenomic modifiers, such as microRNA. One study in post-mortem Brodmann area 46 including 74 matched pairs of schizophrenia, schizoaffective disorder cases and control samples showed a significant gene-miRNA interaction network, including miR-92a, miR-495, and miR-134, which converged with differentially expressed genes in pathways involved in neurodevelopment and oligodendrocyte function [147]. Discrete miRNA alterations in Brodmann area 10 showed that those miRNAs which were downregulated in schizophrenia tended to be synaptically enriched, whereas upregulated miRNAs tended not to be. There was a significant loss of small RNA expression in schizophrenia synaptosomes only for certain sequence lengths within the miRNA range. In another study, 73 miRNAs were significantly downregulated, whereas only one was

up-regulated, and across all expressed miRNAs in synaptosomes, there was a significant inverse correlation between the fold-change of a given miRNA observed in schizophrenia and its synaptic enrichment ratio observed in controls. This points to a possible deficit in miRNA biogenesis, transport, processing or turnover in schizophrenia that is selective for the synaptic compartment [148].

The application of epigenetics to neuropsychiatry is still in its early stages, but these results are encouraging for further investigation. Reviews into epigenetics can be found by [118, 121] and a meta-analysis by [121, 149].

4.6 Orbitofrontal Cortex and Gyrus Rectus

The OFC and GR are found on the ventral surface of the anterior part of the frontal lobe, clearly visible when viewed without dissection, allowing the smooth inward curve of the OFC to be used as a convenient neural landmark in this area.

From the ventral aspect, the most prominent structures are the orbitofrontal indents containing four gyri, the medial-, posterior-, anterior and lateral-orbitofrontal gyri. The GR lies immediately medial to the orbitofrontal region, separated by the olfactory sulcus and bordering on the longitudinal fissure.

The gyrus rectus is located at the anterior end of the frontal lobe, inferior to the PFC on the ventral and medial surfaces, shown in Fig. 4.14.

Fig. 4.14 Location of the gyrus rectus (yellow) and orbitofrontal cortex (green) in coronal section of the anterior part of the pre-genual frontal lobe. The orbitofrontal cortex is split here into the lateral (darker green) and medial (paler green) parts. The dotted redline indicated the midline of the brain

Structural imaging in humans has identified several major connections of the OFC. The first is a substantial fibre bundle to the thalamus and anterior cingulate gyrus, passing inferior to the caudate and medial to the vertical fibres projecting from the thalamus. Secondly, a bundle projecting to the brainstem, travelling lateral to the caudate and medial to the internal capsule and radiations to the parietal and occipital lobes travelling with the inferior fronto-occipital fasciculus. The parietal and occipital projections are likely related to the OFC as an important centre for processing visual and spatial [150], but most famously the OFC has a key role in the brain's reward system, receiving projections from the DA neurons of the ventral tegmentum area, with the substantia nigra (SN) the source of most of the CNS DA. The primary subcortical reciprocal connection appears to be with the amygdala and along with significant projections to the basal ganglia, specifically the caudate, nucleus accumbens and putamen, suggesting the OFC has a key role in the limbic loop.

Typically, three major connections of the OFC are described: a bundle to the thalamus and anterior cingulate gyrus, passing inferior to the caudate and medial to the vertical fibres of the thalamic projections; a bundle to the brainstem, travelling lateral to the caudate and medial to the internal capsule; and radiations to the parietal and occipital lobes travelling with the inferior fronto-occipital fasciculus [150]. The functional anatomical connections of the OFC, receiving projections from the ventral tegmentum area, the nucleus accumbens and part of the striato-thalamoorbitofrontal circuit implicated in addition, has led to the structure receiving attention from neuropathologists in schizophrenia research.

Whilst it has been investigated, OFC structural abnormality in schizophrenia has not been well characterised, likely due to substantial anatomical variability and lack of consistent definitions.

A pair of studies examining the OFC in schizophrenia patients by MRI showed that it was on average 11% bilaterally smaller by volume than controls, with no change observed in the gyrus rectus. In addition to the volume change, the OFC sulcogyral pattern differed between schizophrenia and controls. Whilst schizophrenics in these studies showed poorer performance than controls in cognitive testing, performance was not correlated with OFC volume. When applying anatomical parcellation methods to this data, the results demonstrated a subregion-specific OFC grey matter volume deficit in patients with schizophrenia, independent of OFC sulcogyral pattern, although a later study with mapping statistics suggests that delusion severity is linked with thickness in the OFC. This volume deficit was associated with a longer duration of illness and greater formal thought disorder [46, 151]. More recently, total OFC grey matter volume has been reported to be decreased in schizophrenia but with a lateralised effect, only observed in the right hemisphere [152]. Three other studies reported that patients with schizophrenia exhibited significantly decreased grey matter volumes of the gyrus rectus compared with healthy controls using both MRI and VBM methods, with volumetric decrease negatively correlated with the positive scales on the Positive and Negative Syndrome Scale [153]. A particularly large MRI study of 74 prodromal and 76 controls showed significantly increased grey matter volume in the right gyrus rectus relative to healthy controls,

potentially opening a route for early detection [154]. Recent meta-analysis of 14 VBM and 9 MRI cortical thickness studies shows a significant grey matter volume increase in the right gyrus rectus, echoing the lateralisation of individual studies but adding to the complexity of describing grey matter changes [155]. Echoing the right-side changes in these structures in schizophrenia is examination of resting CBF, where schizophrenia patients with primary and enduring negative symptoms group showed a significant decrease in resting CBF in the right OFC compared to schizophrenia group without this symptomatology profile, again suggesting a link between the OFC and behaviour in the illness [156].

Overall, large histopathological studies suggested no change in either density or somal size of glia or neurons in the OFC in schizophrenia, and no change in the total cortical or specific layer thickness in the OFC or gyrus rectus as observed in the rest of the anterior frontal lobe [74, 157]. Dendritic spines impregnated with a rapid Golgi method were counted on pyramidal neurons in layer III. The mean spine count across the frontal lobe is considerably decreased in schizophrenia, with a control density of 243 mm^{-1} against the schizophrenic 108 mm^{-1} [73, 74]. There is also a significant decrease in density of kainate receptor-positive neurons in OFC grey matter in the schizophrenic group (488 cells/mm^2) compared to controls (618 cells/mm^2), implicating altered GLU function in the schizophrenic OFC and giving a possible direction to further investigation [156].

Molecular investigation has revealed no changes in glucocorticoid receptors (GR) variants GR-1C or GR-1F mRNA expression of the OFC but did reveal the GR-1H mRNA variant was decreased by 22% in schizophrenia, with no corresponding changes in OFC NR1 NMDA-receptor or PSD-95 mRNA, PSD-95 being membrane-associated guanylate kinase and the major scaffolding protein in the excitatory postsynaptic density.

SST mRNA was reduced across the full depth of OFC grey matter in schizophrenia as measured with both in situ hybridisation and qPCR, with the greatest deficit of 67% in layer II. Layer II SST mRNA-reactive neuron density was also reduced in schizophrenia (29%), providing an excellent link between molecular- and neuropathology. The authors conclude that this study demonstrates 'SST interneurons are predominantly linked to the inhibitory interneuron pathology in the OFC in schizophrenia and that increased death receptor signaling mRNAs relate to prominent laminar deficits in SST mRNA in the OFC in schizophrenia' [158–160].

ZNF804A (zinc-finger protein 804A), a strong candidate gene for schizophrenia, is required for normal progenitor proliferation and neuronal migration. The only in vivo endophenotype study of the schizophrenia-associated SNP (rs1344706) suggests a role in functional connectivity. The SNP rs1344706 (A/C), a SNP within ZNF804A, was the first SNP that reached genome-wide significance for schizophrenia, and recent studies have linked rs1344706 to functional connectivity amongst specific brain regions. The effect of rs1344706 genotype on a measure of visuomotor performance speed was examined and, controlling for white matter volumes these same subjects, showed reduced grey matter volumes in several regions comprising the 'default mode network', including the angular gyrus, parahippocampal gyrus, posterior cingulate, medial orbitofrontal gyrus and gyrus rectus. The risk

allele dosage also predicted impairments on a timed visuomotor performance task. In a large cohort study, 230 individuals were genotyped for the rs1344706 SNP and underwent DTI, resulting in statistically significant reductions in fractional anisotropy across a widely distributed brain network, positively associated both with a diagnosis of schizophrenia and with the homozygous presence of the ZNF804A rs1344706 risk variant (A). Furthermore, amongst healthy subjects, risk allele homozygotes showed larger total white volumes than carriers of the other allele, and even amongst healthy individuals, rs1344706 impacted on activity and connectivity on cognitive networks including the dlPFC (see [161] for further elaboration) and that rs1344706 risk allele dose positively predicted increased frontal-temporo-parietal connectivity, suggesting the risk variant in ZNF804A is implicated in both psychosis and theory of mind [113, 161–165].

4.7 Superior, Medial and Inferior Frontal Gyri

The superior frontal gyrus (SFG) is located on the superior part of the frontal lobe and contains multiple cytoarchitecturally distinct sub-regions including Brodmann areas 6, 8, 9 and 32 and containing the supplementary motor system and a part of the promotor cortex [166, 167]. The SFG is found immediately posterior to the PFC on the dorsal surface of the frontal lobe and has been implicated in cognitive roles such as self-awareness [168]. Parcellation schemes of the human SFG and the connection patterns of each subregion remain unclear. The SFG consists of multiple dissociable subregions that have distinct connection patterns. These include the anteromedial part connecting to the anterior and mid-cingulate cortices and part of the default mode network. The dorsolateral part connects within the frontal lobe to the middle and inferior frontal gyri, which are involved in the cognitive execution network. And the posterior part projects caudally within the frontal lobe to the precentral gyrus and subcortically with the caudate, thalamus, and frontal operculum, which are nodes of the motor control network [169].

As part of the Human Connectome Project, Tract examination of the SFG from ten healthy adult subjects as a whole based on its connectivity with other regions, followed by ten cadaveric dissections, were then performed to delineate the location of major tracts integrated within the SFG. This identified four major SFG connections: the frontal aslant tract connecting to the inferior frontal gyrus; the inferior fronto-occipital fasciculus connecting to the cuneus, lingual gyrus and superior parietal lobule; the cingulum connecting to the precuneus and parahippocampal gyrus/uncus; and a callosal fibre bundle connecting the SFG bilaterally [170, 171].

Medial PFC function has a key role in adaptive decision-making. The PFC region receives a broad range of sensory and limbic inputs causing appropriate representations of goals or task rules. Active maintenance of these goals provide a ‘top-down’ signal which influences stimulus-response processing in other areas of the brain. Additionally, the medial PFC guides decision-making by anticipating emotional outcomes and enacting them [172–177]. The MFG lies immediately below the SFG, running from the posterolateral part of the PFC to the motor cortex, and has been

implicated in the control of cognition, nociception, emotional processing and some motor function. The anatomy of the MFG has been broken down into functional sub-regions based on morphology [178, 179], functional connectivity as part of the 'default-network' [180] and structural connections [181–183]. Whilst meta-analysis of fMRI examination reveals a complex structure composing of over 30 functional regions of the MFG, there appear to be three distinct function zones. The anterior part appears to be strongly associated with social cognition, decision-making, affect and episodic memory [184–186]. The medial part is linked more with nociception and control [187–189], although this should be taken cautiously from a neuropathology standpoint as fMRI studies often include the anterior cingulate cortex in this functional region for analysis [178]. The posterior part was found to have roles in both supplementary motor cortex and further nocioceptive processing, with the processing of pain strongly linked from the posterior MFG in relay to the thalamus [171, 190, 191].

The IFG is the most inferior of the three longitudinally orientated frontal gyri. It is implicated in a variety of tasks including language processing, speech production, motor control, interoceptive awareness, and semantic processing, with the triangular and opercular gyral regions of the IFG form Broca's area, a critical region in the formation of language. The position of these structures is shown from an external view in Fig. 4.1 and in coronal cut in Fig. 4.15.

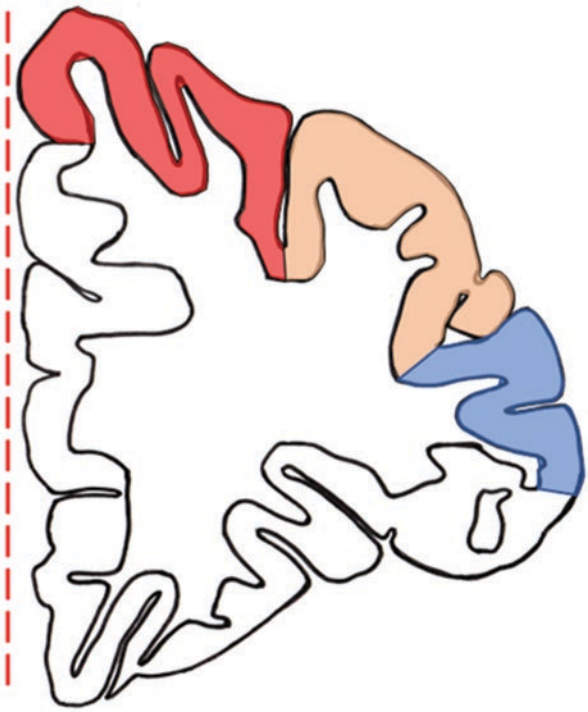

Fig. 4.15 Location of superior (red), medial (orange) and inferior (blue) frontal gyri in coronal section of the anterior part of the pre-genual frontal lobe. The dotted red line indicated the midline of the brain

Four major connections of the IFG have been proposed. These are a white matter bundle rising dorsally to connect to the superior frontal gyrus; the superior longitudinal fasciculus connecting to the inferior parietal lobule, lateral occipital area, posterior temporal areas and the temporal pole; the inferior fronto-occipital fasciculus connecting to the cuneus and lingual gyrus; and the uncinate fasciculus connecting to the temporal pole. Bilateral IFGs are also connected via callosal fibre bundle [192].

Structural imaging has been performed in twin studies examining frontal gyri. A comparison between 26 schizophrenia–unaffected twins and 40 control–control twins showed that grey matter volume was reduced in the MFG and IFG of individuals with schizophrenia relative to controls, with IFG volume also reduced in the unaffected siblings of those with schizophrenia, with cortical grey matter volume intermediate between their affected siblings and controls, possibly suggesting that the IFG is more susceptible to familial risk [193]. Recent meta-analysis of 14 VBM and nine MRI cortical thickness studies suggests that the most prominent grey matter volume finding is decreased bilateral superior frontal gyrus volume in schizophrenia [155]. This has been linked directly to symptomatology, with schizophrenia patients exhibiting significantly decreased white matter volumes of the STG and ITG, with the white matter volume of the STG negatively correlated with the duration of illness [153, 194].

A significant decrease in total cortical thickness has been observed bilaterally across the lateral surface of the frontal lobe in schizophrenia with specific pyramidal layer thinning in layers III and V in the SFG, MFG and IFG, consistent with model E as described in Fig. 4.6 [16], in contrast to earlier examination showing changes in overall cortical thickness, neuronal density or neuronal somal size change [195]. Whilst one study has reported no overall SFG glial change, decreased oligodendrocytes in the SFG grey and white matter in schizophrenia have been reported [196, 197].

Whilst one study has reported no overall SFG glial change, decreased oligodendrocytes in the SFG grey matter in schizophrenia has been reported [196, 197]. The laminar distribution pattern of calbindin-immunoreactive local circuit neurons in Brodmann area 46 is similar in both schizophrenic and control subjects, but the density of calbindin-labelled neurons was 50–70% greater in schizophrenic subjects compared with control subjects, with cortical layers III and V/VI being preferentially affected. This finding is consistent with the findings of shrinkage in layers III and V with a corresponding increase in neuron density in the pyramidal layers [57]. Myoinositol is particularly abundant in astrocytes where it has a key role in regulating in vivo cholinergic activity. Myoinositol is reported to be decreased in schizophrenia in the MFG, suggesting a potential pathway for the disfunction of astrocyte-mediated synaptic transmission [198].

Meta-analysis of 19 studies comprised of data from 557 patients and 584 controls using voxel-based analysis of resting-state regional rCBF to be tightly coupled to resting cerebral glucose metabolism in healthy brains. In schizophrenia patients, discordance between metabolism and perfusion was observed in the SFG, indicating that factors contributing to neurovascular uncoupling (such as inflammation, mitochondrial dysfunction or oxidative stress) likely occur in the SFG, with specific studies suggesting this may have a right hemisphere bias, as well as possible involvement of the IFG [80].

4.8 Motor Cortex

The motor cortex is the posterior-most part of the frontal lobe, found on the anterior side of the central sulcus and running in an arch from the most lateral and posterior part of the frontal lobe immediately above the lateral sulcus between the hemispheres.

The motor cortex consists of several anatomical structures that are all involved in movement. These include the posterior parietal cortex, the premotor cortex, the supplementary motor area and the primary motor cortex. Neurons in primary motor cortex, supplementary motor area and premotor cortex give rise to the descending fibres of the corticospinal tract, the only direct pathway from the cortex to the spine.

The motor region has not received much attention in schizophrenia research. A large fMRI study of 85 schizophrenia patients and 86 fMRI reported no significant differences in BOLD signal in the motor cortex between subjects with schizophrenia and controls [199], but higher resting-state motor cortex functional connectivity in schizophrenia has been linked to changes in decreased fractional anisotropy in connecting parts of the corona radiata [200].

One study has shown decreased neuron density in motor cortex in layer III of the motor cortex in schizophrenia, a possible key finding due to the diagnostic relevance motor changes in the illness could have. This study reported no changes in neuron size, glial density or neuron-to-glia ratio [29]. Other investigations have shown no significant differences in motor cortex volume, neuron density or in the variability of neuronal axis orientation identified in the primary motor cortex in schizophrenia [201].

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Temporal Cortex

5

Matthew Williams

5.1 Temporal Lobe Anatomy

In contrast to the other major lobes, which essentially form a continuous body running anterior to posterior forming the outer surface of the main part of the brain, the temporal lobes lie lateral and ventral. Whilst separated on the lateral surface from the frontal lobe by the lateral fissure, also known as the Sylvian fissure or lateral sulcus, the temporal lobe is continuous with the parietal and occipital lobes at its posterior end. This continuous structure is consistent with integrated sensory functions between these lobes in the overlapping regions, discussed in Chap. 8.

The temporal lobe is characterised by several distinct cortical gyri running in an anterior-posterior alignment (shown in Fig. 5.1), as well as containing the amygdala and hippocampus in the medial part (shown in Fig. 5.2), two structures very familiar to any neuroanatomy student (described in Chap. 6).

The superior temporal gyrus (STG) is the most dorsal gyrus within the temporal lobe, bordering on the lateral fissure which separates the ventrolateral part of the frontal lobe from the dorsal part of the temporal lobe. It contains the primary auditory cortex, located in the transverse temporal gyri crossing the top of the temporal lobe in the wall of the lateral fissure, as well as the auditory association cortex and the lateralised Wernicke's area on the left side. The medial temporal gyrus (MTG) lies immediately below the STG, bounded above by the superior temporal sulcus and below by the inferior temporal sulcus, whilst the inferior temporal gyrus (ITG) lies immediately below the MTG, marking the most ventral part of the temporal lobe.

The parahippocampal gyrus is immediately adjacent to the hippocampus. The entorhinal cortex occupies the anterior part of the parahippocampal gyrus where the

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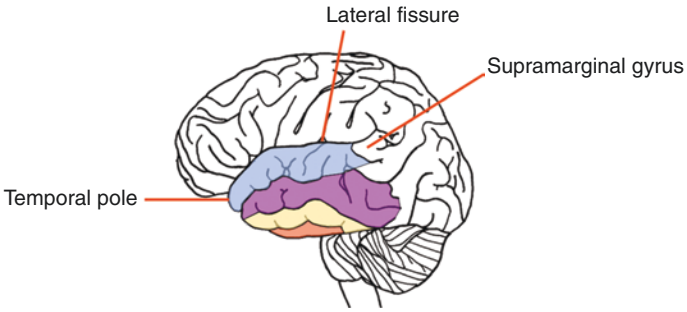

Fig. 5.1 The temporal lobe observed from the sagittal view. From this perspective, the dorsal-most structure is the superior temporal gyrus (blue), with the middle temporal gyrus (purple) and Inferior Temporal Gyrus (yellow) ventral to it. In some cases, the fusiform gyrus (orange), which runs along the ventral surface of the temporal lobe, can be observed in part from the sagittal viewpoint

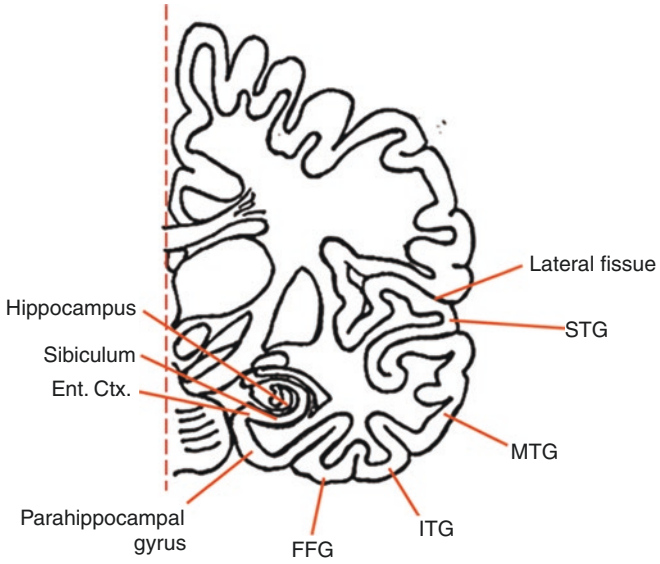

Fig. 5.2 A coronal cut through temporal lobe at the level of the hippocampus. *Ent. Ctx.* entorhinal cortex, *STG* superior temporal gyrus, *MTG* medial temporal gyrus, *ITG* inferior temporal gyrus, *FFG* fusiform gyrus. The lateral fissure is also known as the Sylvian fissure

majority of cortical afferents gather before entering the hippocampus (described in Chap. 6).

The fusiform gyrus (FFG), also known as the occipitotemporal gyrus, runs posteriorly along the inferior surface of the temporal lobe to the ventral occipital lobe. It is ventromedial to the IFG and lateral to the parahippocampal gyrus.

Research in the temporal cortex in schizophrenia has mostly been focused on the STG, due to the presence of the auditory cortex and its potential role in

hallucinations, and the FFG due to reported disfunction in facial recognition and processing. This investigation has yielded intriguing results but has been hampered somewhat but the terminology and organisation of structural and functional anatomy of the temporal lobe. As Van Hoesen describes it 'an example of neurojargon rich in clinical and behavioural meaning, but sparse in neuroanatomical meaning' [1].

Six major association fibre tracts have been identified in temporal lobe function; the uncinate fasciculus, the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus, the middle longitudinal fasciculus, the arcuate fasciculus and the two main interhemispheric commissural fibre bundles corpus callosum and anterior commissure, described in more detail in Chaps. 8 and 11. The human connectome project has suggested a model of four temporal regions based on functional connectivity [2, 3]:

1. The lateral region for semantic processing, superior temporal sulcus, temporal area 1, temporal area 2, anterior and superior temporal gyrus region A.
2. The temporal pole region for emotional processing and other functions, including uncinate connected areas dorsal temporal gyrus and ventral temporal gyrus.
3. The inferior region for visual processing, including inferior lateral fasciculus connected areas.
4. The medial region for memory and visuospatial processing, hippocampus and cingulate system.

However, neuropathological and imaging studies in psychiatric research are organised more by anatomy than by connectivity, at least for the present. The temporal cortex can be divided through the familiar Brodmann areas or by the anatomical distinctions of STG, MTG and the ITG as well as the fusiform, parahippocampal and entorhinal gyri.

At least three anatomical entities qualify as components of the medial temporal lobe. These include the amygdaloid body, the hippocampal formation and the parahippocampal cortices that cover them superficially and are visible on the external surface of the hemisphere. For the greater part of this century, topographical observations, dissection and descriptive data from passive staining methods have formed the principal source of information about the anatomy of the medial temporal lobe. However, in the past two decades, much new information has emerged from experimental neuroanatomical studies in nonhuman primates and from neuropathological studies in humans [1]. The temporal lobe has been thought to have three functionally distinct areas which have minimal interconnections within the lobe, but extensive connections with other parts of the brain, for some time. In this model, the STG contains primary and association auditory areas, the inferotemporal cortex is exclusively a visual association area, and the temporal pole is involved in social behaviour [4].

The temporal neocortical afferent connections to the amygdala have been studied in detail in the rhesus monkey using silver impregnation and autoradiographic tracing methods. A large topographically organised projection to the amygdala was

found to originate from the anterior ITG, MTG and STG and the medial and lateral aspects of the temporal pole and terminating in discrete adjacent regions of the lateral and basal amygdaloid nuclei. The temporal pole projection terminates in the ventral two thirds of the medial one half of the lateral nucleus and in the accessory basal nucleus, the anterior STG projection terminates in the ventral two thirds of the lateral one half of the lateral nucleus, and the anterior ITG/MTG projection terminates in the dorsal parts of the lateral and lateral basal nuclei [5].

The ventral processing pathway has input into the temporal lobe, originating in the striate cortex (V1), and courses through the occipitotemporal cortex (V4) to its anterior temporal target, which then projects into the memory-related areas of the MTG, perirhinal and posterior parahippocampal cortices and from these to the entorhinal cortex [6–9].

The temporal pole area projects densely to the entorhinal cortex and the posterior parahippocampal cortex [2, 10]. Unilateral retrograde horseradish peroxidase injections into multiple diencephalic targets in primate species reveal that the ITG and STG contain a considerable number of labelled cells. A substantial projection arose from the orbitofrontal and the frontopolar cortex, in contrast to the cingulate gyrus containing only very few labelled cells, which the authors conclude that the temporopolar cortex constitutes a cortical area necessary for effective affectional-sensory integration. Interhemispherically, corticocortical connections arose mainly from temporal lobe areas, suggesting a strong connection between the left and right ITG and STG structures [11].

Functionally, the parahippocampal cortex shows stronger connectivity with unimodal and polymodal association cortices, with connections to core nodes of the default mode network. There seems to be little effect of lateralisation on parahippocampal gyrus connective function [12].

Ten healthy adult control human brains analysed by GQI tractography and gross dissection demonstrated connections to the occipital lobe from the FFG, along with longer association fibres that run the length of the FFG gyrus, an important connection given the FFG's role in facial recognition and analysis [13].

5.2 Temporal Lobe Changes in Schizophrenia

Temporal lobe structures and their projections have been suspected to have a key role in the pathophysiology of psychosis since the late nineteenth century. Since lecture in Dorpat in 1887 and his last two papers published in 1919–1920, Kraepelin hoped for a 'natural classification' of psychiatric illness but realised that the level of etiologic knowledge required was not feasible in his lifetime. Therefore, he developed a pragmatic approach based on his clinical method of careful description with detailed follow-up, along with pathological anatomy and later on with genetics and biochemistry [14–17]. The famous findings of ventricular enlargement in schizophrenia have even been suggested to be due to primary changes in the temporal lobe [18].

There have been many structural imaging studies describing the temporal lobe in schizophrenia. Volumetric MRI study reviews suggest reductions in the temporal

lobe overall (~8%), which is composed disproportionately by grey matter shrinkage [19–22]. Schizophrenia patients exhibit widespread cortical thinning predominantly in the temporal regions compared with healthy subjects, a finding which is partially found in schizotypal disorder, which has significantly reduced cortical thickness in the left fusiform and parahippocampal gyri compared with controls. Where both disorders affected similar areas, the evidence suggests that schizophrenia patients had thinner grey matter cortices than those with schizotypal disorder. Recent higher-resolution research has reinforced this finding, with reported overall cortical thinning in the temporal lobe [23]. Further linked with differences within the schizophrenia syndrome, a recent review consisted of 12 studies with 470 patients and 155 healthy controls. Qualitative analyses showed a lower temporal lobe volume in violent vs. non-violent people with schizophrenia [24].

Cortical surface contraction was observed in the schizophrenia group, predominantly in temporoparietal regions. Patients with schizophrenia also exhibited significantly stronger covariance between the right rostral MFG and the right STG than control subjects. Direct comparisons between high and low theory of mind subgroups, where theory of mind is defined as the ability to attribute mental states to ourselves and others, revealed stronger contralateral frontotemporal covariances in the low theory of mind group [25].

In contrast to findings in the frontal lobe, neuropathological analysis of the thickness of the cortical layers in temporal lobe gyri shows no change in overall thickness or by specific layer in schizophrenia [26]. This appears to be contradictory to previous findings, as the structural MRI findings in the frontal lobe were confirmed by neuropathological study of cortical layer thickness, whereas similar temporal findings were not. This could be explained by the location of sampling though, as the majority of temporal grey matter loss is in the anterodorsal part of the lobe, whereas the sections were cut more posteriorly (see Fig. 5.3). Neuron density in

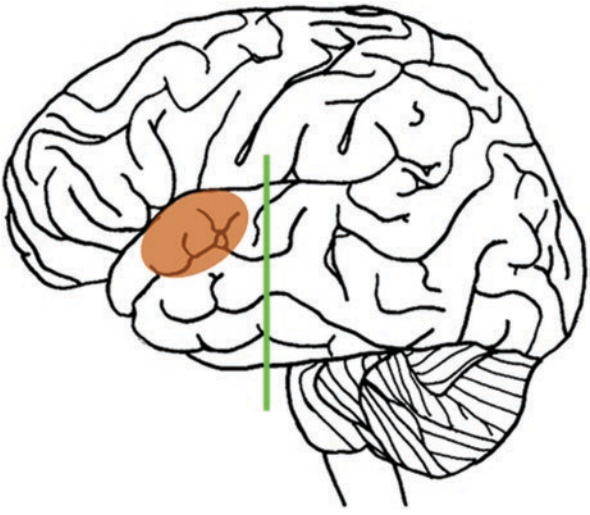

Fig. 5.3 Sagittal view illustrating a possible explanation for a lack of observed neuropathological cortical layer shrinkage in the temporal lobe in schizophrenia. The brown region roughly describes the reported areas of grey matter loss according to the structural imaging studies, whilst the green line indicates the sectioning level of measured slides [26]

overall temporal cortex increased in schizophrenia, consistent with a model of grey matter shrinkage without overall neuronal loss [19, 27].

As discussed in Chap. 3, schizophrenic patients overall exhibit abnormal brain asymmetry. Left temporal lobe parenchymal volume reduction and CSF volume increase have been correlated with the severity of negative symptoms, a finding that meta-analysis revealed to be abnormal temporal lobe asymmetry only, whilst right frontal lobe volume reduction correlated with the duration of illness, independent of symptom severity or schizophrenic subtype [28]. The Sylvian fissure separating the lateroventral part of the frontal lobe from the dorsal region of the temporal is known to be one of the most asymmetric structures of the human brain. Sylvian fissure length measurement in post-mortem brains of 35 schizophrenic patients and 33 matched control subjects showed a significantly reduced length of the left Sylvian fissure compared to the control subjects, whilst the right Sylvian fissure length was unchanged. Sylvian fissure asymmetry was more reduced in male schizophrenics (−24%) than in female patients (−16%) [29]. In a similar manner, recent complex cortical surface analysis reveals that surface contraction was observed in the schizophrenia group, predominantly in temporoparietal regions. Patients with schizophrenia have also been reported to exhibit significantly stronger covariance between the right rostral MFG and the right STG than control subjects [25].

5.3 Superior, Medial and Inferior Temporal Gyri

The STG has been described as the 'most consistently altered neocortical structure in schizophrenia' [30], so it is no surprise that several studies have reported changes here.

Although one MRI examination has reported no STG volume change in schizophrenia [31], the majority of such studies has suggested decreased volume. This has been linked specifically to certain symptoms, which Harrison [19] described as 'One of the few reasonably robust correlations' is that between decreased STG size and the severity of thought disorder and auditory hallucinations [19, 32–35]. This volume decrease has been shown particularly strongly bilaterally in the lateral part of the STG, but does not come with any change in gyrification [36]. Child-onset schizophrenia patients displayed significant enlargement of the right posterior STG showing white matter increases bilaterally in this region. [37]. The total and grey matter volume of the right STG is significantly lower in patients with early-onset schizophrenia than in the healthy volunteers after differences in whole brain volume were controlled. Bilateral STG volumes were positively correlated with the age at onset of psychosis, whilst severity of thought disorder and hallucinations were inversely related to right STG volume [38]. Other lateral findings include reports of the severity of auditory hallucinations in schizophrenia cases to be significantly correlated with volume loss in the left STG and left supramarginal gyrus, possibly demonstrating a pattern of distributed structural abnormalities specific for auditory hallucinations and hallucination-specific alterations [39]. The grey matter volumes of the STG were negatively correlated with the positive scales on the Positive and

Negative Syndrome Scale (PANSS), and those of the STG were negatively correlated with the negative scales. The durations of illness in schizophrenia were negatively correlated with the grey matter volumes of the STG. The white matter volumes of the STG were negatively correlated with the duration of illness [40].

Post-mortem measurements of total cortical thickness, cortical layer thickness and total neuronal numerical density in the posterior STG have been reported unchanged in schizophrenia, although as shown in Fig. 5.3 this may be a result of location of sampling [26, 41, 42].

Neuropathological examination of the STG from 40 adolescents with recent-onset schizophrenia and an equal number of matched controls with symptoms rated by PANSS showed patients had a significantly smaller left anterior STG and that the volume of this region negatively correlated with the severity of hallucinations. The left posterior STG was not significantly smaller in patients than in controls, but its volume negatively correlated with severity of thought disorder, and also that the left anterior STG was smaller than the right STG in patients but not in controls [43].

In interpreting the evidence, it has been suggested that progressive processes in the STG may precede the first expression of florid psychosis [44, 45]. The laterality of findings shows consistency between imaging and post-mortem studies, overall suggesting a similar situation as observed in the amygdala (discussed in Chap. 6) where a repeated anatomical change may directly indicate the cause of specific symptoms.

In situ hybridization studies have shown GAP-43 mRNA was decreased in the MTG, primary visual cortex and anterior cingulate gyrus in schizophrenia, but was unaltered in the STG in a sample of 11 normal subjects and 11 matched subjects with schizophrenia [46]. Significant GAD-ir neuropil reduction was also detected in the right STG layer V of paranoid versus residual schizophrenia cases ($P = 0.042$). GAD-ir neuropil density correlated positively with antipsychotic dosage, particularly in CA1 (right: $r = 0.850$, $P = 0.004$; left: $r = 0.800$, $P = 0.010$). Our finding of decreased relative density of GAD-ir neuropil suggests hypofunction of the GABAergic system, particularly in hippocampal CA1 field and STG layer V of patients with paranoid schizophrenia. The finding that antipsychotic medication seems to counterbalance GABAergic hypofunction in schizophrenia patients suggests the possibility of exploring new treatment avenues which target this system [47].

Glutamic acid decarboxylase (GAD) is a key enzyme in GABA synthesis, catalysing the synthesis of GABA from GLU in the presence of co-enzyme pyridoxal 5′-phosphate (illustrated in Chap. 4), and alterations in GABAergic neurotransmission have been suggested to play a crucial role in the pathophysiology of schizophrenia. Studies of GAD65/67 immunostained-histological sections are evaluated by quantitative densitometric analysis of GAD-immunoreactive neuropil in 16 schizophrenia patient samples (ten paranoid and six residual schizophrenia cases) compared with those from 16 matched controls. Overall, schizophrenia patients showed a lower GAD-ir neuropil density, and GAD-ir neuropil reduction was also detected in the right STG layer V of paranoid versus residual schizophrenia cases. Additionally, GAD-ir neuropil density correlated positively with antipsychotic

dosage. Although the n size of this study is on the low size, the discrimination of the schizophrenia clinical subtypes and relationship to drug dosage is a powerful finding. Previous reports of decreased relative density of GAD-ir neuropil suggests hypofunction of the GABAergic system, and the finding that antipsychotic medication seems to counterbalance GABAergic hypofunction in schizophrenia patients could suggest a possible route by which to explore new treatments. This also suggests that the STG itself may be a particularly affected and diagnostically critical region in schizophrenia [48].

Relative to healthy subjects, patients with chronic schizophrenia have shown grey matter volume reductions in the left MTG (13% difference) and bilateral ITG (10% difference in both hemispheres). The severity of hallucinations was significantly correlated with smaller left hemisphere volumes in the STG and MTG [49]. This is in contrast to earlier MRI quantification showing the volume of MTG grey and white matter was unchanged in schizophrenia [48]. Two assessments of schizophrenia patients and their unaffected siblings by VBM showed there were significant grey matter volumetric differences in schizophrenia in the MTG. In the first, bilateral MTG and STG comparison with healthy volunteers demonstrated that unaffected siblings of schizophrenia patients had significantly lower MTG volumes compared to healthy individuals only in the left MTG, and volume of this region was not different between siblings and patients. Similar results were reported in the second study, except the decreased MTG grey matter was only in the left hemisphere [50, 51].

Post-mortem research has suggested significantly lower numbers of NADPH-d neurons in the MTG grey matter but significantly greater numbers of NADPH-d neurons in MTG white matter. The distorted distribution of NADPH-d neurons in the MTG, which may be explained by disorders in neurodevelopmental such as impaired neuronal migration or an alteration in the death cycle of transitory subcortical neurons, is similar to that found in the prefrontal cortex (discussed in Chap. 4) [52]. Post-mortem samples obtained from 25 schizophrenic brains and 31 non-schizophrenic controls showed decreased levels of SNAP-25 schizophrenics in the ITG [53]. And consistent with reports in the entorhinal cortex, GABA-B receptor protein is decreased in the pyramidal cells of layer V in the ITG in schizophrenia [54].

5.4 Fusiform Gyrus

The FFG lies on the ventral surface of the temporal lobe, running from the anterior part of the temporal lobe until the occipital lobe. It encompasses Brodmann's areas 19, 20 and 37 and has connections with striate and pre-striate visual areas and projects to language-related regions including Wernicke's area in the lateral and superior region of the temporal lobe [55]. Functional imaging has suggested that it may be split into three subdivisions arranged anterior-posterior with different connections in each [56].

The FFG is most well-known for its role in facial recognition. PET studies have shown activation of the FFG in a variety of face perception tasks [57, 58] and fMRI reveals fusiform regions that responds more strongly to faces than non-face images such as letter strings and textures, flowers, houses and hands [59–61]. Although face-specific fMRI activation can also be seen in the superior temporal sulcus and in part of the occipital lobe (termed the occipital face area), the most robust face-selective activation is consistently found on the lateral side of the mid-FFG, now termed the fusiform face area, and more strongly in the right hemisphere than the left [59]. The fusiform face area shows increased blood flow in response to a wide variety of stimuli such as front and profile photographs of faces, line drawings of faces and also animal faces ([62–64], and for binocularly rivalrous stimuli where a face is presented to one eye and a nonface presented to the other, the fusiform face area responds more strongly when subjects perceive a face than not ([65–67].

That there are abnormalities in facial processing in schizophrenia is virtually beyond doubt by now. Multiple studies have identified facial processing abnormalities in schizophrenia, particularly analysis of threat-relevant emotional primes of angry, neutral and happy faces patients where schizophrenia patients have shown normative implicit threat processing for both non-emotional and emotional facial cues, as well as worse performance in object naming compared with the normal population, with fMRI investigation revealing bidirectional communication between the amygdala and fusiform gyrus during facial recognition processing [68–82].

Volumetric imaging studies find reduced volume of the fusiform gyrus in schizophrenia [83]. Patients with first-episode schizophrenia have been reported to have overall smaller relative absolute volumes of fusiform gyrus grey matter compared with controls (9%) and patients with affective psychosis (7%). There does seem to be a small effect of lateralisation of fusiform gyrus size. In the left fusiform gyrus, patients with schizophrenia have shown an 11% reduction compared with controls and patients with affective psychosis, whereas right fusiform gyrus volume is decreased in schizophrenia compared with controls by around 8%. Also the volume of the right fusiform gyrus, consistent with the right inferior temporal gyrus and right inferior occipital gyrus, negatively correlated with the duration of illness and positively correlated with onset age across all patients with chronic schizophrenia, and the extent of facial memory deficit in schizophrenia has been correlated with the degree of volume reduction of the anterior fusiform gyrus [84]. Whilst not reported consistently some investigations have shown sex difference with respect to age at onset where the degree of asymmetry for both gyri increased with age at onset in men but not in women [44, 85, 86]. Neuropathological examination of formalin-fixed brains from 27 control subjects against 31 patients with schizophrenia showed left-greater-than-right volume asymmetry was present in the comparison subjects, but that this asymmetry was reversed in the fusiform gyri of the schizophrenic patients [55].

Face recognition neurons in the inferior temporal region of the monkey cortex are clustered in functional columns that extend across the cellular layers in a mosaic arrangement approximately 400 μm in diameter [87]. Structurally they consist of

groups of smaller mini-columns that emerge from the migration of cells towards the brain's surface during embryonic formation of the cerebral cortex, implicating the development of neuron arrangement as a key issue in facial recognition. Two key neuropathological studies in schizophrenia have examined changes in cortical mini-columns in the FFG. In human, neuropathological investigation of FFG mini-column spacing in 11 schizophrenia cases against 13 matched controls showed mini-columns are asymmetrically wider in the right hemisphere of control subjects, whilst mini-columns are less dense in schizophrenia, particularly in the left hemisphere of females and the right hemisphere of males. Wider mini-column spacing is consistent with reduced cell density and is linked to altered ageing in schizophrenia [88]. The second study examined the morphologic characteristics of subicular dendrites in subjects with schizophrenia using the rapid Golgi impregnation of archival brain specimens on samples from schizophrenia ($n = 13$) and mood disorders ($n = 6$) against control cases ($n = 8$). Spine density on apical dendrites of the subicular pyramidal cells determined at a fixed distance from the cell body was significantly lower in the schizophrenia and mood disorder groups than in the control group. Amongst the mood disorder cases but not in the schizophrenia cohort, diminished spine density was apparently related to a strong family history of major psychiatric diseases. This is consistent with neuropathological examination of glial cells in the cingulate cortex (discussed in Chap. 7). There are no significant effects of diagnosis on non-apical subicular dendrites nor on the dendrites of neocortical pyramidal cells in the FFG [89–91].

Pyramidal cell density was reduced in schizophrenia, whilst on-pyramidal cell density was reduced in layer III of the left hemisphere in schizophrenia and were larger in the schizophrenia cohort. Glial cell density was unaltered across diagnostic groups [88]. The pyramidal layers are of particular interest as they are the major pyramidal cell layers involved in intra- and inter-hemispheric connections found to be altered in schizophrenia [26, 92]. And these results are consistent with the findings across the brain suggesting decreased connectivity linked to neurodevelopmental errors.

5.5 Entorhinal and Parahippocampal Cortices

The entorhinal cortex, shown in Figs. 5.4 and 5.5, is anatomically consistent with the parahippocampal gyrus and is the source of the majority of hippocampal input, although there is also entorhinal projection to the posterior cingulate cortex (described further in Chap. 7).

The first clear demonstration of neuropathological change in the entorhinal cortex was published in 1986 with 20 cases of schizophrenia out of 64 in the study reported to have clear disorganisation of neurons in cortical layers II and III. This disorganisation involved layer II neurons found in layer III and also not clustered regularly as reported in control cases, as well as an overall decreased number of layer III neurons in schizophrenia cases. This change in neuronal arrangement, without similar changes reported in glial cells, led the authors to state this supports

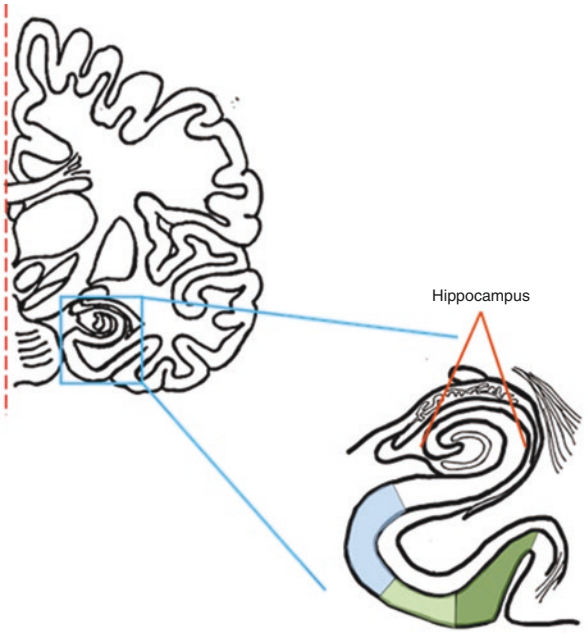

Fig. 5.4 The anatomical subdivisions of the parahippocampal gyrus and entorhinal cortex seen in coronal section. The parahippocampal gyrus is split into three main divisions. Green represents an area referred to as the parahippocampal cortex, often subdivided into medial (dark green) and lateral (pale green) parts, whilst the entorhinal region is shown in blue. Dotted red line shows the midline of the brain [93]

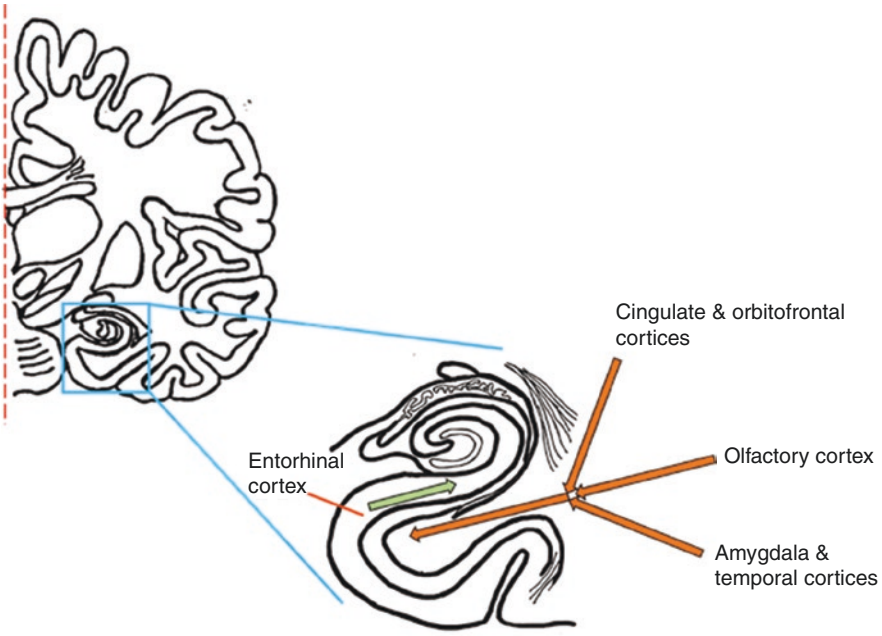

Fig. 5.5 The location and primary connections of the entorhinal cortex seen in coronal section. The inputs (orange) and hippocampal output (green) are shown. Dotted red line shows the midline of the brain

a neurodevelopmental issue desiring the specific period of development in which laminar arrangement occurs. A parallel study also reported a smaller volume of the entorhinal cortex in schizophrenia, without glial changes between diagnostic groups [94, 95].

Later studies to determine whether schizophrenia is associated with abnormalities in neuronal migration in the entorhinal cortex using Nissl-stained sections through three cytoarchitectonic subdivisions of the entorhinal cortex in post-mortem brain specimens in two groups, from 10/31 schizophrenic subjects and 10/45 matched normal comparison subjects, respectively, showed no qualitative differences in cytoarchitecture between the groups ([96, 97]. In contrast, other examinations of entorhinal cortex neurons using spatial point analysis, a quantitative technique used to map the relative positions of neurons, suggested statistically significant changes in distribution that may be too subtle for the naked eye to detect also in layers II and III [98]. The finding of disordered layer II neurons was replicated in another paper, although the schizophrenia *n* size was only 6 and came from postleucotomy patients, with the 16 control cases having several post-leucotomy and thalamectomy cases within them. Additionally this study showed a changed appearance in the overall shape of the entorhinal cortex, the structure having a ribbed or roughened appearance [99], which is in contrast to similar investigation showing a shooting of the primary cingulate cortex in schizophrenia (as described in Chap. 7), and also in contrast to the overall reports of cortical smoothing globally (as described Chap. 3). Structural imaging has suggested entorhinal cortical thinning and decreased folding index in schizophrenia as compared to matched controls, consistent with the broader model, and that thinning is linked to symptom severity [100, 101]. In discussion of the heterogeneity of these findings, several authors have suggested that these results are due to the natural variability within the entorhinal cortex, which shows both allocortical structure and considerable variability along the anterior–posterior axis [102], with the repeated studies showing examining neuronal organisation suggested to be effected by small *n* sizes [96, 103, 104].

A subsequent post-mortem study has reported a decrease in tyrosine-hydroxylase-expressing neurons in the entorhinal cortex in schizophrenia [105]. Tyrosine hydroxylase is the rate-limiting enzyme of catecholamine biosynthesis catalysing the synthesis of dihydroxyphenylalanine, commonly known as DOPA, from tyrosine, and has been found to be significantly increased in nigral DA-producing neurons in schizophrenia [106–109], suggesting a neuropathological marker of decreased connectivity in this structure. In a possible functionally similar findings, GABAB-receptor protein has been found to be decreased in the pyramidal cells of the entorhinal cortex and layer V pyramidal cells in the inferior temporal cortex of post-mortem brains in schizophrenia [54].

DTI examination of the parahippocampal gyrus demonstrates connectivity between the parahippocampal gyrus and the anterior temporal lobe, orbitofrontal areas, posterior temporal lobe and extrastriate occipital lobe via the lingual and fusiform gyri as well as direct connectivity between the parahippocampal gyrus and the hippocampus itself, consistent with previous histological tract-tracing studies in

animals [110]. The parahippocampal gyrus receives input from heteromodal association areas of the cortex and gives rise to the perforant path that projects to the hippocampus and thereby transmits information into the limbic circuit.

In relation to the comparison subjects, schizophrenic patients had lower parahippocampal gyral volume of the left side. Interestingly, a sex difference was reported with regard to age at onset and degree of parahippocampal asymmetry, which increased with age at onset in men but not in women, adding substance to the view that the sex-related dimension of symmetry/asymmetry [55]. Reductions in volume and cortical thickness of the parahippocampal gyrus have been shown in post-mortem studies [111–116] although there have also been negative reports [55]. A particularly large post-mortem study conducted in the 1980s examined the brains of 232 patients with diagnosed of schizophrenia or affective disorder over a collection period of period of 22 years. These were assessed in coronal section at the level of the interventricular foramen and showed significantly thinner parahippocampal cortices in schizophrenia but not affective disorders [113].

Given the critical role the parahippocampal and entorhinal cortices play in the perforant pathway into the hippocampus and the significant findings of early studies, it is likely time for more detailed investigation of these structures using modern techniques.

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The Amygdala, Hippocampus, Fornix and Nucleus Basalis

6

Matthew Williams

6.1 Amygdala Structural Anatomy

The amygdala is an almond-shaped structure in the anterior part of the medial temporal lobe, superior and anterior to the temporal horn of the lateral ventricle, adjacent to tail of the caudate nucleus and anterior to the hippocampus (shown in Fig. 6.1). The amygdala is not a single mass but is comprised of up to 12 subnuclei [1, 2] which often merge with the adjacent non-amygdala structures or have further subdivisions [3]. The subnuclei are further compartmentalised into regions. The main regions are the basolateral region consisting of the basal, lateral and accessory basal nuclei and the corticomedial region comprising of the cortical, medial and central nuclei. The basolateral region is proximal to the lateral ventricle and the entorhinal cortex and is considered the deeper nuclear group whilst the more superficial corticomedial group is in the part of the amygdala immediately below the striatum (shown in Fig. 6.2).

Cytoarchitecture differs between species and despite substantial conservation of functional anatomy within mammals, it is difficult to establish clear homologies for subdivisions, especially with differing nomenclature used between research groups [3, 4]. Amygdala subnuclei are typically identified by the histology of stained cell density, configuration, shape and size and the paths of fibres. The basolateral amygdala (BLA) has spiny pyramidal-like neurons and spine-sparse stellate cells, thus resembling the nearby entorhinal cortex. Neurons in the central nucleus of the corticomedial group (CMA) resemble the medium-sized spiny neurons of the adjacent striatum rather than the oval neurons dominating the CMA [3].

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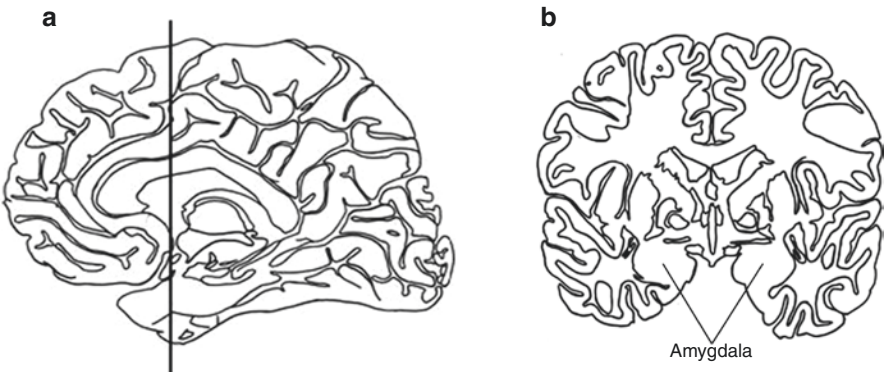

Fig. 6.1 (**a**) Sagittal view showing anatomical position of amygdala denoted by the vertical line. The amygdala lies in the anterior part of the temporal lobe, anterior to the hippocampus and is superior and anterior to the temporal horn of the lateral ventricle. (**b**) Coronal cut at the level of the amygdala illustrating the location of the bilateral nuclei in the medial region of the temporal lobe

6.2 Functional Anatomy of the Amygdala

Amygdala is a part of the limbic system and is thought to play an important role in the generation and recognition of emotion assigning emotional and motivational valence to sensory stimuli, processing of representation of the disposition and intentionality of others and affect control [2, 5]. It has been implicated in emotional blunting in animal models via classical conditioning [6] and dysfunction of this structure has been discussed previously as a potential mediator and cause of the emotional processing abnormalities observed in patients with schizophrenia [7, 8]. The two units most implicated in the control of emotional processes are the basolateral nucleus and the central nucleus of the CMA. The BLA is an evolutionarily newer division of the amygdala, associated with the neocortex [1, 9]. It is associated with Pavlovian learning and influences complex behaviour due to its connections with prefrontal cortex and ventral striatum. The CMA regulates parts of the brainstem and influences behavioural, autonomic and neuroendocrine responses via projections to the hypothalamus and midbrain and the reticular formation. The predominant projections to and from the amygdala are shown in Figs. 6.3 and 6.4.

The networks of γ-aminobutyric acid-ergic (GABAergic) interneurons in the amygdala are key inhibitory circuits [20]. This critical neurotransmitter is necessary for keeping a balance between neuronal excitation and inhibition [21]. The BLA contains both glutamatergic principal neurons and GABAergic interneurons [22]. The glutamatergic neurons are firmly regulated by a comparatively small population of GABAergic inhibitory neurons. Destruction of GABAergic inhibition in the BLA can cause behavioural hyperexcitability, such as increased anxiety, depression and emotional dysregulation [23]. The CMA serves as a major output nucleus of the amygdala by converging inputs from the BLA [24]. In contrast with the BLA, the CMA is only composed of GABAergic neurons [25].

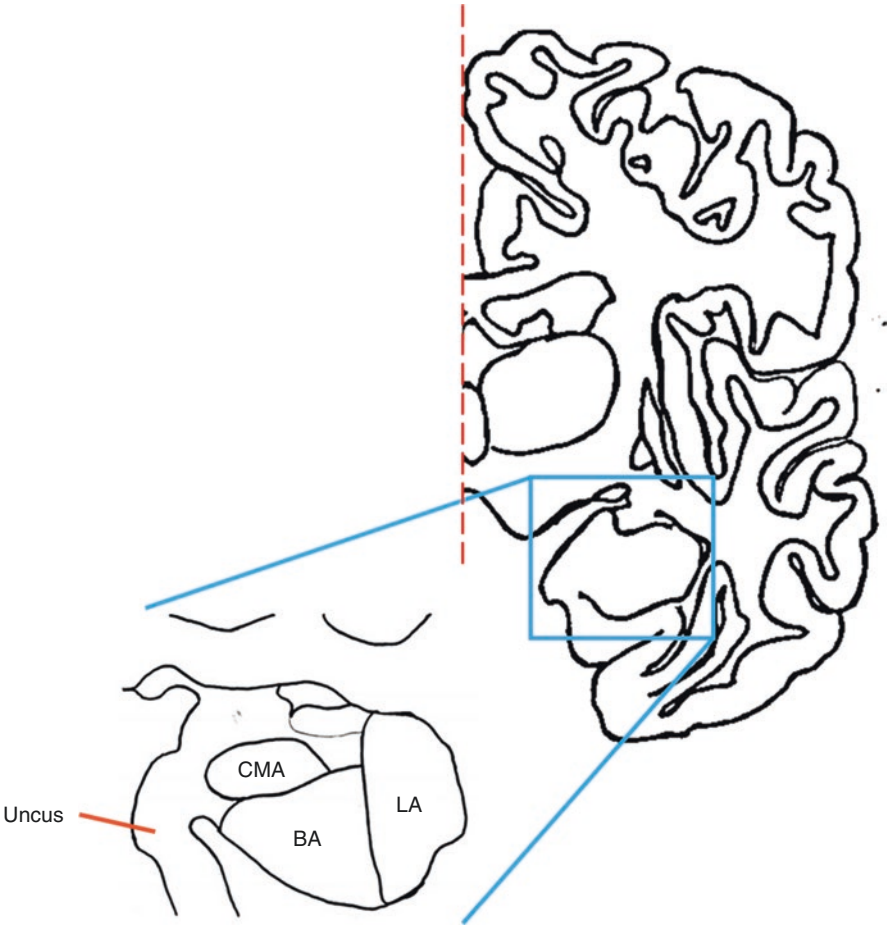

Fig. 6.2 Coronal section through the amygdala. *LA* lateral amygdala, *BA* basal amygdala, LA and BA together form the functional grouping of the basolateral amygdala (BLA), *CMA* corticomedial amygdala

The nuclei receiving afferents are predominantly those in the BLA, the primary sensory input region of the amygdala, receiving inputs for auditory, somatosensory, olfactory and taste [1, 3, 26]. Afferents are easier to understand if they are split into subcortical and cortical domains. Subcortical inputs are from the midline thalamic nuclei, the subiculum, the CA1 region of the hippocampus, the hypothalamus and substantia innominata, the nucleus of the solitary tract, olfactory structures, parabrachial and thalamic projections that transmit nociceptive information to the amygdala.

The amygdala receives sensory inputs from the overlying temporal/auditory cortex, secondary taste cortex via the orbitofrontal cortex, somatosensory cortex via the insula and the posterior orbitofrontal cortex [3]. Corticoamygdala projections give

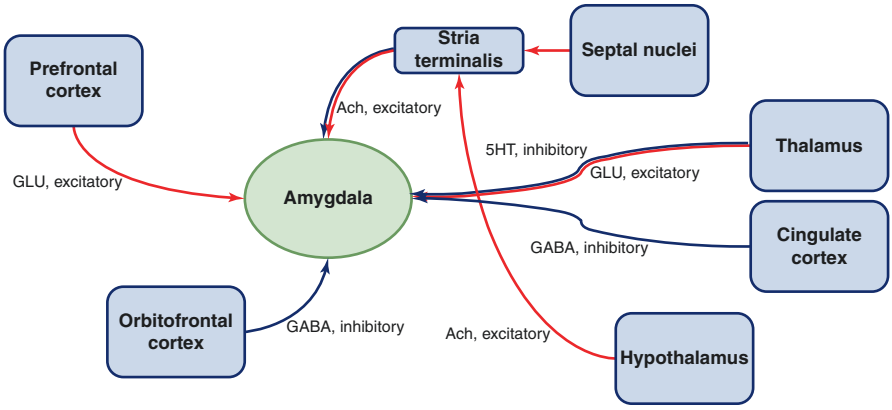

Fig. 6.3 Dominant afferents to the amygdala. Connection from the septal nuclei are composed of GABA and GLU fibres. Thalamic projections to the amygdala, mostly relays from cortical inputs, are 5HT-mediated GLU fibres. Direct projection from prefrontal, cingulate and orbitofrontal cortical areas are composed primarily of GLU and GABA fibres. *Ach* acetylcholine, *GABA* gamma(γ)-amino-butyric acid, *5HT* serotonin, *GLU* glutamate. *Blue* inhibitory fibre, *red* excitatory fibre [10–16]

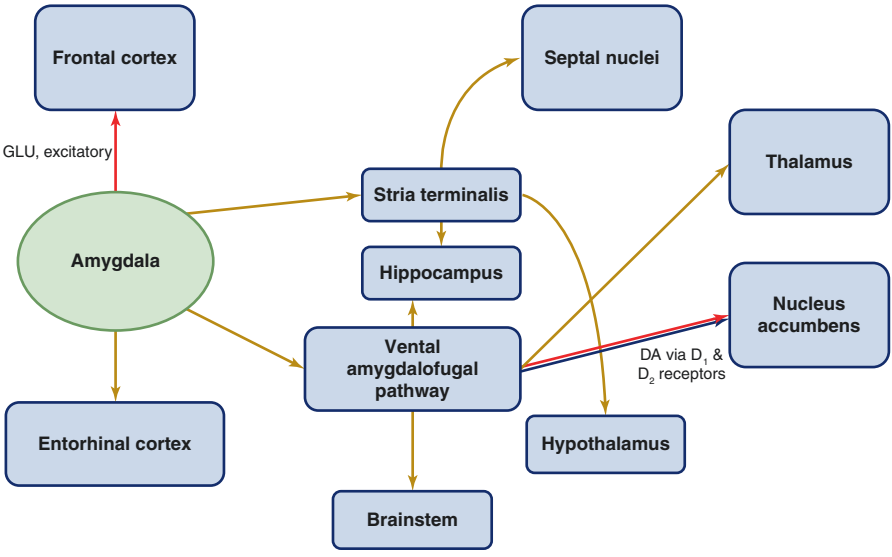

Fig. 6.4 The two major efferent pathways from the amygdala are through the stria terminalis and the amygdalofugal pathway. Dopaminergic projection from the amygdala to the nucleus accumbens terminates in both excitatory D_1 and inhibitory D_2 synapses, suggesting a complex regulatory process. *5HT* serotonin, *GLU* glutamate. *Blue* inhibitory fibre, *red* excitatory fibre, *brown* no clear dominant neurotransmitter type reported or agreement between species [11, 17–19]

sensory stimuli emotional and motivational significance and are also involved in arousal and attention. Cortical inputs from the auditory and other sensory systems arise from the association areas, rather than from the primary cortical regions, and all sensory association areas have direct access to the BLA. These areas are also linked to the prefrontal cortex through long association fibre bundles which means that all conscious sensations are subject to cognitive evaluation. Cortical areas provide the amygdala with a more elaborate representation than could come from the thalamic, subcortical inputs.

Subcortically a particular efferent of relevance projects from the amygdala, through the stria-terminalis to the ventral tegmentum area (VTA). It is sometimes referred to as the 'extended amygdala' and is implicated the regulation of anxiety states in rodent models [13]. The GABA-mediated hypothalamic-stria-terminalis amygdala pathway, in conjunction with input from the nucleus accumbens, has been suggested to be a component of schizophrenia, particularly with relevance to psychosis in the disorder [27].

The BLA projects to the central nucleus of the CMA, the main output site of the amygdala, from which there are two major efferent pathways: the stria terminalis and the ventral amygdalofugal pathway. The stria terminalis emerges from the CMA and the follows the curve of the caudate nucleus, accompanying the thalamostriatal vein along the upper surface of the thalamus and projects to the septal area and the hypothalamus and on to the medial forebrain bundle. Some fibres of the stria terminalis terminate in a bed nucleus above the anterior commissure, sometimes suggested as an extension of the amygdala. The second efferent pathway is the ventral amygdalofugal pathway which projects medially meeting the lateral hypothalamus and the basal ganglia, particularly the nucleus accumbens and the head of the caudate.

A frequent feature observed in schizophrenia is emotional dysfunction [28, 29]. The reduction of emotional perception and expression during increased subjective emotional arousal and reactivity has reported in schizophrenia [7], with positive psychotic symptoms reported in association with lesions and atrophy of the amygdala in epilepsy as well as schizophrenia [30, 31], implicating this structure and the wider limbic system in the symptomatology of this disorder.

6.3 Amygdala Neuropathology in Schizophrenia

The neuropathology of the amygdala has had little attention in schizophrenia. Early studies used Nissl staining to examine neuron numbers in the BLA [32], and somatostatin and neuropeptide-Y-like immunoreactivity in various amygdala subnuclei, both studies reporting no significant changes in schizophrenia compared with controls [33].

But more recent studies have reported a total mean neuron decrease in the BLA and amygdala neuron number in schizophrenia but no change in neuron density [34, 35]. Whereas morphology measures of neuron length, nuclear area and nucleolar

volume in BLA and CMA nuclei in age-matched cases of schizophrenia against control cases showed decreased nuclear and nucleolar size in schizophrenia, also in the BLA only [36]. Functional amygdala changes are implicated in the illness as well, with peri-neuronal nets reduced in the BLA [37]. The BLA has been reported to be smaller with decreased total neurons in schizophrenia, although one study found this effect was not significant when medication was taken into account, possibly indicating an effect of antipsychotics [35], a common factor in other studies [5, 38, 39].

Similar alterations are seen in the few papers looking at amygdala glial cells. In schizophrenia, there has been reported, GFAP-reactive astrocyte density was unchanged in contrast to an increase of an order of magnitude of chondroitin sulphate proteoglycan-positive glial cells across the amygdala nuclei. Chondroitin sulphate proteoglycans are expressed across the CNS during development and modulating synaptic connections in adulthood, and their presence acts to inhibit regeneration, preventing repairs to damage in the brain (reviewed in [40]). Consistent with similar findings in the entorhinal cortex, these findings specific to schizophrenia as similar bipolar disorder cases did not show the effect in either structure [37]. The authors suggest that changes in these functionally relevant molecules in schizophrenia point to a pivotal role for extracellular matrix–glial interactions in the disorder pathogenesis and may be involved in the neurological disturbance of neuronal migration, synaptic connectivity and neurotransmission. Oligodendrocyte densities were increased in the schizophrenic BLA with no corresponding change in the CMA [41].

Detailed examination of serial myelin-stained sections has shown the amygdala, hippocampal formation, and parahippocampal gyrus was significantly smaller in the schizophrenic group. [42]. In schizophrenia, stereological analysis revealed a decreased volume in both the lateral and basal nuclei of the amygdala leading to an overall reduction in total amygdala volume [34, 35]. In contrast to the general understanding that structural imaging reveals a decrease in amygdala volume of up to 10% in schizophrenia, post-mortem studies have suggested no overall change [43, 44], with three post-mortem studies examining total amygdala size showing no change in SZ [5, 32, 44].

6.4 Input from Imaging Studies

Whilst neuropathological studies have been performed in schizophrenia, the majority of findings are from imaging sciences (reviewed in [43]). Quantitative imaging of the amygdala and hippocampus in schizophrenia began in the early 1990s with a range of studies over the following decade producing results showing either no volumetric decrease or a trend of decreased size of both the amygdala-hippocampal complex (AHC) and the temporal lobe in general in schizophrenia, with decreased volumes of structure and hemisphere reported to be related to negative or positive symptomatology [45–50]. A key early meta-analysis of 18 MRI studies examining the AHC concluded that ‘Future quantitative magnetic resonance imaging studies evaluating the hippocampal volume should measure the hippocampus and

amygdala separately and compare the volumetric reduction in these structures to that observed in other grey matter areas' [51]. Patients diagnosed with schizophrenia presented significantly lower amygdaloid volumes bilaterally, with significant correlations reported between the amygdaloid volumes and either the duration of the disease or the symptom severity [38].

A more recent review of 49 structural MRI, 27 DTI and 18 resting-state functional MRI studies shows researchers have evidence for reduced left, right and total amygdala volumes in schizophrenia relative to controls even when restricted to cases in the early stage of illness. Apart from volume, amygdala morphometry studies show heterogeneous amygdala deformity in schizophrenia [52]. The AHC has been reported to be smaller in schizophrenia patients over time in longitudinal studies, with differences between diagnostic groups constant over the same period [53, 54]. Particularly interesting is the MRI data showing decreased amygdala grey matter in the left temporal lobe in not only schizophrenia patients but also their parents, with a weaker but significant changes in the pattern in amygdala connectivity described by fMRI also observed between parent and offspring [55].

The constant findings between amygdala size and shape in schizophrenia, changes present before or early in SZ onset and shared with first-degree relatives certainly suggest a key role for this limbic structure in both the onset and development of pathophysiology in schizophrenia.

As discussed above, amygdala dysfunction may contribute to affective symptoms observed in schizophrenia. Functional imaging has demonstrated increased amygdala activity when shown both neutral and fearful faces [56]. Functional imaging studies show that patients with schizophrenia have significant empathetic deficit with amygdala hypofunction correlating with the severity of negative symptoms [57].

This now appears to be a fundamental change in schizophrenia as well as in first-degree relatives. The Edinburgh High-Risk Study of initially healthy adolescents with at least two affected relatives has found that AHC volumes are reduced premorbidly but not to schizophrenic levels, suggesting that further volume reductions may be associated with the onset of schizophrenia. AHC volumes appear to be genetically mediated in families with a dominant pattern of transmission, whereas FL and basal ganglia volumes are more generally related to individual genetic burden in schizophrenia high-risk subjects [58–61].

Whilst the amygdala has not been studied in as much detail as other CNS structures, there does seem to be a remarkably clear trend for BLA disruption in schizophrenia, with the CMA largely unaffected. Given the clear division of the roles of the BLA and CMA in amygdala [34], this could describe a process where sensory and emotional inputs to the amygdala are disrupted with outputs relatively unaffected, possibly describing a clear step-change in the disrupted network. Consistency of this nature suggests this structure should be a key focus of greater examination. Of course, additional studies may introduce the heterogeneity of results so common in the field. But with the rare situation of a clear neuropathological distinction, this structure likely deserves further research.

6.5 Hippocampus Structural Anatomy

The hippocampus is a lateralised structure on the medial surface of the temporal lobe, beginning immediately posterior to the amygdala and projecting caudally and superiorly into the fornix. It is a double-curved sheet of three-layered cortex containing three distinct regions, the dentate gyrus, the hippocampus proper (or corpus ammonis, CA, split into four sections CA1–4) and the subiculum, with the subiculum acting as a transition region between the CA and the parahippocampal gyrus. The hippocampus proper is also split into four CA fields, strips which continue longitudinally through the structure. Due to its anatomy, it is often the first structure students learn to recognise thanks to the distinctive double-c arrangement, composed of the CA region and dentate gyrus, that composes the hippocampal body when cut coronally (Fig. 6.5).

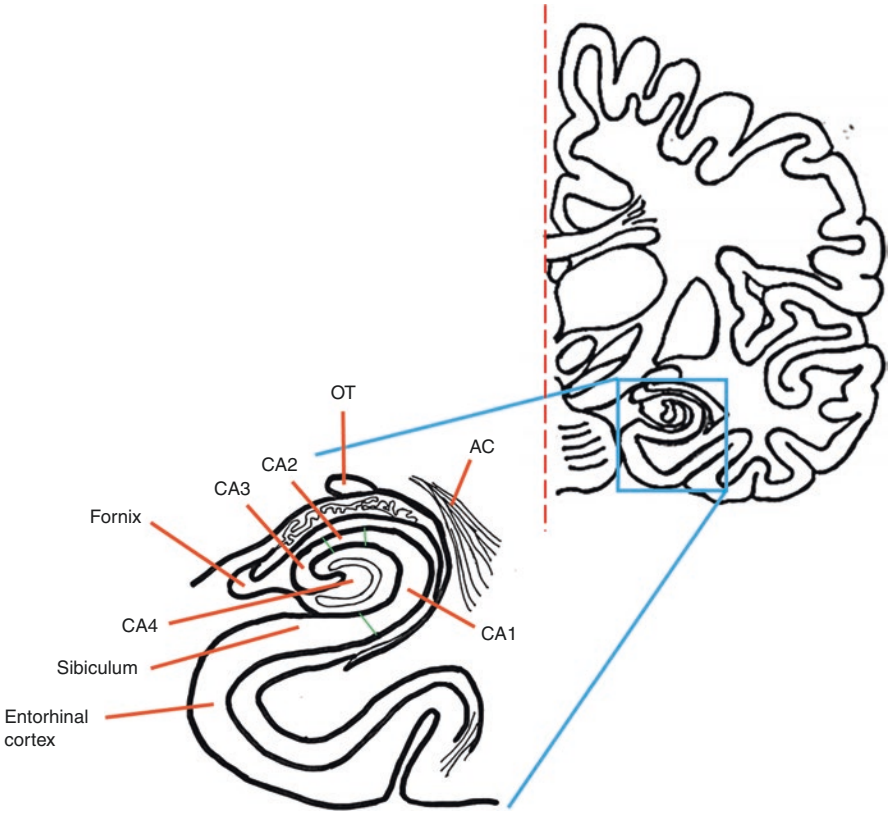

Fig. 6.5 Coronal cut at the level of the hippocampus with expanded diagram showing the hippocampal internal structure outlined in blue. Whilst some hippocampal efferents arise from pyramidal neurons within the hippocampus itself, the majority arise from the subiculum. *CA* cornus ammonis, *AC* anterior commissure, *OT* optic tract, *IC* internal capsule. Dotted red line indicates midline of brain

Most of what we call cortex in humans is actually neocortex, referring to the fact that it is found quite recently in vertebrate evolution. Modern reptiles have a three-layered paleocortex (or paleopallidum) and archicortex (or archipallidum). Whilst almost all of the cerebral cortex in humans is neocortex, this evolutionary process has left its mark in the human brain in the olfactory or piriform cortex and the hippocampus, both retaining their older three-layered structure in an example of evolutionary conservation over time.

The hippocampus is characterised by pyramidal neurons arranged in the familiar three-layered structure described by CA1–4 and the dentate gyrus. These are known as the principle cells and are primarily glutamatergic. However, there are also non-primary neurons throughout the structure. These are non-pyramidal and are mainly GABAergic cells, known as hippocampal interneurons, and are subdivided based on protein colocalisation with parvalbumin, calbindin and calretin differentially throughout these cell layers.

6.6 Hippocampus Functional Anatomy

The hippocampus is one of the most well-known structures in neuroanatomy, often the first one students learn to recognise due to its distinctive shape. It could be said that the major organisational pathway is of fibres from the entorhinal cortex projecting into the hippocampus with the main output pathway being the fornix. Whilst this is roughly true the reality, as always, is more complicated. The dominant information pathway through the hippocampus is from the entorhinal cortex passing into the dentate gyrus, itself is composed of pyramidal neurons which generate axons for connection within the hippocampus only, projecting through CA2–3 to CA1 then into the subiculum, which in turn neurons project to the neocortex directly or into the fornix. The subiculum is the zone of transition between the pyramidal layers of the hippocampus proper and the parahippocampal gyrus and as such changes from the three-layered allocortical organisation to the six-layered neocortical structure. The main afferent and efferents of the hippocampus are shown in Figs. 6.6 and 6.7.

6.7 The Hippocampus in Schizophrenia

Post-mortem examination of the hippocampal formation size in schizophrenia was first focused on in 1986, where study of 13 schizophrenia cases and 11 controls belonging from the Vogt collection showed that the volume of the whole hippocampal formation, the whole pyramidal band, the hippocampal segments CA1–CA2, CA3 and CA4 were decreased, with no significant volume reduction of the alveus and fimbria hippocampi and subiculum [62]. A repeat study by the same group again demonstrated decreased hippocampal volume soon after [63]. Within a decade, two meta-analyses containing 18 imaging studies with a total patient number of 522 and a total control number of 426 had confirmed this finding. The first meta-analysis suggested a mean bilateral volume reduction of 4%, whereas the

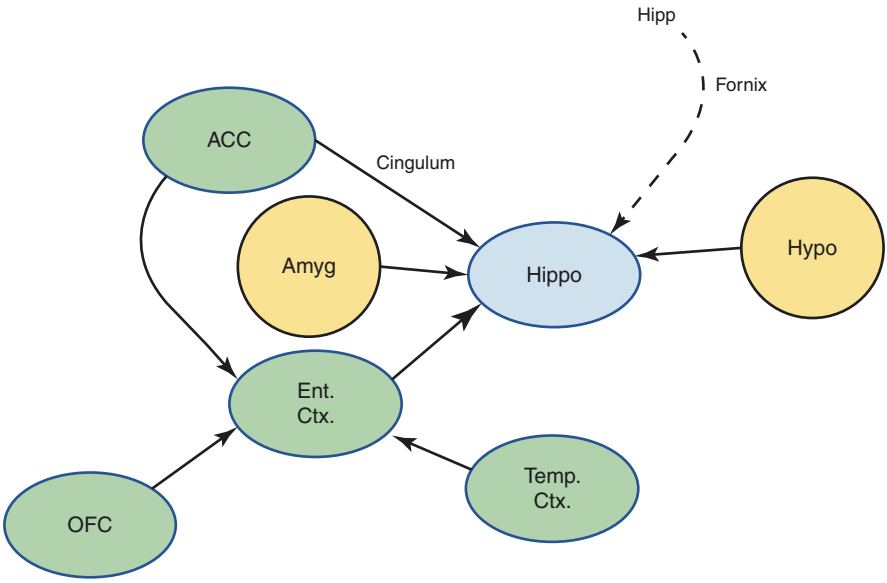

Fig. 6.6 Main afferent connections to the hippocampus (Hipp). Dashed line indicates reciprocal connections from contralateral hippocampus via the fornix. The majority of connections come from the entorhinal cortex (Ent. Ctx.). *ACC* anterior cingulate cortex, *Amyg* amygdala, *OFC* orbitofrontal cortex, *Hypo* hypothalamus, *Temp. Ctx.* temporal cortex

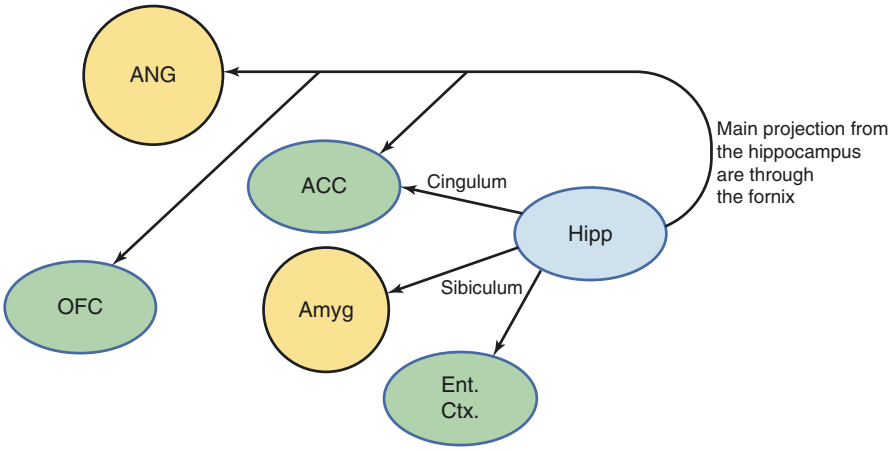

Fig. 6.7 Main efferent connections from the hippocampus (Hipp). *Ent. Ctx.* entorhinal cortex, *ACC* anterior cingulate cortex, *Amyg* amygdala, *OFC* orbitofrontal cortex, *ANG* anterior nuclear group of the thalamus

second meta-analysis indicated that the inclusion of the amygdala in the region of interest significantly increased effect sizes across studies but that the mean volume reduction of the hippocampus in schizophrenia was closer to 2%. No laterality differences were observed in these data [51]. An overall decrease in hippocampal

volume has been reported in schizophrenia using high-resolution structural MRI [64], although no similar change was found in comprehensive post-mortem examination. However, there may be a loss of hemispheric change similar to that seen with brain torque, as discussed previously, and these conflicting results have been implicated to be sex-related, possibly complicating interpretation of these findings [65].

Quantitative imaging of the amygdala and hippocampus in schizophrenia began in earnest in the early 1990s with a range of studies over the following decade producing results showing either no volumetric decrease or a trend of decreased size of both the amygdala-hippocampal complex and the temporal lobe in general in schizophrenia, with decreased volumes of structure and hemisphere reported to be related to negative or positive symptomatology [45–50].

More recently, this has been confirmed by structural MRI examination showing that patients with first-episode psychosis had significantly reduced whole hippocampus volume, as well as of CA1, CA4, granule cell layer, subiculum and presubiculum subfields. Smaller whole hippocampal volume, as well as CA1, molecular layer, subiculum, presubiculum and hippocampal tail volumes were significantly associated with a longer patient untreated period [66], possibly suggesting that hippocampal volume reduction is progressive.

An early study investigating the anterior and middle hippocampal regions demonstrated that cell disarray is most pronounced at the CA1–prosubiculum and CA1–CA2 interfaces [67], a finding which has been credited for originating the neurodevelopmental hypothesis of schizophrenia and supported by cytoarchitectural abnormalities suggested changes in early neuronal migration in layer II of the entorhinal and cingulate cortices (see Chaps. 5 and 7; [68, 69]). However, whilst neuropathological examination into the hippocampus has been quite detailed since it has suffered from the heterogeneity of results so typical of the field. Multiple studies, particularly in the earlier years of neuropathological study, have reported no change in hippocampal neuron density [70, 71].

Multiple studies have reported no change in the number of pyramidal neurons or organisational disarray across CA2–4 for the controls, and schizophrenic cases have suggested extensive neuronal disarray at the CA1–prosubiculum and CA1–CA2 boundary. In CA1, the schizophrenia cases had a significant reduction of pyramidal neuron numbers of up to a third, and these pyramidal neurons were smaller across CA1–4. Of particular note is the report from Falkai and Bogerts that pyramidal cell loss in CA1–4 was more distinct in the paranoid than in catatonic patients [67, 72–76]. Examination of both types of hippocampal neurons show no change in the size of pyramidal cells, whilst non-pyramidal neurons were found to be selectively reduced by approximately 40% in CA2 of the schizophrenia group [77], with smaller neurons reported in schizophrenia in other studies [72, 73, 78, 79]. The densitometry of neuron size and shape measured by microtubule-associated protein (MAP2) immunoreactivity has been reported increased in the left subiculum and left hippocampus, whereas that of MAP2 and MAP5 is decreased in one third of schizophrenia cases [80, 81], although the n sizes of these studies are small (schizophrenia groups having five or eight cases).

A repeat analysis of a previous set of samples has shown a significantly lower hippocampal cell count in schizophrenia, but more significantly reported disorientation of pyramidal cells in the CA1–3 subregions of schizophrenia samples, with a negative correlation between the total number of cells and the number of disoriented cells, consistent with previous reports of pyramidal neuron disorganisation in schizophrenia [67, 74, 82, 83].

Zaidel et al. published two post-mortem studies in 1997 examining the hippocampus. The first of these was a morphometric post-mortem study of neuronal density in sections from the dentate gyrus, CA4, CA3, CA1 and subiculum of 22 schizophrenia cases against 18 normal subjects, where neuronal density was increased in the right CA1 [78, 79]. The second examined post-mortem tissue of 17 normal individuals and 14 individuals with schizophrenia, examining size, shape and variability in orientation of pyramidal neurons in hippocampal subfields CA1–CA4 and the subiculum. Neurons of the schizophrenia cases were smaller than those of the normal subjects in the left CA1, left CA2, and right CA3 subfields, and neuronal shape differed from that of the normal subjects in the left CA1, left subiculum, and right CA3 subfields. There were no reported group differences in variability of neuronal orientation, with no statistically significant asymmetries were observed. Even these two studies show contrasting findings on neuronal size in schizophrenia, although the changes in shape are particularly interesting [78, 79].

The synapses formed between the axons of dentate granular neurons and CA3 pyramidal neurons are key connections in hippocampal circuitry, and abnormalities in these circuits have been associated with the difficulties schizophrenic patients have with disturbances in memory and spatial learning, as well as in integrating emotional experiences with cognitive processes. Schizophrenia has been characterised by reduced size and changed dendritic organisation, with decreased total number and binding potential of GLU receptors (discussed below), with detailed examination of Golgi-stained neurons revealed increased spine density in CA3 pyramidal cell apical dendrites and an increase in the number of synaptic projections of these CA3 pyramidal neurons [84, 85]. Rapid Golgi impregnation of archival brain specimens used to measure the morphologic characteristics of subicular dendrites in subjects with schizophrenia with subjects without psychiatric disease using Sholl analysis to measure the extent of dendritic trees in the subiculum and fusiform gyrus. Spine density was significantly lower in the schizophrenia than in the non-psychiatric control group, with evidence of a significant interaction with strong family history of major psychiatric diseases [86]. Whilst the causes of these specific protein and neuropathological changes is not well understood, additive effects between childhood trauma and brain-derived neurotrophic factor methionine carriers on volume loss of the hippocampal CA4, dentate gyrus and CA2–3 have been reported in schizophrenia patients [87], suggesting again neurodevelopmental and/or progressive change in the illness.

Two studies have reported a reduction in oligodendrocyte numbers in the CA4 subregion in the anterior portion of the hippocampus, although one found this only in the left CA4 [88, 89]. A more recent paper has used linear regression to examine oligodendrocytes in the posterior hippocampal subregions CA1, CA2/3, CA4, the

dentate gyrus and subiculum in the post-mortem brains of ten schizophrenia patients and 11 age- and gender-matched healthy controls. The authors report a positive relationship between hippocampal oligodendrocyte number and the volume of the hypothalamus, a brain region connected to the hippocampus, which is important for cognition [90]. These studies seem to suggest an anterior-posterior alteration in oligodendrocyte number in the schizophrenic hippocampus, but further studies need to be conducted to confirm this finding.

Astrocytes are the primary locus for the biosynthesis of glutamate from glucose. Through the tricarboxylic acid cycle, the glycolysis product pyruvate is converted into α-ketoglutarate, which is then catalysed into glutamate by aspartate aminotransferase [91]. Post-release from synaptic vesicles GLU acts as a neurotransmitter activating post-synaptic AMPA/kainite receptors to mediate fast excitatory synaptic transmission and to activate post-synaptic NMDAr's to depolarise membrane potential, allowing the influx of calcium ions. Excess synaptic GLU is cleared extremely rapidly primarily by the four types of excitatory amino-acid transporter (EAAT1–4) found in local fibrillary astrocytes (discussed in greater detail in Chap. 12; [92]).

Astrocyte numbers have not been reported to be changed in the hippocampus in schizophrenia in the same manner as oligodendrocytes [89, 93]. The use of S100β, a calcium-binding protein expressed by oligodendrocytes and astrocytes, as marker in post-mortem studies has also showed no change in S100β-immunopositive glia in the hippocampus in paranoid schizophrenia [94]. The understanding of S100β as a cell marker and as a quantifiable biomarker of cellular stress in psychiatric conditions and in more general neurological damage is still not well understood, and so caution should be taken when examining these results in schizophrenia (discussed in Chap. 4 [95]). There is some evidence for microglia change, although as the most recent review authors state, 'Further subdivision indicates that the effects were mainly found in brain areas outside the hippocampus' [96].

Altered regulation of the neuronal growth-associated membrane phosphoprotein GAP-43, found at high levels in the developing brain, has been suggested to be dysregulated in schizophrenia. In the mature human brain, GAP-43 is found at high levels primarily in association with cortices and in the hippocampus, and it has been suggested that this protein marks circuits involved in the acquisition, processing and/or storage of new information. Because these processes are known to be altered in schizophrenia, we proposed that GAP-43 levels might be altered in this disorder. Quantitative immunoblots revealed that the expression of GAP-43 is increased preferentially in the visual association and frontal cortices of schizophrenic patients and that these changes are not present in other neuropsychiatric conditions requiring similar treatments. Examination of the levels of additional markers in the brain revealed that the levels of the synaptic vesicle protein synaptophysin are reduced in the same areas, but that the abundance of the astrocytic marker of neurodegeneration, the glial fibrillary acidic protein, is unchanged. In situ hybridization histochemistry was used to show that the laminar pattern of GAP-43 expression appears unaltered in schizophrenia. We propose that schizophrenia is associated with a perturbed organisation of synaptic connections in distinct cortical associative areas of

the human brain and that increased levels of GAP-43 are one manifestation of this dysfunctional organisation [97].

These observations along with converging postsynaptic hippocampal protein changes suggest that homeostatic plasticity mechanisms might be altered in schizophrenia hippocampus. If hippocampal pattern separation is diminished due to partial dentate gyrus failure and also if pattern completion is accelerated and increasingly inaccurate due to increased CA3 associational activity, then it is conceivable that associations could be false and, especially if driven by anxiety or stress, could generate psychotic content, with the mistaken associations being laid down in memory, despite their psychotic content, especially delusions and thought disorder [98].

6.8 Glutamate in the Hippocampus

As primary hippocampal neurons are glutamatergic, the hippocampus has been investigated as part of the glutamatergic hypothesis of schizophrenia [99].

Proton magnetic resonance spectroscopy examining GLU in the left hippocampus and left hippocampus subfield volumes in 54 antipsychotic-naive cases of schizophrenia with first-episode psychosis against 41 controls suggested no significant group difference in hippocampal GLU, but that hippocampal GLU was significantly higher in patients who had remained untreated with drugs for over 12 months, compared to those with a shorter untreated period and compared to controls. However, no significant association between hippocampal GLU and hippocampal total or subfield volume [66]. The relationship between the period schizophrenia patients are untreated with drugs and clinical outcome is found across various lengths of follow-up periods according to a review of 26 studies, suggesting the untreated period influences the long-term course of the illness. [100]. A meta-analysis of 28 studies containing a total of 647 cases of schizophrenia with 608 controls examining in vivo GLU concentration in schizophrenia measured by proton magnetic resonance spectroscopy found lower GLU concentrations that progressively decreased with age in frontal brain regions, but did not find significant glutamate differences between schizophrenia and control groups in the hippocampus [101], in contrast to a more recently published study showing decreased GLU specifically in the dentate gyrus in schizophrenia [102].

Analysis of 15 publicly available tissue-expression datasets on schizophrenia and bipolar disorder, representing various brain regions from eight different cohorts of subjects (332 controls against 341 schizophrenia cases, with 129 bipolar disorder cases also included) revealed an increase in the expression profiles of cortical astrocytes and a decrease in the expression profiles of fast-spiking parvalbumin interneurons in schizophrenia [103].

The heterotetrameric NMDA-receptor (NMDAr) is widely distributed throughout most of the brain and is a critical postsynaptic mediator of activity-dependent synaptic plasticity. This receptor is composed of two obligatory GluN1 subunits with either two GluN2 subunits or a combination of GluN2 and GluN3 subunits. The GluN1 subunit is encoded by a single gene (GRIN1), which has eight different splice variants. There are four GluN2 subunits (GluN2A-D) and two GluN3

subunits (GluN3A-B) that are encoded by separate genes, GRIN2A-D and GRIN3A-B, respectively [104]. It was also noted that agonist mGluR2/3 ameliorates symptoms of psychosis in rodent models of schizophrenia [105]. Hippocampal studies have reported reduced GluN1 levels in the dentate gyrus of patients with schizophrenia using proton magnetic resonance spectroscopy and in situ hybridisation against the obligatory NMDAR1, NMDAR2a and NMDAR2b subunits in post-mortem samples, with similar trends in the CA3 region [102, 106, 107]. The GluN2B-containing NMDA receptors (GluN2B/GluN1) and their associated post-synaptic membrane protein PSD95 were both increased in schizophrenia in CA3 but not CA1 [85], whilst the number of hippocampal somatostatin-positive and parvalbumin-positive interneurons, as well as the overall hippocampal level of somatostatin, parvalbumin and glutamic acid decarboxylase mRNA were all reduced in schizophrenia [76]. Autoradiography has shown no changes in NR1 or PSD-95 in the dentate molecular layer in schizophrenia [108], and a specific loss of the mRNA that encodes a non-NMDA GLU receptor was found in hippocampal tissue obtained from six patients with schizophrenia, when compared to similar samples from eight controls, supporting suggestions of aberrant glutamatergic function in schizophrenia via changes in receptor quantity [109].

In schizophrenia, there is a decreased expression of EAAT2 in the hippocampus of post-mortem brain samples [110], although it should be noted that these were exclusively elderly patients with schizophrenia and age may have been a factor in the study.

Two synaptic-vesicle proteins, rab3a and synaptophysin, have been studied on post-mortem brain tissues in schizophrenia and healthy controls, showing significantly reduced levels of both proteins in hippocampus in the schizophrenia tissue, possibly indicating reduced synaptic density as a prominent feature of the molecular neuropathology of schizophrenia [111].

Multiple studies have reported significant associations between schizophrenia and certain haplotypes of SNPs in the gene-encoding dysbindin-1 at 6p22.3. Dysbindin-1 is best known as dystrobrevin-binding protein 1 and may thus be associated with the dystrophin glycoprotein complex in postsynaptic sites in the brain. Compared to controls, the majority of cases in two schizophrenia populations displayed presynaptic dysbindin-1 reductions of up to 42% at hippocampal formation sites lacking neuronal dystrobrevin. The reductions occurred specifically in terminal fields of intrinsic, glutamatergic afferents of the subiculum, the hippocampus proper and the inner molecular layer of the dentate gyrus. An inversely correlated increase in vesicular GLU transporter-1 occurred in inner molecular layer of the dentate gyrus of the same schizophrenia cases, occurring without axon terminal loss or neuroleptic effects on dysbindin-1 or vesicular GLU transporter-1, indicating that presynaptic dysbindin-1 reductions independent of the dystrophin glycoprotein complex occur in schizophrenia and are related to GLU alterations in hippocampal formation connections [112–114].

Ultrastructural morphometric study of synapses between hippocampal axon terminals and branched dendritic spines of pyramidal neurons of the CA3 region showed a significantly reduced volume fraction of spines, a reduced total number of invaginated spines, a reduced number of spines forming synapses per neuron in

schizophrenia. Study of hippocampal white matter using similar electron microscope techniques to examine myelinated fibres in the hippocampus in schizophrenia demonstrated atrophy of axon due to the alteration of myelin sheath [84, 115].

6.9 GABA in the Hippocampus

A suggested basis of the modified GLU transmission is increased GLU release in the hippocampus due to the dysfunction of inhibitory interneurons. Reduced activation of NMDAr's on inhibitory interneurons leads to increased release of GLU by pyramidal hippocampal neurons [116, 117], and hypofunction of NMDAr's on GABA inhibitory neurons results in a hyperactivation of GLU neurons, leading to excess GLU release and therefore to neuronal damage [118, 119].

Investigation of glutamic acid decarboxylase (GAD)-immunoreactivity, a key enzyme in GABA synthesis, by evaluation of the distribution of the 65 kDa-isoform of GAD (GAD65) has revealed potential GABA changes in schizophrenia. In one such study where the hippocampus of 12 normal controls and 13 schizophrenic subjects matched for age and post-mortem interval the results show no significant difference in the density of GAD65-immunoreactivity in sectors CA1–4 and their various sub-laminae. However, in relation to neuroleptic use, a significant positive correlation between the density of GAD65 immunoreactivity and drug dose was found on both pyramidal and non-pyramidal neurons in CA2, CA3 and CA4. The two neuroleptic-free schizophrenia cases showed the lowest density of GAD65 immunoreactivity in the study. This supports the hypothesis of an intrinsic problem with GABA-ergic activity in the hippocampal formation of schizophrenia and demonstrates dose-related increases in relation to neuroleptic exposure [120]. In a more recent study, GAD65/67-immunostained sections were assessed by quantitative densitometric analysis of GAD-immunoreactive neuropil in the hippocampal CA1 field and dentate gyrus in 16 post-mortem schizophrenia patient samples, split into two illness groups of ten paranoid and six residual schizophrenia cases, compared with those from 16 matched controls. Schizophrenia patients showed a lower GAD-immunoreactive neuropil density, more prominently in the right CA1, with the result more prominent in the paranoid diagnostic subgroup. The extent of GAD-immunoreactivity neuropil density correlated positively with antipsychotic dosage, particularly in CA1. The authors suggest that decreased relative density of GAD-immunoreactivity neuropil suggests hypofunction of the GABA-ergic system, particularly in hippocampal CA1 field with paranoid schizophrenia, and that the discovery that antipsychotic medication appears to counterbalance GABA-ergic hypofunction in schizophrenia patients suggests the possibility of exploring new treatments which target this system [121]. The levels of somatostatin, parvalbumin and GAD67 mRNA expression have been reported as being reduced in schizophrenia tissue, providing evidence for a specific defect of hippocampal interneurons with implications for models of hippocampal dysfunction [76, 122].

In the hippocampus, 25% of GABAA receptors are α5-GABAAr's [123, 124]. Comparative anatomical examination of GABAA receptor subunits α1, α2, α3, α5,

β2, β2/3 and γ2 expression in the human amygdala and hippocampus shows that in the amygdala field fraction analyses showed the highest α1 expression in the BLA whereas α5 and γ2 where prominent in the CMA and amygdalo-hippocampal and parahippocampal-amygdala areas. In the hippocampus, α1 and α3 were accentuated in the dentate gyrus, CA1 region, and subiculum, whereas α5 expression was unchanged. In both hippocampus and amygdala, α2 was homogenously distributed. The intensity of subunit expression also varied in the neuropil, neuronal somata and cellular processes in the subregions. GABAAr's containing subunit α1 showed the strong expression in the BLA and α3 pronounced expression in the subiculum [20]. In studies originally conducted for use in epilepsy research, using [^{11}C]flumazenil and [^{123}I]iomazenil to index GABA receptor levels has not found differences between schizophrenia patients and healthy controls. However, these radiotracers are not GABA subtype selective and show similar levels of uptake both in neocortex and limbic regions and therefore unable to detect differences in specific GABA receptor subtypes. In contrast, the inverse GABAA receptor agonist [^{11}C]Ro15-4513 is a radioligand that binds with greater affinity to the α5 subunit of the GABAA receptor when compared with other subunits [20, 125–132]. Investigation of the α5 GABAA receptor [^{11}C]Ro15-4513 shows reduced binding in the hippocampus was negatively correlated with negative symptom scores in patients with schizophrenia. There was also significantly lower [^{11}C]Ro15-4513 volume of distribution in the hippocampus of antipsychotic-free patients, but not in medicated patients, and a significant positive correlation between [^{11}C]Ro15-4513 volume of distribution and total PANSS score in antipsychotic-free patients. These findings suggest that antipsychotic-free patients with schizophrenia have lower α5-GABAARs levels in the hippocampus, consistent with the hypothesis that GABA hypofunction is a key factor in the pathophysiology of the disorder [133, 134]. Study of the regulation of the GABA system across the hippocampus showed down-regulation of GAD67 in CA1–3 in schizophrenia. Network generation for GAD67 contained 25 genes involved in the regulation of kainate receptors, TGF-beta and Wnt-signalling as well as transcription factors involved in cell growth and differentiation. In schizophrenia, IL-1beta, GRIK2/3, TGF-beta2, TGF-betaR1, histone deacetylase 1, death associated protein and cyclin D2 (CCND2) were all significantly up-regulated [123]. These results show a disrupted underlying network of regulation beneath the GABA changes reported in schizophrenic hippocampi, but caution must be taken in interpretation as change in causative versus compensatory mechanisms may be occurring.

In early development, the α2 and α3 subunits are highly expressed, and there appears to be an α2/α1 subunit switch in many brain regions soon after birth as the α1 subunit becomes more abundant [124, 135–138]. Altered hippocampal subunit expression has been suggested to be caused by developmental stressors affecting this subunit change throughout life, an effect that might explain different pharmacological sensitivity [139]. The α1 subunits are expressed on cell bodies and proximal dendrites of pyramidal cells whilst α2 subunits are preferentially located on cell bodies and the axon-initial segment of pyramidal cells [140]. Therefore, a more 'immature' subunit expression pattern in the brain of schizophrenia patients may predispose to altered GLU expression and pharmacological response. Given the

various sensitivities of various α subunits to GABA and GABAAr's, this altered pattern of subunit expression may well explain the disrupted pharmacology of GABAAr's in schizophrenia [141–144].

6.10 The Fornix

The fornix is a bundle of mostly efferent fibres projecting from the hippocampus. It begins as an array of fibres which collect on the ventricular surface of the hippocampus known as the alveus. These fibres then move medially to form the fimbria of the hippocampus, bundles which rise dorsally from the rear of the hippocampus, near the level of the splenium, to form the body of the fornix crus of the fornix immediately below the corpus callosum. The crura converge beneath the callosal midline, where a small proportion of fibres are exchanged with the callosum via the hippocampal commissure, to form the fornix body. This continues anteriorly and descends towards the anterior commissure, nearing which it diverges laterally once more into the columns of the fornix, also known as the anterior columns (shown in sagittal cut in Fig. 6.8). The majority of the columnar fibres

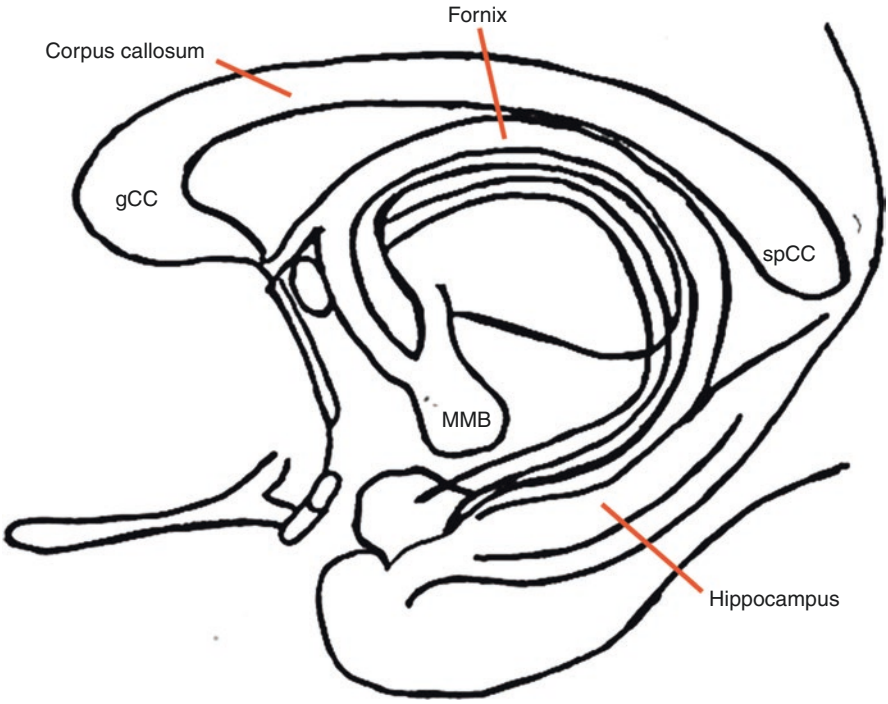

Fig. 6.8 Sagittal view of the fornix projecting from the posterior part of the hippocampus to the underside of the corpus callosum, running beneath the callosum along the midline then descending into the pre-optic region of the brain at its most anterior point. *gCC* genu of the corpus callosum, *spCC* splenium of the corpus callosum, *MMB* mamillary body

continue ventrally to the hypothalamus via the post-commissural fornix where they end in the mammillary bodies. A smaller proportion of fibres separate anterior to the anterior commissure and project through to the septal nuclei and ventral striatum via the pre-commissural fornix.

The hippocampal-fornix projection is part of the classic Papez circuit [145], suggested to have a key role in spatial and verbal memory and memory retrieval which are processes involved in schizophrenia [146, 147], and fornix body volume is a predictive factor of cognitive decline according to a longitudinal study of 102 healthy elderly patients, which was not observed in the hippocampus [148].

Structural MRI consistently shows decreased fractional anisotropy in the fornix in chronic schizophrenia [146, 149–153]. Hippocampal volume also correlates with the mean diffusivity in the fornix in patients, suggesting a structural relationship between these structures in disease that is also reported in Alzheimer's disease, epilepsy and multiple sclerosis [148, 150, 154–158]. Whilst neuropathological studies of the fornix in schizophrenia report no differences in fibre number or axonal myelin thickness when examined under high-resolution oil-immersion microscopy, they have shown increased fibre density compared with controls [159–161], possibly illustrating how anatomically unchanged axonal fibres are packed more densely in the fornix, explaining both the imaging and neuropathological findings.

6.11 The Nucleus Basalis

Whilst not typically thought of as a specifically frontal- or temporal-lobe nucleus, the nucleus basalis is a bilateral structure found on the ventral surface of the frontal lobe, immediately below the anterior commissure at the rostral-caudal level of the amygdala body (shown in Fig. 6.9). The NB contains a number of large oval neurons responsible for the manufacture of acetylcholine for transportation throughout projections from this nucleus throughout the cortex (shown in Fig. 6.10). Direct histological examination has shown larger NB oval neuron soma in schizophrenia, possibly reflecting differential quantities of acetylcholine produced in this structure. The NB has shown glial change in schizophrenia, with a significant decrease in oligodendrocyte density reported. Whilst no overall change in astrocyte density was shown in the same investigation, the ratio of gemistocytic to fibrillary astrocytes showed a decreased fibrillary astrocyte proportion in schizophrenia [162]. Given the alternative roles that astrocytes have in these two morphological states, discussed in Chap. 12, these results imply a change in astrocytic function and neuronal interaction beyond simply changes in cell number or density.

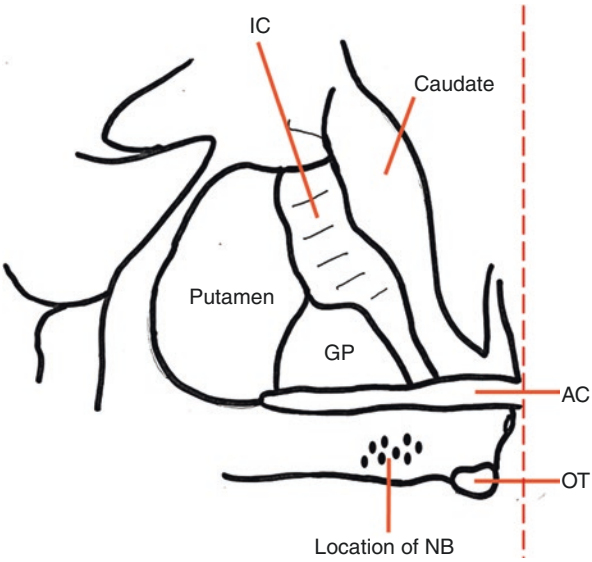

Fig. 6.9 Location of the nucleus basalis (NB). Image shows the location of the distinctive large oval neurons of the NB in coronal section at the level of the amygdala. The NB is found at the ventral surface of the brain, below the anterior commissure (AC) and close to the optic tract (OT). *IC* internal capsule, *GP* globus pallidus. Dotted red line shows the midline of the brain

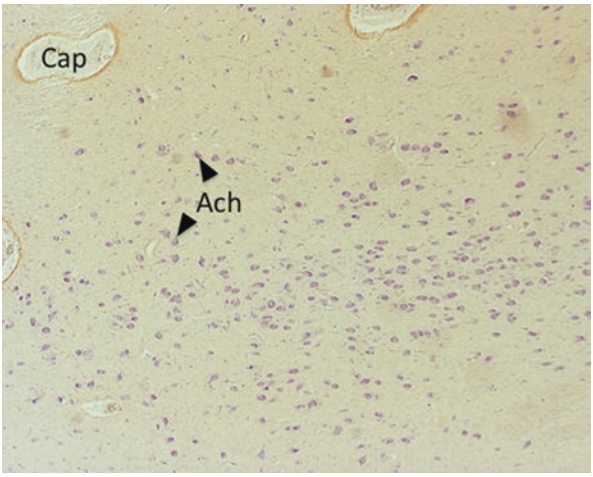

Fig. 6.10 Coronal section of haematoxylin-stained nucleus basalis, characterised by large oval neurons. The nucleus can be seen to have a dense band of oval neurons through the centre, with a more diffuse distribution of these neurons around. *Ach* acetylcholine-producing large oval neuron, *Cap* capillary

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The Cingulate Cortex

7

Matthew Williams

7.1 Structure and Organisation

The cingulate cortex has been of particular interest in schizophrenia research. Not fitting neatly into the four-lobe organisation of the brain, the primary cingulate gyrus instead runs along the outer surface of the corpus callosum. The cingulate cortex is present on the medial side or inner side of the cerebral cortex, consisting of cingulate gyrus and its continuation into the cingulate sulcus, lying immediately above the corpus callosum on the medial surface of the brain, starting next to the subgenual Brodmann area 25 it follows the callosal genu before running posterior along the dorsal callosal surface until it reaches the splenium where again it folds underneath the posterior end of the callosum before terminating adjacent to the retrosplenial area. Whilst structurally consistently a single structure, the primary cingulate cortex functionally changes along its length. Most of the investigations in schizophrenia research have been in the anterior part of the cingulate cortex due to the anterior cingulate role in the limbic loop. Although bilaterally similar in shape and size, neuropathological examination of 40 control brains has revealed some structural asymmetry with double sulcus more common of the left side [1].

Functionally this cortical structure also has considerable variation across different regions, despite having no clear segregation in its organisation in structure [2–6]. Whilst there is still some debate about what structures make up the cingulate cortex, particularly as there appears to be inconsistency between humans, other primates and rodents, the primary regions are generally agreed upon to be the anterior cingulate cortex (ACC, Brodmann areas 24 and 33), the posterior cingulate cortex (PCC, Brodmann area 25) and the retrosplenial region (Brodmann areas 26, 29 and 30), shown in sagittal cut in Fig. 7.1. In addition, Brodmann areas 25 (located ventral to area 24 in the subgenual region) and area 32 (following the outer surface of

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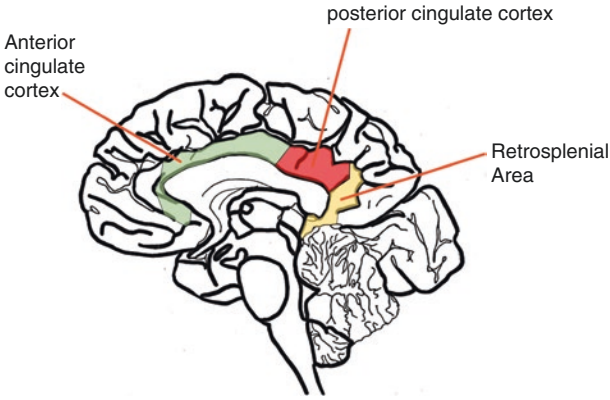

Fig. 7.1 Cingulate cortex shown in sagittal section. The main region of the cingulate cortex. The green area is the anterior cingulate cortex (Brodmann areas 24 and 33), the red area shows the posterior ventral cingulate cortex (Brodmann areas 23 and 31) and the yellow area is the retrosplenial region (Brodmann areas 26, 29 and 30)

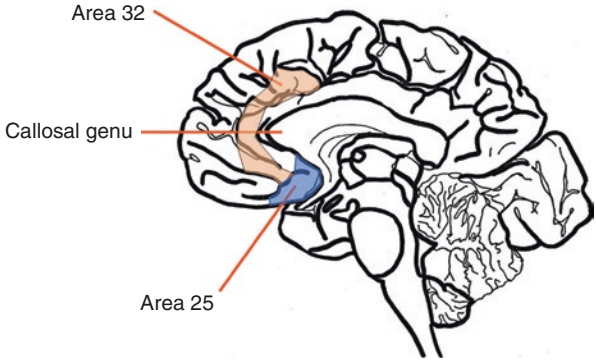

Fig. 7.2 Brodmann areas 25 (blue) and 32 (orange) shown relative to the callosal genu in sagittal section near the midline

area 24 on the anterior part) are often included as part of the 'greater cingulate' (shown in Fig. 7.2).

Regional specialisation within the cingulate has been studied for over a century. Brodmann first defined the anterior and posterior cingulate cortex even though these subregions are heterogeneous in cytoarchitecture, neural pathways and task-related activations. More recently, Vogt established the widely accepted four-region model on the basis of integrated neurobiological version [7, 8].

The cingulate cortex has been shown to have a diverse collection of functional roles, involved in a considerable array of limbic and cognitive functions such as movement, emotional regulation, self-awareness, memory formation, orientation and navigation, imagination and future [3, 5, 6, 8–27].

The ACC lies on the medial surface of the cerebral hemisphere, covering the anterior part of the corpus callosum, extending from the subgenual ventral terminus, continues rostral to the genu of the corpus callosum following the dorsal surface (shown in Fig. 7.3) and has been the primary focus in neuropsychiatric research.

The dorsal anterior cingulate area 32 refers to a subdivision of the cytoarchitecturally defined cingulate region, forming an outer arc around the ACC. The cingulate sulcus defines its inner boundary and the superior rostral sulcus its ventral boundary. Cytoarchitecturally it is bounded internally by the ACC, externally by medial margins of the agranular frontal area 6, intermediate frontal area 8, granular frontal area 9, frontopolar area 10 and prefrontal area 11 [7].

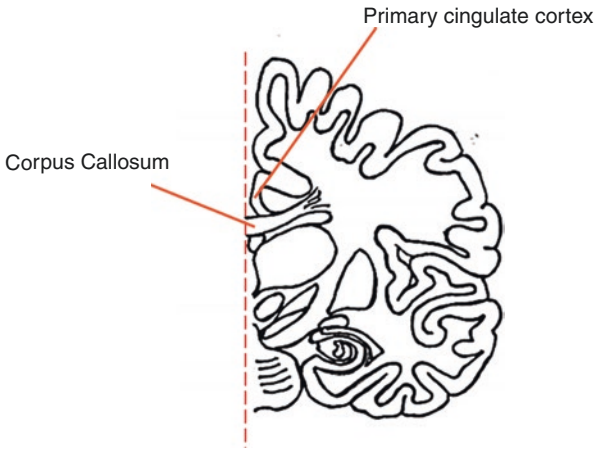

Fig. 7.3 Cingulate cortex shown in relation to corpus callosum in coronal section at the level of the hippocampus. Dotted red line indicates midline of brain

The most posterior region of the ACC is often referred to as the midcingulate cortex (MCC). It is often described separately from the ACC as posterior region is different from the perigenual ACC in terms of connections and functions, and the differentiation of ACC and MCC was proposed [28]. The MCC is not just a caudal ACC but rather it is qualitatively unique with key differences based on cytological phenotypes and other types of findings (as reviewed in [29, 30]). There has been some discussion as to whether the subgenual region of the ACC contains a clear cortical layer IV, although more recent review suggests this may be due to differing anatomies of subgenual ACC and area 25 [31–37].

The extent of area 25 is still not agreed, largely due to inconsistency of the anatomy in non-human primates, but its caudal position within the subcallosal region, lying adjacent to the lateral septum of the basal forebrain, is generally agreed upon [38–40]. A key role of area 25 is involvement in visceral control and feedback mechanisms involving the regulation of autonomic and endocrine functions in studies of non-human primates and humans [38].

A recent study in marmosets suggests that areas 25 and 32 have causal and directly opposing roles in the regulation of the cardiovascular and behavioural correlates of negative emotion. In novel Pavlovian fear conditioning pharmacological inactivation of area 25 decreased the autonomic and behavioural correlates of negative emotion expectation, whereas inactivation of area 32 increased them via generalisation. These findings are consistent with models of rodent and primate prefrontal functional similarity and provide insight into the role of areas 25 and 32 in neuropsychiatric disorders [41].

7.2 Functional Connections

The cingulate cortex shows a complex array of connections that varies by the region of the cingulate. Whilst the axonal projections to and from areas of the cingulate cortex have been studied for many years in humans and non-human primates, there is still a lack of certainty over the precise functional cingulate connections. However, there are pathways that are well characterised in humans and non-human primates.

The ACC regulates autonomic function by direct projections to the brainstem including those to the nucleus of the solitary tract and dorsal motor nucleus of the vagus and receives significant amygdala input, although some do project to the MCC [33, 34, 42]. Cingulate projections to the spinal cord and anterior parietal lobe afferents are associated with MCC but not ACC [43–45]. Primary ACC/MCC connections are shown in Fig. 7.4. Further connections between the ACC and MCC and structures in the frontal lobe developed from primate research have been confirmed by meta-analysis of PET scans. The observations are consistent with known anatomic connectivity in these cortical regions as defined in non-human primates [46]. The perigenual ACC has anatomical connections with several frontal gyri, the insular cortex and the temporal pole, whilst the MCC is anatomically connected with the thalamus via the anterior thalamic radiation (discussed further in Chaps. 10 and 11). The MCC area is also anatomically correlated with motor-related regions, specifically the primary motor cortex and premotor area as well as extensive connections to frontal lobe cortices [34, 47–52].

Functional connectivity studies of the PCC have revealed differing patterns of connections between the dorsal and ventral PCC areas. The dorsal PCC (dPCC) has

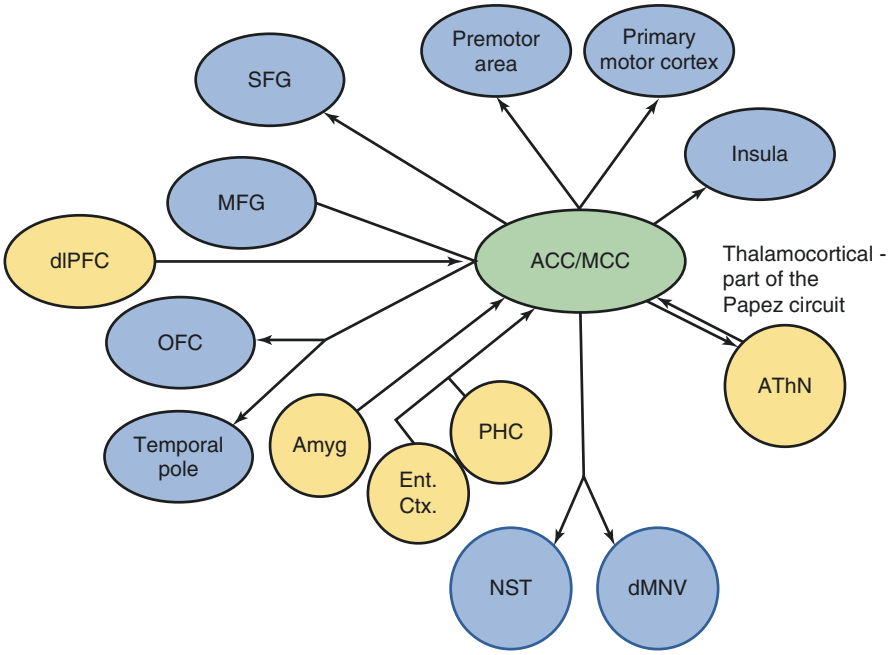

Fig. 7.4 Main connections of ACC. Projection destinations from the ACC/MCC are shown in blue, originating structures for primary projections to the ACC/MCC are shown in yellow. *SFG* superior frontal gyrus, *MFG* medial frontal gyrus, *OFC* orbitofrontal gyrus, *NST* nucleus of the solitary tract, *dMNV* dorsal motor nucleus of the vagus, *dlPFC* dorsolateral prefrontal cortex, *Amyg* amygdala, *Ent. Ctx.* entorhinal cortex, *PHC* parahippocampal cortex, *AThN* anterior thalamic nuclei

prominent connections to the frontal lobes as well as the cingulate motor area, supramarginal gyrus, the inferior frontal gyrus, angular gyrus and the adjacent posterior ACC [25, 34, 44, 45, 53–59]. In contrast, the ventral PCC (vPCC) region shows increased functional connectivity with the parahippocampal cortex, ventromedial prefrontal cortex and angular gyrus when compared to the dPCC clusters. These regions are traditionally associated with the default mode network, and the vPCC is known to mediate an intermediate stage of information processing between visual recognition in the visual cortex and emotion-related substrates and is involved in internally directed cognition such as memory retrieval and planning. These regions were not only active during simple emotions driven by faces or scripts but also activated by non-emotional scripts or faces. Both regions demonstrate connections with the parahippocampal cortex, a precentral gyrus that is involved in spatial and motor systems, and the higher-level visual cortex, which is involved in motion and object processing [5, 6, 60–62].

The retrosplenial of the posterior cingulate cortex has been implicated in an organism's spatial navigation and orientation using fMRI and resting-state functional connectivity combined with spatial tasks.

At rest, both ventrolateral and dorsomedial subregions of the retrosplenial complex were functionally connected to the hippocampus and parahippocampus regions both involved in spatial orientation and navigation. However, the ventrolateral subregion of the retrosplenial complex displayed more positive functional connectivity with ventral occipital and temporal object recognition regions, whereas the dorsomedial subregion activity was more correlated with dorsal activity and frontal activity, as well as negatively correlated with more ventral parietal structures. These findings provide evidence for a dorsomedial to ventrolateral functional specialisation within the human retrosplenial complex that may shed more light on the complex neural mechanisms underlying spatial orientation and navigation in humans [4, 25, 63, 64].

Lesions in the retrosplenial cortex, primarily involving Brodmann area 30, reported in patients have been instructive into confirming this area's function. In a key review, all such cases impaired learning of new routes and defective navigation in familiar environments complaining they 'could not use preserved landmark recognition to aid orientation', the issue generally resolving within 8 weeks of onset. The majority of functional neuroimaging studies involving navigation or orientation in large-scale space report activation of the bilateral retrosplenial cortex, whilst navigating within the environment, the retrosplenial cortex complements the hippocampal contribution to topographical orientation by updating the individual's location as the frame of reference changes [65]. The greater processing of these functions appears to be lateralised, with evidence for right medial temporal lobe involvement in navigation and hippocampal inputs received from and convey to right retrosplenial cortex has a similar spatial preference, whereas the left temporal cortex and left retrosplenial cortex appear involved with more general aspects of episodic memory [16].

7.3 Neuropathology in Schizophrenia

Neuropathological research has revealed alterations in the cellular and synaptic architecture of the cingulate, whilst imaging work has identified ACC abnormalities that correlate with the disorder's characteristic symptoms and cognitive deficits [66, 67]. However, the precise ACC subregion affected and the nature of the underlying changes have varied across published literature, making it difficult to discern their pathophysiological significance [68].

7.4 Cingulate Volume and Shape

Whilst the reported cortical grey matter global decrease in schizophrenia can be detected as an overall loss across the entire brain, with a corresponding overall increase in cortical density in schizophrenia [69], it is a regional phenomenon particularly focused in the frontotemporal regions [36, 70, 71], and the periaqueductal grey matter thickness around the third ventricle in schizophrenia [72, 73]. Imaging studies have not only suggested a decrease in overall cortical grey matter in schizophrenia but that is also present before the first episode (reviewed in [70]). This has led to the proposal of the 'reduced neuropil hypothesis,' suggesting reduction in inter-neuronal neuropil in the brain, focusing on the frontal, cingulate and temporal cortices, is a critical feature of cortical pathology in schizophrenia, representing a functional change in cortical circuit function [74].

Whilst earlier structural MRI studies up to around 2001 were generally consistent that there was no volumetric change in ACC volume in schizophrenia [75–79], with the exception of one study reporting ACC volume decrease in schizophrenia [80]. More recent studies have shown more heterogenous results. Several of these were regarding identification and presence of the paracingulate sulci in schizophrenia against control cases [68, 81–86], whereas others showed alterations in cingulate volume or thickness in schizophrenia in a lateralised manner [87–90], with a similar number of studies over the same period showing decreased whole-gyral or grey-matter volume bilaterally [68, 91–94]. This variation may be due to onset or duration, as one structural imaging study has reported decreased cingulate grey matter volume in the first-episode schizophrenia [95], although another has shown this change correlates with cannabis use [96].

Analysis of the overall surface of the brain in imaging studies has revealed a subtle but significant effect of cortical flattening where the overall surface of the brain shows significant flattening of the sulci and gyri when examined using structural MRI [97, 98]. The subtle nature of this effect, detectable only by complex mathematical analysis of the entire brain surface, means that neuropathological detection of such a phenomenon is likely impossible, although in areas of intense focus and suspected significant grey matter change in schizophrenia may be possible. One study has reported incidence of bifurcation of the primary cingulate crown in the subgenual ACC was significantly decreased in schizophrenia (17% incidence) compared to controls (55% incidence), bipolar disorder (56% incidence) and

depression (55% incidence), possibly a marker of increased brain smoothing or altered gyrification reported in schizophrenia [32, 99].

Overall, post-mortem examination suggests there is no evidence to say there is consistent change in cingulate total or layer-specific volume, but there may be changes in thickness, if true indicating a change in shape of the ACC [32, 100–106].

7.5 Cingulate Neurons

Perhaps inevitably, with the focus of post-mortem studies in the schizophrenic cingulate cortex, there is considerable heterogeneity of results. Whilst some studies have suggested there is no change in ACC pyramidal or interneuron density in schizophrenia [107, 108], other studies have reported changes, although some are very specific. Three studies have reported changes in neuron density, particularly pyramidal cell density, in layer V of the ACC, although two of these reports decreased neurons in schizophrenia [109], and broader study of the ACC cortical thickness reported decreased neuron density across layers II–VI [110]. Layer II of the ACC has shown specific changes in schizophrenia, with decreased neurons reported from direct stereological examination and confirmed by meta-analysis [67, 111], and a possible 25% drop in GABA-neurons in the ACC layer II in schizophrenia [112]. This complexity of findings may not be a result of typical heterogeneity of results in the field but instead reflective of an uneven change across neuronal populations as there is some evidence of neuronal clumping or clustering changes in schizophrenia that alters depending on cell type ([105, 107, 111]. Similarly, examination of neuron size has revealed contradictory findings with both no neuron size change [108, 109] and decreased neuron size in pyramidal layers III and V in schizophrenia [110]. TH-immunoreactive neurons are not changed in number or density in schizophrenia [113].

Examination of parvalbumin-immunoreactive neuronal soma showed an increase in density in layer V of the ACC, consistent with the reported shrinkage of this region in schizophrenia [36, 114]. The density of GAD67 mRNA-containing neurons was decreased by 53% in layer II and 28% in layer V. Examination of GAD67 mRNA- and NR2A mRNA-co-expressing neurons showed that density was decreased by 73% in layer II and 52% in layer V in schizophrenia [115]. Whilst the density of von Economo neurons (VEN), large bipolar projection neurons, in layer V of the ACC was not changed in schizophrenia, the VEN density in the right ACC correlated with the age of the first episode onset and inversely with the duration of the illness. VEN of patients with schizophrenia contained significantly more lysosomal aggregations compared with tissue from unaffected controls, showing illness-specific changes within the neurons themselves in schizophrenia that were not present in local pyramidal cells [116, 117].

In situ hybridisation studies have shown that GAP43 and GAD67 mRNA-containing neurons that co-expressed GluR5 mRNA were decreased by 43% and 40% in layer II of the ACC in schizophrenia, even though the density of the GAD67 mRNA-containing cells that expressed GluR6 mRNA, and the density of cells that

not containing GAD67 mRNA but expressed the mRNA for the GluR5 or GluR6 subunit was not altered. Therefore, GLU modulation of inhibitory interneurons via kainate receptors containing the GluR5 subunit appears to be selectively altered in the ACC in schizophrenia [118, 119].

7.6 Cingulate Fibres and Capillaries

In the ACC, the number of GABA cells expressing mRNA for the NMDA NR2A subunit was significantly decreased in subjects with schizophrenia and bipolar disorder, most prominently in layer 2.

In the normal human ACC, only approximately 10% of all CB-containing cells expressed NR2A mRNA. However, compared with the normal control subjects and subjects with bipolar disorder, the density of CB+/NR2A+ neurons in layer 2 was increased by 41–44% in subjects with schizophrenia, whereas the amount of NR2A mRNA/CB+ neurons was unchanged. Conclusions: These observations suggest that, in schizophrenia, a number of CB-containing cells that normally do not express NR2A might become NR2A-expressing or, perhaps not mutually exclusively, the number of CB-expressing cells might be increased, and these cells express NR2A. The findings of this study highlight the notion that glutamatergic innervation of subsets of GABA cells might be differentially altered in schizophrenia and bipolar disorder [120].

The neuronal organisation and patterns of afferent innervation are abnormal in the ACC in schizophrenia. Presynaptic protein immunoreactivities were assessed in 16 elderly controls, 19 elderly subjects with schizophrenia and 24 subjects with Alzheimer's disease by tissue assays with the monoclonal antibodies EP10 and SP4, which recognise synaptophysin, and the monoclonal antibodies SP6 and SP14, which detect syntaxin and synaptosomal-associated protein-25-kd immunoreactivities. In subjects with schizophrenia relative to controls, these presynaptic proteins were increased in the ACC, directly opposite to the findings in cases with Alzheimer's disease [121, 122]. Syntaxin and neural cell adhesion molecule immunoreactivity were significantly elevated in schizophrenia possibly indicating the presence of less mature synapses. Elevated syntaxin immunoreactivity is consistent with increased GLU afferents to the ACC, and combined with the neural cell adhesion molecule to synaptophysin ratio results suggests that synaptic function in this region in schizophrenia may be abnormal [123].

The ACC in schizophrenia has been reported to have increased density of small and large calibre vertical fibres, repeatedly shown in layers II and III, axospinous and dendritic synapse density, and TH-immunoreactive fibres in layers V and VI, with no corresponding change in horizontal axons [113, 124–126]. Ultrastructural examination of the ACC has revealed an overall decrease in synaptic density, and specifically a 30% decrease of axospinous synapses in layers III, V and VI in schizophrenia cases [124, 127]. Additionally, mean capillary diameter was significantly decreased in the dorsal and subgenual ACC in bipolar and unipolar depression cases, both in layers III and V, whereas schizophrenia patients were comparable

with controls [128]. Ultrastructural examination of the ACC has revealed an overall decrease in synaptic density and specifically a 30% decrease of axospinous synapses in layers III, V and VI in schizophrenia cases [124, 127].

7.7 Cingulate Glia

Several studies have reported no overall changes in glial cells in the ACC in schizophrenia [105, 129], although examination of the ACC cortical grey matter using Cavalieri's method did find a 33% decrease in total glia in schizophrenia [130]. Reinforcing the findings in analysis of neuronal specific changes in the layer V of the ACC, a 20% decrease in overall glial density has been observed in this layer, although multiple comparisons have made this conclusion less certain [108]. In contrast other studies have reported ACC glial changes in schizophrenia, with decreases in glial density in layers V with an increase in glial size in layers I, III and V [108, 110]. Also higher glial densities in layers V–VI than in layers II–III in both controls and patients with schizophrenia have been shown [129]. The total number of glia has been reported to decrease in the ACC of familial depression (24% decrease) and bipolar disorder (41% decrease) cases, with the familial nature of the cases seeming to be more important than the specific diagnosis [102, 105].

Studies examining specific glial cell types rather than total glia have produced more revealing findings. There are reduced ADAM12-reactive oligodendrocytes in ACC white matter in schizophrenia [131, 132], discussed in Chap. 11, but no change in cingulate grey or white matter oligodendrocyte number, density or clustering as identified using histology staining [35, 37, 133, 134]. Consistent with other studies, no differences are reported in HLA-DR-immunoreactive microglial density, although ameboid microglial cells were lateralised towards the right hemisphere in healthy subjects but not in the schizophrenia group [106, 135].

GFAP-labelled astrocytes have been shown to be decreased in the ACC cortical grey and white matter, with an overall decrease in GFAP area fraction and increase in clustering in schizophrenia [35, 136], with further experiments suggesting the astrocyte decrease is made up primarily due to a loss of fibrillary astrocytes (discussed in Chap. 12), similar to observations made in the nucleus basalis [35, 37]. This was found only in schizophrenia and not in either major depressive disorder or bipolar disorder, suggesting a change unique to this illness. The decrease in astrocyte density in depression is only found in the ACC grey matter, in contrast to also in the white matter in schizophrenia, suggesting a different effect of these disease states on astrocytic migration. This data also reinforces the idea that the ACC is a vulnerable structure in mental illness generally. The profile of astrocyte density across the crown of the ACC shows the highest density in layer I and VI and a lower density in the other cortical layers in schizophrenia [35, 37]. The higher astrocyte density in layer VI is consistent with previously reported GFAP mRNA density in the ACC, but the high astrocyte density in layer I has not been previously reported. Previously, GFAP mRNA quantified using relative optical density measures from a labelled riboprobe in situ hybridisation showed decreased GFAP mRNA in the

white matter and layer I in schizophrenia [137]. This may suggest that in the molecular layer of the ACC, there is a high density of astrocytes with a low expression of GFAP. GFAP has previously been suggested as a marker for astrocyte activation [138, 139], possibly implying that layer I astrocytes may be in an inactive state. Astrocytic D-serine has been shown to regulate neuronal long-term potentiation and regulates NMDA receptor-dependant plasticity in local synapses [140], indicating a possible link between the decreased astrocyte density observed in the ACC in schizophrenia and the suggested decreased function or output of that structure [141, 142]. As schizophrenia is often described a disorder of both function and connectivity, it is not necessarily expected that oligodendrocytes would not decrease, both as their role in maintaining axonal myelin would be one route of connective disruption if affected and with the reported expression decrease of myelin-related genes [133, 143–149]. A decrease in astrocyte density could affect the functioning of the ACC as astrocytes are involved in cell firing and regulation of oligodendrocyte function. A decrease in astrocyte activity may reflect abnormal function and myelination in these areas, although the lack of change in oligodendrocyte density suggests that abnormal myelination may not be the underlying cause of ACC dysfunction.

7.8 Posterior Cingulate

The PCC has been implicated in the pathology of schizophrenia partly because of its sensitivity to NMDAr antagonists. Quantitative autoradiography to investigate the binding of [(3)H]pirenzepine, [^{3}H]AF-DX 384 and [^{3}H]muscimol, which respectively label M1/4 and M2/4 muscarinic and GABAA receptors, in the PCC of schizophrenia against controls found [^{3}H]pirenzepine binding was significantly decreased in the superficial (−24%) and deep (−35%) layers of the PCC in the schizophrenia group. In contrast, a substantial increase in [^{3}H]muscimol binding was observed in the superficial (+112%) and deep layers (+100%) of the PCC in the schizophrenia group. No difference was observed for [^{3}H]AF-DX 384 binding. Further analysis showed a significant inverse correlation between [^{3}H]pirenzepine binding in the deep cortical layers and [^{3}H]muscimol binding in the superficial layers, and negative correlations were also found between age and [^{3}H]pirenzepine binding in both superficial and deep cortical layers and between age of schizophrenia onset and [^{3}H]AF-DX 384 binding. Whilst the exact mechanism causing these alterations is not yet known, a possible increased acetylcholine and down-regulated GABA stimulation in the PCC of schizophrenia is suggested by the authors [150, 151].

7.9 Areas 25 and 32

No change has been reported in neuron or glial density in area 25 in schizophrenia [129], although research has been slowed somewhat by comparative neuroanatomical issues, with an analogue of primate area 25 not being easily identifiable in

rodents [38] and the definitions of the subgenual region in previous studies of the cingulate in human neuropathology studies.

Recent immunocytochemical studies have shown a dramatic decrease in MAP 2 and neurogranin a loss of either is suggestive of dendritic lesions as neurogranin is an upstream regulator of calcium and calmodulin. A direct action of this pathway is the phosphorylation of MAP 2, which is required for microtubule stabilisation. There is a significant loss of neurogranin and calmodulin-labelled pyramidal cells in layers III and V of area 32 using area fraction analysis [66, 152–154].

7.10 Summary

Neuropathological study of the cingulate cortex has produced many results demonstrating changes in neurons and synapses in schizophrenia. The findings of these projects do seem to consistently find neuropathological changes in the ACC in schizophrenia in layer V, providing intriguing evidence and a good candidate for more detailed research into the precise changes into the cortical columns and cortical circuits in this disorder.

Even though the cingulate cortex has been the subject of considerable anatomical examination for some time, it is clear that between cytoarchitecture, functional mapping and tract tracing, we are only approaching a useful model of its function. Neuropathological study has focused on the anterior parts of the cingulate due to the implied involvement of this region from the emotional-cognitive symptomatology observed in schizophrenia. There is considerable evidence now for widespread functional change in the anterior cingulate, and neuropathology is now providing an overview as to how this may cause functional change in schizophrenia.

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Parietal and Occipital Lobes

8

Matthew Williams

8.1 Parietal Lobe Anatomy

The parietal lobe has its anterior limit at the central sulcus, separating it from the motor cortex at the posterior end of the frontal lobe. It continues posteriorly until in turn meeting the anterior end of the occipital lobe, although the parietal-occipital division is not as clear-cut anatomically as between the frontal-parietal lobes (shown in Fig. 8.1). The anatomical structures guiding the boundary between these lobes are the parieto-occipital sulcus and the pre-occipital notch, between which a line is often drawn to define the boundary. On the inferior surface, the parietal lobe is bounded by the lateral sulcus, and more medially by the calcarine and subparietal sulci (shown in Fig. 8.2). There are three areas on the lateral surface of the occipital lobe: the

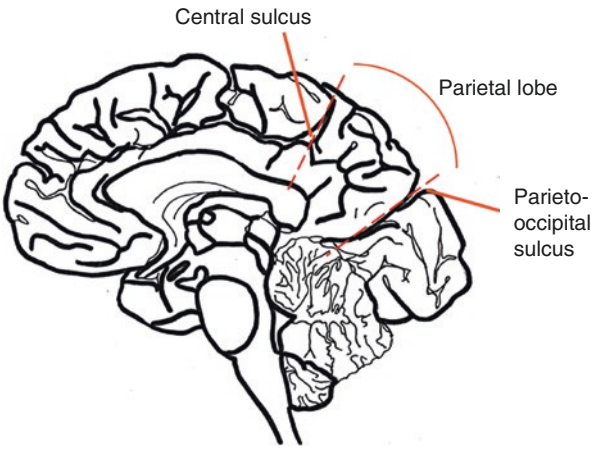

Fig. 8.1 Sagittal diagram showing location of parietal lobe. Dotted red lines mark the extent of the parietal lobe, the central sulcus marking the anterior extent and the parietal-occipital sulcus marking the posterior end

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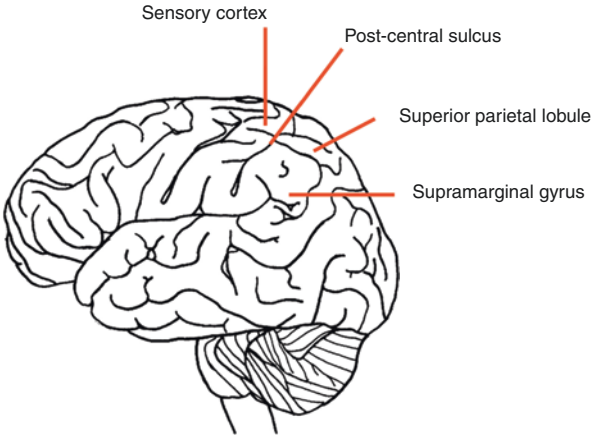

Fig. 8.2 Illustration of the structures of the parietal lobe lateral surface

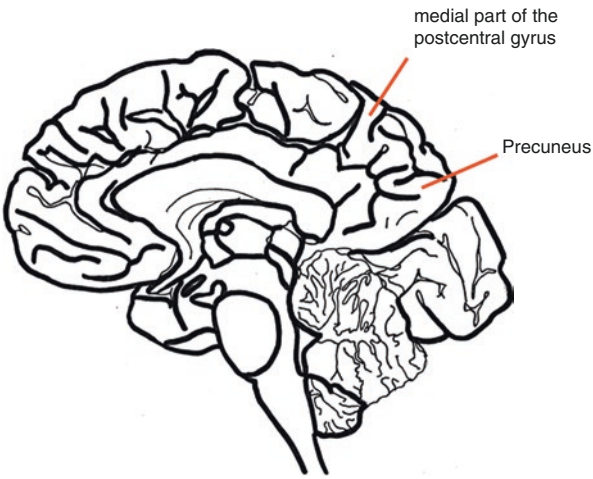

Fig. 8.3 Illustration of the structures of the parietal lobe medial surface

postcentral, superior and inferior parietal gyri. The medial part of the parietal lobe is mostly composed of the medial part of the postcentral gyrus and the precuneus, a smaller structure bounded by the sub-parietal and calcarine sulci, the marginal part of the cingulate sulcus and the parieto-occipital sulcus (shown in Fig. 8.3).

The inferior parietal lobe is greatly expanded in humans compared to other primates and matures late in human development, consistent with its importance in higher-order functions, and evidence from neuroimaging studies suggests that the inferior parietal lobe is involved with a wide range of functions.

The inferior part of the parietal lobe contains the angular gyrus, which borders the posterior end of the superior temporal sulcus, and the supramarginal gyrus which borders the end of the lateral sulcus.

Different patterns of fissurisation have been described as asymmetrically distributed in the inferior parietal lobe, indicating increased folding predominantly on the

left side, which may indicate a larger cortical results in increased processing capacities. The lateralised nature of the inferior parietal lobe, specifically the accessory postcentral sulcus and the intraparietal sulcus is particularly affected by the lateralised affect and possibly involved in linguistic working memory [1]. Related to this, neuropathological examination of nine control brains showed the lateralis posterior nucleus, itself related to the asymmetric inferior parietal lobule, and showed a significant left-sided bias in eight of them [2, 3]. Coupled with the similar asymmetry seen between the lateral posterior nucleus of the thalamus, discussed in Chap. 10, this suggests asymmetry of functionally associated groups, of particular importance in the examination of schizophrenia.

The superior parietal lobule has been of some focus in schizophrenia research. Brodmann area 5 is found primarily on the superior surface of the parietal lobe, immediately posterior to the sensory cortex and forms part of the superior parietal lobule. Brodmann area 7 contains the bulk of the superior parietal lobule, consisting of the precuneus and extending down the parietal lobe both laterally and medially.

Both Brodmann areas 5 and 7 have substantial projections to the pretectal area and the deeper layers of the superior colliculus. This parietal-mesencephalic connection is amplified by a fibre connection from the inferior parietal lobule to the lateral region of the circumaqueductal grey matter. Both the parietal lobules were found to project to the pontine nuclei, and parieto-subthalamic connections have also been traced from Brodmann areas 5 and 7 to the zona incerta. A further subcortical projection from the posterior parietal cortex involves the nucleus reticularis thalami and the nucleus lateralis posterior thalami. The inferior lobule projects directly to the nucleus lateralis dorsalis and to the mediodorsal region of the nucleus lateralis that closely adjoins the lateralis dorsalis and the intralaminar nucleus centralis. The superior parietal lobule contains a substantial projection to the ventrolateral region of nucleus lateralis posterior. Projections also exist from the parietal lobe to the claustrum and body of the caudate, and more significantly have substantial efferent connections with the dorsal putamen [4].

The temporal–parietal white matter connections between the inferior parietal lobule and superior temporal gyrus as part of the superior longitudinal fasciculus or medial longitudinal fasciculus have been reported in by DTI studies, but higher temporal–parietal connections of the superior parietal lobule with the temporal lobe have been less well studied. These temporal–parietal connections are suggested to play a key role in processes such as attention, memory, emotions and language.

Temporal–parietal connections have been categorised into the anterior and posterior connectivity groups and subcategorized each one into the superior– or inferior–parietal lobe connections [5]. The temporal–parietal junction has been examined in some depth which is reviewed in Igelström and Graziano [6].

Also identified by post-mortem dissection in conjunction with tract tracing imaging are the bundles of the inferior longitudinal fasciculus, running both medially and inferiorly alongside the fibres of the middle longitudinal fasciculus, connecting the inferior parietal region to the inferior temporal gyrus. The inferior longitudinal fasciculus connects the prefrontal regions to the medial temporal lobe projecting posteriorly parallel to the medial longitudinal fasciculus and terminating via fibres

into the occipital lobe and has been the subject of considerable discussion. There are distinct pathways connecting the frontal lobe more generally with the supramarginal gyrus via the superior longitudinal fasciculus [7].

Overall, Burks et al. [7] identify three major connections of the inferior parietal lobe:

1. Short association fibres connect the supramarginal and angular gyri, in turn connecting these gyri to the superior parietal region.
2. Fibre bundles from the inferior parietal lobe connect to the frontal lobe by joining the superior longitudinal fasciculus near the termination of the Sylvian fissure.
3. Fibre bundles from the IPL connect to the temporal lobe by joining the middle longitudinal fasciculus just inferior to the margin of the superior temporal sulcus.

8.2 The Parietal Lobe in Schizophrenia

The parietal lobe may have a critical role in future methods of early diagnosis of schizophrenia. There has been a described process for grey matter loss in the brain in early schizophrenia, beginning in the parietal lobe then moving to the temporal lobes before affecting the frontal lobes, with the parietal changes occurring very early in the illness [8–10]. This pattern matches that observed in childhood onset schizophrenia [11], and fractional anisotropy reductions are reported in the parietal lobe of adolescent-onset schizophrenia [9, 12], and also consistent with the progressive process of grey matter loss in the posterior part of the superior temporal gyrus, towards the temporal–parietal boundary, preceding the first expression of florid psychosis [13]. This has been suggested to support the neurodegenerative model of schizophrenia [12, 14].

A study examining presynaptic protein immunoreactivities in four cortical regions derived from 16 elderly controls, 19 elderly subjects with schizophrenia and 24 subjects with Alzheimer's disease was conducted in 1997. Brain samples were assayed with the monoclonal antibodies EP10 and SP4 to recognize synaptophysin, and the monoclonal antibodies SP6 and SP14 to detect syntaxin and synaptosomal-associated protein-25-kd immunoreactivities. The presynaptic proteins were increased in the cingulate cortex but were unchanged in the temporal, frontal and parietal cortices in the schizophrenia cases relative to controls, but were decreased in the frontal, temporal and parietal samples in Alzheimer's disease cases when compared with controls [15].

In a case report of a 25-year-old schizophrenia patient with abnormal parietal encephalomalacia, the patient had poor nutrition and frequently had upper respiratory infections during childhood and adolescence, showing severe schizophrenia symptoms such as visual hallucinations for 2 years. We found that the patient had a lesion consistent with the diagnosis of encephalomalacia in her right parietal lobe and slight brain atrophy [16].

Yildiz et al. (2011) asked 'Do the parietal lobes matter' [17]. Whilst it is very early to conclude a positive response to this, the evidence strongly supports a role of the parietal lobes in schizophrenia and warrants more detailed research.

8.3 Occipital Lobe Anatomy

The occipital lobe is located at the most posterior part of the brain, encompassing three Brodmann areas 17, 18 and 19. It is separated from the parietal lobe on its anterior end by the line drawn between the parieto-occipital sulcus and the pre-occipital notch and forms the region projecting rearwards to the occipital pole. The lateral surface of the occipital lobe has an erratic arrangement and shows considerable variation between individuals, and hence the region is referred to as the lateral occipital gyri. The medial surface of the occipital lobe is composed of the cuneus in the superior part, the lingual gyrus in the central part and the occipitotemporal gyrus in the most inferior part adjacent to the posterior end of the temporal gyrus (shown in Figs. 8.4, 8.5 and 8.6).

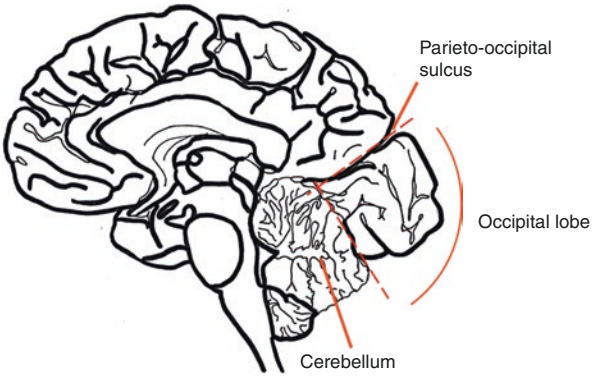

Fig. 8.4 Sagittal diagram showing location of occipital lobe. Dotted red lines mark the extent of the occipital lobe, the parietal-occipital sulcus marking the anterior end

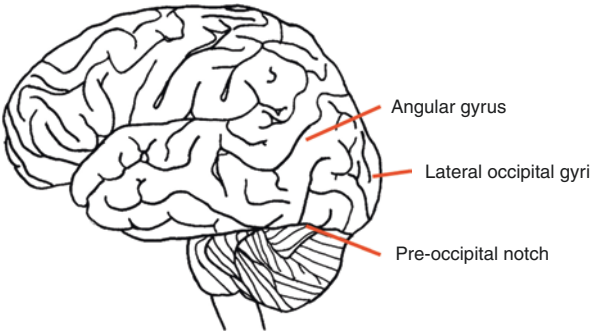

Fig. 8.5 Illustration of the structures of the occipital lobe lateral surface

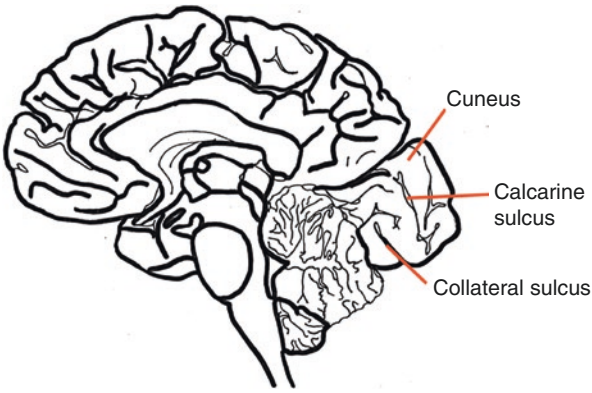

Fig. 8.6 Illustration of the structures of the occipital lobe medial surface

The occipital lobe is almost exclusively with the processing of visual information with the primary visual cortex located almost entirely within the calcarine sulcus cortical surfaces and the rest of the lobe broadly termed the visual association cortex.

The occipital lobe contains five major connections named the inferior frontal occipital fasciculus, vertical occipital fasciculus, optic radiation, forceps major and inferior longitudinal fasciculus [18]. For interest in schizophrenia research, possibly the most important occipital connection is the inferior frontal occipital fasciculus connecting the basal temporal, superior parietal and occipital lobes to the frontal lobe. A precise role of this structure is not fully determined but is thought to have a key role in language understanding, semantics and production as well as attention, memory, visual processing and image recognition [19–22]. As with other brain regions, the occipital hemispheres are connected by the corpus callosum, with the splenium and the caudal callosal area containing the interhemispheric fibres [23].

8.4 The Occipital Lobe in Schizophrenia

Similar to the parietal lobe, the occipital lobe has received less examination than other regions of interest, although it is generally agreed that the evidence supports a reduction of the overall volume of the occipital lobe in schizophrenia [24–34].

As referred to in the section on gross pathology, Chap. 3, occipital bending is more prevalent amongst schizophrenia patients than healthy subjects with a prevalence in schizophrenia patients of 13/37 (35.1%) than in control subjects of 6/44 (13.6%). Also reported in this study was that schizophrenia patients have different grey matter–white matter proportions [35]. Occipital bending is a neurodevelopmental phenomenon, and it has been suggested that OB ‘twist’ creates a prominent shape difference between the left and right posterior temporal regions and a larger left planum temporale [36]. This therefore supports a developmental underpinning to the development of schizophrenia with auditory–verbal hallucinations. With the addition of enlarged lateral ventricles, pressure may be applied to the surrounding structures, effectively displacing them in medial, anterior and posterior directions.

Consistent with this hypothesis, Zhao et al. [37] reported 'interhemispheric fissure bending' to be more frequent in schizophrenia than in controls and the amount of OB to be more pronounced. Those findings suggested that torque occurs in various regions along the midline, not only in the occipital lobe. Furthermore, they recently reported occipital asymmetry in a group of medication-naive schizophrenia subjects [38].

The same study reported increased white matter volume in the left precalcerine region, consistent with this being the cause of the observed rightwards bending [35]. However, further examination is required to determine if this is the cause of occipital bending or a result of other factors distorting the shape of the occipital lobe during development. Also, we must bear in mind that whilst statistically more common in schizophrenia, occipital bending is only observed in 35% of cases reported.

One structural MRI study of 25 men with chronic schizophrenia against 28 control cases showed a reduced grey matter volume visual association area of 11%, but no differences in the primary visual area grey matter volume. The authors suggest that the reduced bilateral visual association area could be a neurobiological substrate of some of the deficits observed in early visual processing in schizophrenia [39]. White matter integrity, described by fractional anisotropy, was reported as decreased in the left occipital white matter in schizophrenia [40].

A larger study of structural imaging from 103 individuals comprising 39 patients with first-episode schizophrenia and 64 healthy controls volume change using voxel-based morphometry and fractional anisotropy revealed that patients with first-episode schizophrenia had lower white matter volume in the right temporal-occipital region corresponding to the inferior longitudinal fasciculus. Further analyses of diffusion anisotropy in the right temporal-occipital region revealed lower planar anisotropy and higher linear anisotropy in schizophrenia, with anisotropy changes also found to be correlated with severity of delusions [41]. Consistent fractional anisotropy reductions in the white matter of the right deep frontal and left deep temporal lobes were identified in first-episode schizophrenia patients relative to healthy controls, with fibre tracking showing the main tracts involved were the cingulum bundle, the left inferior longitudinal fasciculus, the left inferior fronto-occipital fasciculus and the interhemispheric fibres running through the corpus callosum [42]. First-episode psychosis patients show reduction of grey matter in the occipital lobe. The age of disease onset was a key factor revealing a gradual decrease in parietal and occipital lobes of schizophrenia patients over illness duration. These results suggest that an earlier onset of psychosis is linked to an earlier illness-related disruption of structural brain development, which could be more pronounced in schizophrenia than in other psychoses [33].

A recent review of 82 studies conducted by Tohid et al. [43] suggest that patients with schizophrenia often show structural changes in the occipital lobe with functional and metabolic changes which are also commonly reported. Moderate quality evidence, due to large sample size and no consistency and precision, found that the white matter integrity is reduced in the occipital cortex compared with healthy individuals, moderate to low quality evidence, described as inconsistent and imprecise, suggests a higher frequency of reversed asymmetry in the occipital lobe in

schizophrenia. Progressive changes in grey matter volume were reported across longitudinal MRI scans. Significantly greater reductions were reported over time in schizophrenia compared with controls, the occipital grey matter decrease is around 70%, whilst the occipital white matter decrease is 46%.

Altered regulation of the neuronal growth-associated membrane phosphoprotein GAP-43, found at high levels in the developing brain, has been suggested in schizophrenia. Quantitative immunoblotting from post-mortem tissue has revealed that the expression of GAP-43 is increased preferentially in the visual association of schizophrenic patients, and also levels of synaptophysin are reduced in the same areas, but the abundance of the astrocytic marker GFAP is unchanged (see Chap. 12 for further discussion). In situ hybridization has shown that the laminar pattern of GAP-43 expression appears unaltered in schizophrenia, which the authors suggest is associated with a 'perturbed organization of synaptic connections in distinct cortical associative areas of the human brain, and that increased levels of GAP-43 are one manifestation of this dysfunctional organization' [44]. Further in situ hybridization studies have shown GAP-43 mRNA was decreased in the primary visual cortex in schizophrenia, but was unaltered in the superior temporal and dorsolateral prefrontal cortices in a sample of 11 normal subjects and 11 matched subjects with schizophrenia [45].

Neuropathological examination of the density of dendritic spines on the basilar dendrites of Golgi-impregnated pyramidal neurons in the superficial and deep portions of layer III primary visual cortex showed no significant effect of diagnosis on spine density [46], although there was no change due to a schizophrenia diagnosis or due to antipsychotic use. Samples obtained from 25 post-mortem schizophrenic brains and 31 control cases showed that normal levels of synaptophysin were observed in schizophrenia in the primary visual area [47].

Whilst there is little to report on the neuropathology of the parietal and occipital lobes in schizophrenia, the evidence presented in recent years makes the case for renewed study in these regions.

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The Basal Ganglia

9

Matthew Williams

9.1 The Basal Ganglia

The basal ganglia refer to a variety of subcortical neuronal structures with roles such as motor learning, executive functions and behaviour and emotions. Basal ganglia refers to nuclei embedded deep in the brain hemispheres such as the striatum or caudate-putamen and globus pallidus (GP), although typically includes structures located in the diencephalon such as the subthalamic nucleus (STN) and mesencephalon such as the substantia nigra (SN). It was clinical observed that during the twentieth century which showed that lesions of the lenticular nucleus, the grouping of the putamen and globus pallidus (GP), and the subthalamic nucleus (STN) was associated with Parkinsonism, dystonia and hemiballismus [1, 2].

The basal ganglia can be roughly categorised into input nuclei, output nuclei and intrinsic nuclei. Input nuclei are those structures receiving incoming information from different sources such as the cortex, nigra of thalamus. The caudate, putamen and the nucleus accumbens (NAcc) are input nuclei. The output nuclei are those structures that project from the basal ganglia to the thalamus and consist of the internal part of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). The intrinsic nuclei such as the external segment of the globus pallidus (GPe), the STN and the substantia nigra pars compacta (SNc) are located between the input and output nuclei in the information pathway. Cortical and thalamic efferent information enters the striatum where it is processed within the basal ganglia system, output nuclei (GPi and SNr) project mainly to the thalamic VNG, themselves relaying projections to the frontal cortex [3].

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9.2 Caudate

The caudate is a dense subcortical nucleus composed of spiny neurons and forms the striatum along with the putamen. The caudate forms the medial part of the striatum with the putamen forming the more lateral area. They are often considered a single functional unit separated by the striatal white matter tract known as the internal capsule (IC) (Fig. 9.1). It has much in common with the putamen, receiving dopaminergic inputs from the nigrostriatal pathway, specifically originating from the midbrain reticular formation (A8 dopamine cells) and the SNc (A9 dopamine

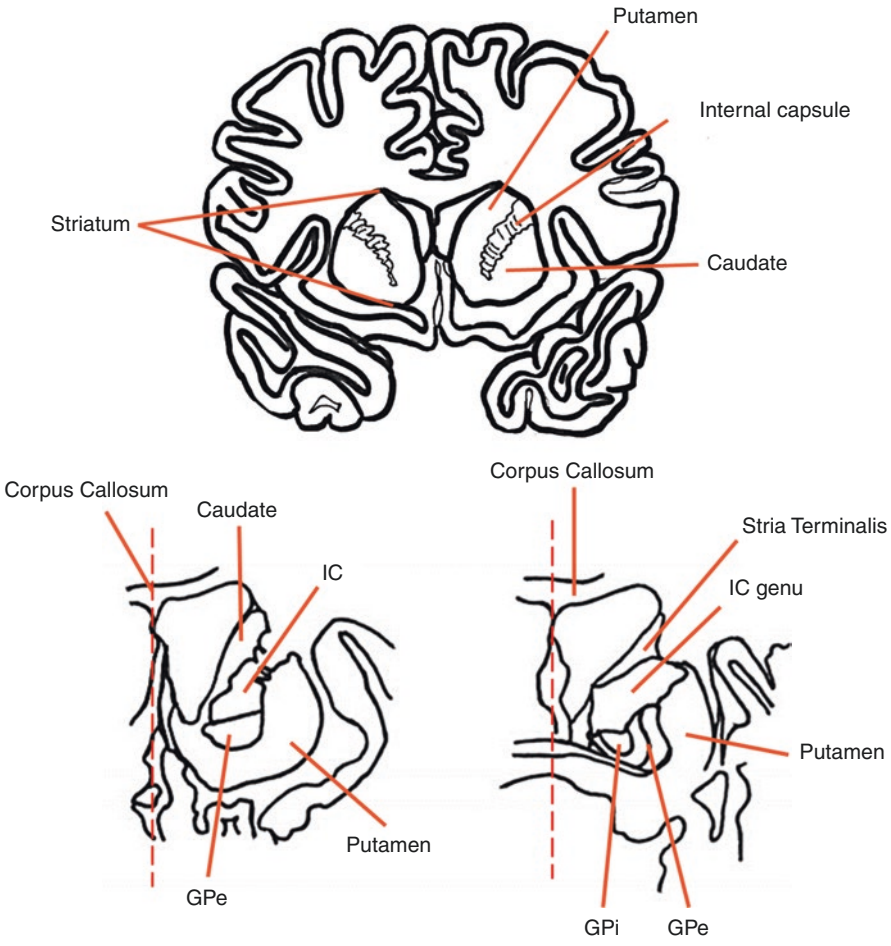

Fig. 9.1 Coronal view of the striatum. The striatum is composed of the caudate and putamen on either side of the internal capsule (IC), the primary white matter structure of the basal ganglia. Lower images show schematics of the striatum at its anterior end (lower left) and more posteriorly (lower right). Dotted red line represents the midline of the brain. *IC* internal capsule, *GPi* globus pallidus internal part, *GPe* globus pallidus external part

cells) [4, 5]. The caudate also receives projections from the dlPFC and the premotor cortex and in turn sends projections to the GP as well as reciprocal projections to the SN. There are also complex and reciprocal connections between several thalamic nuclei and the caudate, (reviewed in [6, 7]). The functional connections clearly show why the caudate is thought to play an important role in cognition and movement, whilst damage to this structure has been observed to result in schizophrenia-like behavioural change, suggesting a possible role for the caudate in this illness [8, 9]. Functionally the caudate is part of the cortico-basal ganglia-thalamic loop, suggested to be the key network regulating motivation, planning and cognition for the development and expression of goal-directed behaviours [6, 10].

The primary focus of investigation of the basal ganglia in schizophrenia has to do with the DA system and the various sites of antipsychotic drug action in the striatum. The DA-projection from the SN to the striatum is known as the nigrostriatal pathway and is the most well-characterised long DA-pathway in the brain. The nigrostriatal pathway is formed from axons projecting from the large DA-producing neurons in the SN, identified above as A8 and A9 cells, and rises dorsally to terminate in the superior part of the striatum across areas of the caudate and putamen. Imaging and neuropathological investigation of striatal DA have found that elevated DA-synthesis capacity is seen in the origin of DA neurons in the SN as well as their striatal terminals in schizophrenia, linked to severity of psychosis in patients. The increased nigrostriatal DA is likely to be a result of excess production in DA-positive nigral oval cells [11–13].

The caudate is reported to show a decrease in total volume in schizophrenia, contrary to the effect described in the adjacent putamen, although some authors have suggested this is the result of medication rather than the fundamental biology of the illness [14, 15]. However, imaging studies have shown that the decrease of caudate volume is also found in antipsychotic-naïve first-episode patients [16], and ultrastructural examination of the spiny neurons of the striatum show changes in spine shape and axon density in the caudate. Spine pruning, the process of losing neuronal spines, has been shown to be correlated strongly with long-term antipsychotic medication use. This has specifically been implicated in models of circuit control of striatal DA, and progressive spine pruning strongly effecting elevated frontal cortical excitation of pyramidal neurons as a result of striatal hyperdopaminergia [17, 18]. But these findings are not totally consistent, with conflicting results suggesting increased caudate volume in first-episode schizophrenia, with volume increase proportional to greater amounts of antipsychotic medication and younger age at the time of the first scan [19, 20], possibly arguing against drug treatments being the cause of caudate changes [21, 22].

Volumetric MRI studies show decreases of 8–9% in caudate volume in the offspring of patients with schizophrenia [23], although other investigations have not reported similar changes in first-degree relatives [24]. If these alterations are borne out by further research we must accept that not all of these offspring would develop schizophrenia. Therfore any neuroanatomical alterations are more likely to reflect a measure of susceptibility, the causation of which could be due to excessive synaptic pruning or some problem in normal development [25]. Meta-analysis of the caudate

in schizophrenia has tended to show a volumetric change, suggesting decreasing caudate size more common [26]. Caudate volume is often reported to be reduced in first-episode schizophrenia, with progressive decreases reported over time in a dose-dependent manner with medication [16, 27, 28]. This is consistent with meta-analyses suggesting increased loss of basal ganglia grey matter over time in chronic schizophrenia compared to the first episode, and the complexity of reported findings specifically in the caudate over time shows this requires more detailed investigation [29].

Stereological studies have, somewhat typically, produced conflicting findings. Initial findings suggested that the caudate has higher neuron counts in schizophrenia [30], but more recent studies have concluded that the caudate has shown similar neuropathological changes to the putamen, with a decreased total number of neurons in schizophrenia [31]. The possible causes of such directly conflicting results may well be down to the stereological methods, a controversial subject that has been discussed elsewhere [32, 33]. Ultrastructural morphometric study of myelinated fibres in the caudate in schizophrenia demonstrated atrophy of axon due to the alteration of myelin sheath [34], possibly indicating disruption of signal transmission in the caudate-related networks described previously. Treatment-responsive schizophrenia subjects had about a 40% decrease in the number of mitochondria per synapse in the caudate nucleus and putamen, whilst treatment-resistant cases had normal values. A decrease in mitochondrial density in the neuropil distinguishes paranoid from undifferentiated schizophrenia.

Mitochondrial hyperplasia occurs within axon terminals that synapse onto dopamine neurons, but mitochondria in dopamine neuronal somata are similar in size and number. In schizophrenia, mitochondria are differentially affected depending on the brain region, cell type, subcellular location, treatment status, treatment response and symptoms [35].

Whilst a reported change in caudate volume in first-episode schizophrenia and the offspring of schizophrenia patients suggests a more fundamental biological alteration of the caudate in this illness, the interaction of antipsychotic drug treatments and cortical volume suggests a more complex situation. Changes in ultrastructural factors show that caudate size is only a small part of the issue, with changes in spine density and myelination likely having significant effects on neuron–neuron communication and hence network function. Further work is required to elucidate the role the caudate plays in schizophrenia and other disorders, particularly in functional network roles and changes in specific cell types in this structure. We are only at the start of detailed examination of the caudate in schizophrenia, with likely relationships to genetics, development, age of onset and drug treatments.

9.3 Putamen

The putamen is one of the basal ganglia nuclei and part of the striatum. It is a large structure clearly visible in coronal section through the striatum (see Fig. 9.1). Historically, it has been associated with motor function as Parkinson's-induced

putamen lesions can cause involuntary muscle tremors or movements, and putamen atrophy in Huntingdon's can result in jerky and unpredictable movements. In recent years, increased research into this region has suggested a far broader range of functions for the putamen, including a critical role in schizophrenia and psychosis.

The putamen, along with the adjacent caudate, is composed predominantly of medium spiny neurons. There is a complex mixture of cell types by chemistry with GABA-ergic cells making up around 95% of striatal neurons, with adenosinergic, dopaminergic, glutamatergic and substance-P containing neurons all present in smaller numbers within the putamen and striatum as a whole. These spiny neurons are densely packed and have many connections with each other, making pathways within the putamen extremely difficult to elucidate.

By far the largest input to the striatum is from the cortex, with all regions of the cortex represented, known as the corticostriatal pathway. The corticostriatal pathway does not equally split between the caudate and putamen, reflecting functional differences between these nuclei. The putamen receives input from the somatic sensory cortex in the parietal lobe, the extrastriate visual cortex and the auditory association region of the temporal lobes. The caudate nucleus mainly receives cortical projections from multiple association cortices. Frontal lobe input to the striatum is functionally from motor systems for both nuclei. Within these inputs, there is structural organisation, as visual and somatic sensory cortical projections are topographically mapped within different regions of the putamen.

The main output structure for medium spiny neuron axons is the thalamus, although major pathways also project from the striatum to the GP and NAcc, as well as reciprocal projections back to the DA regions of the VTA and SN [36, 37]. There is also functional separation within the striatum, with dorsal medium spiny neurons mainly involved in motor regulation, controlling limb, body and eye movement, whilst in contrast ventral medium spiny neurons are linked to behaviour, regulating reinforcement, aversion, reward and motivation systems [10, 38].

When examining basal ganglia involvement in schizophrenia, the key findings are to do with the DA-system and the site of antipsychotic drug action. Immunohistochemical studies show the presence of intrinsic DA neurons which are not normally abundant in the striatum. The density of these neurons increases after lesioning of the nigrostriatal pathway, suggesting that they might serve as a compensatory mechanism for the lack of striatal DA [39]. They display a very particular pattern of striatal distribution being especially abundant in the anterior-dorsal part of the striatum. In the human brain, the highest concentration of DA receptors is in the basal ganglia, with D_1 and D_2 receptors showing the greatest density in the striatum [40–42]. Whilst D_1 receptors are found in high concentrations in the corpus of the caudate, the medial putamen and the NAcc, the highest are found in the lateral putamen [40, 42, 43]. The D_2 receptor has a similar distribution with high concentrations observed in the corpus of the caudate, the lateral and medial putamen and the NAcc [45–47]. Despite the co-localisation of the D1 and D2 receptors in the striatum being somewhat similar to the location of the dopamine receptors on striatal cells, the projections are quite different [48]. D_1 receptors are found exclusively post-synaptically on GABA-ergic striatonigral cells, which predominantly project

ventrally to the SN [49]. In contrast, D_2 receptors have a predominantly presynaptic location and are found on GAB-ergic striatopallidal cells, the projections of which head out of the striatum into the GP, another of the basal ganglia structures [49, 50].

Changes in the shape and size of the putamen in schizophrenia have been attributed to the consequences of antipsychotic and neuroleptic treatments, supported by animal studies and human MRI scans [15, 51, 52]. However, ultra-structural examination of the spiny neurons of the striatum shows changes in spine shape and axon density in the adjacent caudate, not the putamen, arguing against drug treatments as a cause [21, 22], and larger putamen sizes have been reported to be increased in schizotypal disorder without anti-psychotic treatment [53]. A case where a 38-year-old man with no relevant family history experienced a lacunar infarct of the putamen region in the left basal ganglia and developed persecutory delusions and delusional memory, worsening over time until referral to a psychiatric unit suggests a functional link to psychosis [54].

Such is the relationship between putamen size and cognitive and mood function that some studies have suggested a correlation between them. Patients with good outcome schizophrenia have larger relative mean putamen, but not caudate, size than poor outcome patients or controls. A lateralised effect was observed too with this enlargement more prominent for the dorsal putamen and right hemisphere. Striatal size was not related to whether patients were currently being treated with atypical or typical neuroleptics or whether they had been predominantly treated with typical or atypical neuroleptics over the past 3 years. This suggests the possibility that the expansion of putamen size may be a physiological correlate of neuroleptic responsiveness or that small putamen size at disease onset may be a predictor of outcome [14]. Stereological examination of the putamen in schizophrenia confirmed the imaging finding of decreased volume and showed a decrease on total neuron number [31]. Repeated amphetamine treatment, known to stimulate striatal DA, has been shown to increase dendritic spine density on putamen medium spiny neurons [55], suggesting that the number of cells and overall size are not the only factors in the interaction between schizophrenia, drug treatment and patient outcome. The putamen specifically and striatal structure in general have not been well researched in mental illness, and changes to this system are not well understood but is clearly of critical importance in the symptomatology of schizophrenia.

The evidence suggests that the DA activity from the nigrostriatal pathway provides direct or indirect trophic and functional support to the putamen. Whether this is done by known mechanisms, such as growth factors or direct stimulation of neurons by connecting synapses, or by some other mechanism is not clear.

9.4 Internal Capsule

To anyone familiar with the basal ganglia during dissection, the distinct structure of the IC substantial as a large white matter tract running through from the superior to the inferior surfaces of the striatum is well known (shown in coronal section in

Figs. 9.1 and 9.2) Whilst it may be typical to focus on the subcortical grey matter in the nearby basal ganglia and thalamus, the internal capsule is a complicated structure in its own right, made up of multiple substantial white matter tracts with roles in several key pathways.

The IC is the large white matter structure lying between the caudate and putamen in the anterior basal ganglia and between the caudate head, putamen and thalamus more caudally. It has a key role in whole brain function with almost all neural connections to and from the cerebral cortex running through it, as well as being the primary route of thalamic fibre tracts. As shown in Fig. 9.2, there are smaller fibre tracts within the IC. The corticobulbar tracts relays signals from the motor cortex to the motor nuclei of the cranial nerves and other brainstem targets, whilst the corticopontine tract has descending fibres from the cerebral cortex through internal capsule, through the cerebral peduncle to the pontine nuclei. Also, there are descending fibre tracts known as the corticospinal fibres which run from the cerebral cortex through the IC to the spinal neurons and interneurons. The superior thalamic radiation has multiple fibres rising from the body and leaving the medial surface of the posterior limb of the internal capsule towards the thalamus, before being redirected to the parietal lobe for processing of general sensation information. Other fibres projects from the cerebral cortex to basal ganglia structures, such as the putamen

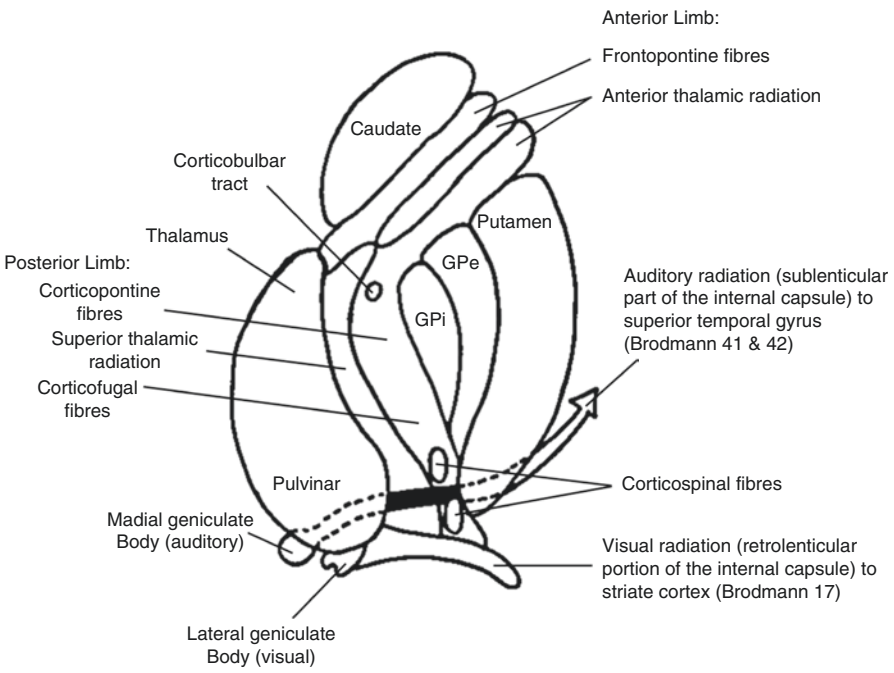

Fig. 9.2 Schematic of coronal cut of stratum showing the anterior and posterior limbs and genu of the internal capsule. *GPi* globus pallidus internal, *GPe* globus pallidus external. Medial surface to left

and caudate, as well as disparate subcortical structures. These fibres fan out above the IC to connect to the whole cerebral cortex in a fan-like structure called the corona radiata, where they merge and entwine with cerebral–cerebral connections in the centrum semiovale of each hemisphere.

Anatomically, the IC is a continuous sheet which forms the medial boundary of the lenticular nucleus and continues round to partially enclose the lenticular nucleus caudally and inferiorly. The inferior region is where the fibres descending to the cerebral peduncle are funnelled, whereas the superior surface is the direction of fibres destined to move into the corona radiata.

The IC in schizophrenia has been examined using imaging methods by several studies. Multiple studies have consistently shown that compared with controls, patients with schizophrenia displayed significantly lower fractional anisotropy (FA) in the left IC as measured by diffusion tensor imaging [56]. Whilst this finding has been repeatedly demonstrated, further details have shown the typical confusion that schizophrenia research is known for. Some of these studies have suggested that the decreased FA is present in the posterior limb [57–60], whilst others on the anterior limb [61]. Whilst most studies have shown a lateralised FA change, they often disagree on whether it is in the left or right hemisphere [57, 59, 60, 62]. More recent, and perhaps more sensitive, examination has shown FA decrease in schizophrenia in the cerebral peduncle [59] and the corona radiata [60], suggesting this may be a functional change in axon alignment and function rather than specifically and structural one. Interestingly, FA changes in the IC have been reported to be linked to cognitive performance in the disorder. Anterior limb FA correlated positively with performance on measures of spatial and verbal declarative/episodic memory in schizophrenia [61], and reductions in IC anisotropy have been linked with poor outcomes in schizophrenia, with right hemispheric changes more significantly associated with positive symptomatology [63, 64]. As IC FA changes have been reported in first-episode schizophrenia cases, it may be that FA in this structure predate the onset of illness, suggesting a possible method of diagnosis prior to first episode [58].

Structural MRI studies have suggested significant volume reduction in the bilateral anterior limbs of the IC [65], although more recent examination has shown a significant increase in volume in the anterior limbs [66]. However, multiple reports have shown white matter density is decreased in IC independent of volume [67–69]. Similar to the implications of decreased FA, volumetric IC changes have been associated with symptomatology. Patients with poor-outcome had significantly smaller dorsal areas than healthy comparison subjects, but good-outcome patients did not differ from healthy comparison subjects. Larger relative volumes of the caudate, putamen, and thalamus are reported to be associated with larger volumes of the internal capsule in healthy comparison subjects and good-outcome patients, consistent with frontal-striatal-thalamic pathways. Larger ventricles were associated with smaller internal capsules, particularly in healthy comparison subjects. These findings are consistent with the FA data, suggesting disruption of IC fibres in poor-outcome schizophrenia patients [70].

Myelin-related genes have been examined in the IC in schizophrenia due to the ICs role in the cortico-striato-thalamic circuits [71]. The results are complex, but the

authors show decreased CNP, GALC, MOG and MAG mRNA expression in schizophrenia, as well as increased ALDH1L1 and GFAP mRNA in schizophrenia [72], suggesting a possible change in astrocyte function as well as the myelin-related roles. Whilst only a single study, this suggests possible routes for further molecular and neuropathological roles of glia in IC white matter disruption.

Overall, there is considerable evidence for significant disruption of white matter tracts within the IC, although narrowing down the precise causes and effects has proved elusive. As Holleran *et al*. state, 'These deficits can be driven by a number of factors that are indistinguishable using *in vivo* diffusion-weighted imaging, but may be related to reduced axonal number or packing density, abnormal glial cell arrangement or function, and reduced myelin' [57]. To establish the extent of internal disruption in schizophrenia, and possible causes of the findings described above, we require experiments to examine the axonal arrangement and glial cell biology of this structure, and the genetic and molecular factors that may underlie the local regulation of white matter to elucidate the causes of the observed changes.

9.5 Globus Pallidus

The GP is a ventromedial structure of the basal ganglia. It is flanked laterally by the striatum and inferior to the thalamus. Whilst the GP is structurally a consistent nucleus, functionally it can be split into two sections, the more medial internal part (GPi) and the lateral external part (GPe).

In contrast to the medium-spiny neurons of the striatum the GP is predominantly made up of larger parvalbumin-positive disc-shaped aspiny GABA-ergic neurons with large number of dendrites and pathologically appears far denser than adjacent basal ganglia structures. The GPe, structurally lying immediately medial to the striatum, predominantly receives inputs directly from the striatum by means of a pronounced GABA-ergic pathway, making up the majority of synaptic nuclei within this structure. The primary output of the GPe is composed of GABA-ergic projections to the STN, located inferior of the GPi. In turn the STN has a substantial glutamatergic projection to the GPi tracing an indirect pathway from the striatum via GPe.

The GPi is found more medial than the GPe but still receives a similar direct GABA-ergic inhibitory cluster of projections directly from the striatum. The GPi has two major outputs, the first to the thalamus via two pathways. The lenticular fasciculus is one output pathway which projects via the IC whilst the ansa lenticularis projects ventrally around the IC. These meet at the thalamic fasciculus and terminate in the ventral anterior and ventrolateral parts of the thalamus, which in turn project excitatory glutamatergic pathways to the premotor and frontal cerebral cortices, areas involved in cognition, planning and initiation of movement. This feedback pathway is involved in regulating the level of excitation in the premotor cortex and thus giving a mechanism for basal-thalamic-cortical regulation of movement. The second major Gpi output is a cluster of glutamatergic outputs to the SNr, suggested to regulate nigral DA release, and thus provide a feedback loop for the

nigrostriatal tract. Various experimental manipulations, including microdialysis in rodent and PET in primate models, have shown a role of the GP and STN in regulating somatodendritic DA release in the SN under normal and experimental conditions [73], and probabilistic computation has added to the anatomical argument that the GP is the critical regulatory step from striatal output to the thalamus [74]. This is summarised in Fig. 9.3.

The returning cortical input to the striatum activates inhibitory neurons to the GP, decreasing activity in the tonically active neurons in the GP which then decrease the inhibitory action on ventral anterior and ventrolateral parts of the thalamus. The conclusion of this pathway is therefore disinhibition of thalamic excitation of the cerebral cortex and thus greater activation of the cortex. In the case of the motor cortex activation of the direct pathway would increase the ease of initiation and ease of movement. The GP is also connected with structures involved in reward circuitry such as the NAcc, habenula and the VTA, although further research is required to identify the GP-specific role in these circuits [76, 77].

Structural MRI imaging studies have shown conflicting results, with studies often showing no overall change in size in the GP in schizophrenia but a change in shape, whilst others suggest that GP size is changed. One analysis of basal ganglia relative size and shape suggests that the GP was significantly larger overall, with another study showing increased GP size and altered shape in schizophrenia on the right side only, a lateral change which seems unique within the basal ganglia. Enlargement of basal ganglia structures has typically been found to be related to antipsychotic medication, although the study determining the lateralised effect found no such effect of medication taken at the time of study [15, 78–80].

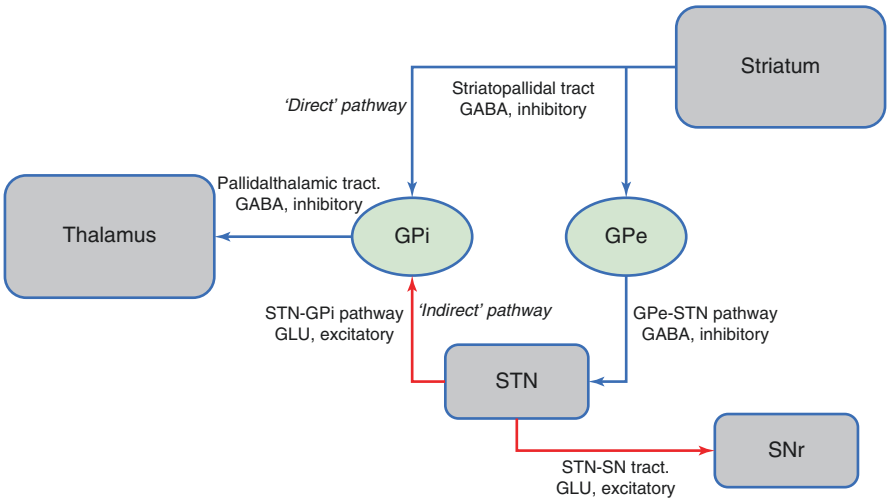

Fig. 9.3 Circuit diagram of the major connections of the GP. Blue—inhibitory pathways, red—excitatory pathways. *STN* sub-thalamic nucleus, *SNr* substantia nigra pars reticulata, *GABA* gamma-amino-butyric acid, *GLU* glutamate [75]

The size increase in GP in schizophrenia has been suggested to be related to the total psychotic symptoms. One study showing GP enlargement in schizophrenia with psychosis also showed GP shrinkage in schizophrenia cases without psychosis, with the GP smaller even than unaffected controls [80]. Dysfunctional interhemispheric connections of the GP has been proposed as the primary site for cognitive disturbance in first-episode schizophrenia measuring negative symptoms and cognitive impairment in functional MRI examination [81].

Despite the intriguing imaging results and the key role the GP plays in regulating striatonigral and striatothalamic circuits, direct neuropathological investigation of the GP is thin on the ground in schizophrenia. One landmark study has reported that the GPi decreased in volume by 20% whilst the GPe was not changed when systematically examined in sections through the structure using histological staining [82]. One early study suggested increased iron, termed 'mineralisation', of the GP in schizophrenia, although follow-up studies failed to replicate this effect [83–85]. As has previously been mentioned, animal studies using microdialysis have revealed that the striatopallidal pathway from both GP nuclei regulates SN and VTA dopaminergic cells. Although so far direct investigation of binding potential change of D_2 receptor in the pallidus using PET show inconclusive results in both schizophrenic patients and high-risk individuals [86, 87].

High-risk individuals have shown more interesting results in other studies. Teenagers at high risk of developing schizophrenia have left GP size increased by a small but significant average of 1% compared to non-high-risk controls, with a more pronounced increase with age. This suggests that the increased size may predate schizophrenia first-onset, and GP enlargement may not be down entirely to antipsychotic action [88].

In a similar finding, voxel-based morphometry examination with structural MRI has shown increased grey matter in the GP in first-degree relatives of schizophrenia patients as well as those patients themselves [89]. GP deformation was also observed in unaffected relatives of schizophrenia patients, albeit to a lesser degree than those suffering with schizophrenia [80].

Although the role of the GP in modulating striatal output to the thalamus and midbrain has good supporting evidence, the GP's role in other, less prominent circuits is not well understood. There have been few good quality studies to investigate the cognitive- and movement-related role of this structure in both normal controls and schizophrenia patients, and a woeful lack of direct examination at the cellular level using any type of pathological techniques. Additionally, the problems of interpreting the results we have obtained are compounded by the known effects of antipsychotic medication. This makes the GP a prime candidate for further examination in schizophrenia from both a basic neuroscientific stance and in future drug development.

9.6 Nucleus Accumbens

Historically, the NAcc has been of interest in neuropsychiatric disorders due to its proposed role in addiction, particularly with morphine, cocaine and amphetamine, thought to be due to drug-mediated release of DA from the VTA and SN. More

recently, nicotine addiction has been suggested to work through this pathway [90, 91]. The NAcc is a basal ganglia nucleus, sometimes described as part of the ventral striatum although it is distinct from the two primary striatal nuclei, the caudate and putamen, and is a central part of the cortico-ganglia-thalamic loop [92]. The NAcc is directly continuous with the main dorsal part of the striatum, and often described as part of the striatal complex. However, it has some structural distinction compared to the putamen and caudate as it is split into a core and a shell [93]. The core is largely continuous with the rest of the striatum and is composed of similar spiny neurons which predominantly form the output neurons of the NAcc, although the shell has independent projections to the bed nucleus of stria terminalis and lateral hypothalamus [93, 94]. The NAcc also receives a distinct collection of DA neurones directly from the VTA, the DA nucleus that lies adjacent to the SN. This is known as the mesolimbic pathway and has been strongly implicated in addiction [95]. Whilst the main output structure for striatal medium spiny neuron axons is the thalamus, major pathways also project to the GP and the NAcc, as well as reciprocal projections back to the DA regions of the VTA and SN (Shepherd 2013). There is a reciprocal feedback loop of GABA projections from the NAcc to the ventral pallidum and VTA, and there are glutamatergic projections from the PFC, hippocampus and amygdala. The amygdala glutamatergic projection to the NAcc in particular has been suggested as key in modulating cue-triggered motivated behaviours [96], and the PFC regulates NAcc dopaminergic output by glutamatergic projection [97]. Hippocampal projections to the NAcc arise from the subiculum, the most inferior part of the hippocampal formation, lying between CA1 and the entorhinal cortex (discussed in Chap. 6). The ventral subiculum exerts a strong regulatory role on activity of DA projections from the VTA via glutamatergic mechanisms localised within the NAcc [98, 99]. The precise pattern of inputs to the NAcc is complicated, but the projections from the cortex, thalamus and amygdaloid are topographically organised (see Groenewegen et al. [100] for review), meaning that only in limited parts of the nucleus do interactions between these inputs occur.

The structure as a whole has evidence of change in schizophrenia, with a 42% decrease in NAcc volume and 50% decrease in neuron number reported [101, 102], but this is in contrast to other studies of the same regions showing no changes [103]. Post-mortem studies have mostly suggested that the NAcc shows no overall change in volume in schizophrenia, although one small scale ($n = 9$) stereological study did report an overall increase in NAcc size [31, 101, 104, 105]. Some imaging studies have suggested decreased volume [16, 106]. The right NAcc and caudate higher neuron numbers in schizophrenia [30], with another study showing no change in NAcc neuron number [31]. The possible causes of such strongly conflicting results may well be down to the stereological methods [33].

The very large ENIGMA project scanning over 2000 schizophrenic brains compared to more than 2500 controls showed the NAcc was smaller in schizophrenia, as well as similar findings in smaller studies [16, 106]. This has not been consistently reported in large imaging studies, with striatal volumes, including the NAcc, showing no change in schizophrenia [82].

The NAcc has a potentially important role in the biology of schizophrenia as it is part of a complex processing loop of cortico-striato-nigral-thalamo-cortical circuits [107], which has been assumed to be a prime system for the elevated DA levels in schizophrenia, based on its functional properties and evidence of antipsychotic drug action [108–110]. DA turnover was not increased in schizophrenic patients but, as assessed by the spiroperidol-binding technique, there was a significant increase in post-synaptic receptor sensitivity. The change in the dopamine receptor occurred in NAcc, putamen and caudate nucleus [111–118]. Ultrastructural examination of the NAcc shows that appearance, size and density of mitochondria were normal in the nucleus accumbens [35], but that NAcc synapses show a 19% increase in the density of asymmetric axospinous synapses in the NAcc but not that in the shell in schizophrenia. Similarly postsynaptic densities of asymmetric synapses had 22% smaller areas in the core NACC but again not in the shell, suggesting increased excitatory input to the NAcc core in schizophrenia [119]. The cortico-striato-nigral-thalamo-cortical circuits have been suggested to be a prime system for the elevated DA levels in schizophrenia, based on its functional properties and evidence of antipsychotic drug action therein [108, 110]. The changes in DA receptors occurred in the NAcc, putamen and caudate nucleus [113, 114]. Initially, studies found no change in possible DA-receptor sensitivity in the NAcc, but one later neuropathological study has reported potential decreased DA-sensitivity change [116, 118].

Amphetamine administration yields an NAcc neurotensin response which can be blocked using a dopamine D1 antagonist, suggesting a physical as well as functional variation in dopamine receptor subtypes throughout the NAcc. These differing regulatory pathways moderated by DA receptors clearly have significant implications for the role of antipsychotic medication in schizophrenia treatment. The NAcc has also been shown to be involved in stress-activated activation of the DA system and thus may be related to schizophrenia symptoms influenced by stress. Information transfer from ventral to dorsal striatum, essentially the mesolimbic pathway, relevant to antipsychotic medication depends on both striato-corticostriatal and striato-nigro-striatal sub-circuits. Although the functional integrity of the former appears to track improvement of positive symptoms of schizophrenia, the latter has received little experimental attention in relation to the illness. Compared with non-refractory patients, treatment-resistant individuals exhibited reduced connectivity between ventral striatum and SN. Furthermore, disturbance to corticostriatal connectivity was more pervasive in treatment-resistant individuals [120]. Controlled treatment of antipsychotic medication in rats such as haloperidol shows significant intermediate-early gene mRNA in the striatum, particularly strongly in the NAcc. In contrast clozapine produces a similar Fos-response in the NAcc but not the rest of the striatum [108, 110]. As with the other basal ganglia, the role of the NAcc is poorly understood given its clear critical role in both the pathophysiology of schizophrenia and in the role antipsychotic medication plays in the treatment of the disorder. Further examination is needed in this structure and the associated subcortical networks, to better target future treatments.

9.7 Substantia Nigra

The substantia nigra (SN) is a paired midbrain structure that lies immediately ventral to the cerebral peduncles at the level of the superior colliculus (Fig. 9.4) and has a critical regulatory role in the CNS. The dysfunction of this structure is implicated in the pathology of several serious illnesses. Substantia nigra translates from the Latin as 'black substance' as it is recognised by its characteristic black/brown-stained appearance, a result of the neuromelanin granules contained within the DA neurons as a by-product of DA metabolism (shown in Fig. 9.5). This is an easily observable phenomenon in Parkinson's disease where decreased DA synthesis causes a loss of neuromelanin formation in these cells and thus the loss of the dark colouration normal to the SN. The SN is the predominant DA-producing structure of the brain, along with smaller DA-producing cell populations in the VTA, hypothalamus and zona incerta.

Structurally the SN is often split into two distinct regions: the SN pars compacta (SNpc) and the SN pars reticulata (SNpr). The SNpc, the inner layer of the SN closest to the cerebral aqueduct, is a densely packed structure containing the large DA-producing neurons, modulated by accompanying interneurons, and is the source of the DA projections to the striatum, GP and the SNpr. Input into the SNpc occurs via GABA-ergic and glutamatergic feedback mechanisms from striatal and GP regions [121–124], with the SNpc receiving almost all its regulatory input from the GP with a small input from the frontal lobe. By contrast, the SNpr is larger but far more diffuse and comprised of much smaller, GABA-neurons than the SNpc, and occupies the outer layer of the SN. These neurons receive the SNpc DA projections and send GABAergic projections to the ventral anterior and ventrolateral thalamus, the superior colliculus and to the pedunculopontine complex, a brainstem nucleus caudal to the SN. These subdivisions have a reciprocal set of internal connections making a functional loop from the SNpc to the striatum, back to the SNpr to regulate the SNpc. The causes of excess SNpc DA in psychosis or decreased SNpc DA in Parkinson's disease are not well understood, but a key focus of interest is the SN-striatal loop. Internal connectivity also occurs via glutamatergic and GABA-modulated interneuron–dendritic interactions, modulating DA activity of the SN both within and between the SNpc and SNpr [121, 125, 126].

In schizophrenia the primary interest in the SN is due to it being the origin of the nigrostriatal pathway, the most prominent SN DA projection with axons from the SNpc DA neurons ascending into the striatum in a topographic manner, although with a distinct cluster that terminates in the dorsal putamen. This pathway is part of the basal ganglia loop, a functional system thought to have an important regulatory role in cognition. DA pathways from the SN and VTA are shown in Fig. 9.6.

DA influence on striatal medium spiny neurons is receptor-specific, with D_1 (excitatory) and D_2 (inhibitory) receptors leading to excitatory and inhibitory striatal responses, which permit discrimination of motor programs to suit the required task, the dominant function of the nigrostriatal pathway. Historically, psychosis has been treated using first-generation antipsychotics, which primarily bind to the D_2 receptors and have slow dissociation rates. D_2 receptors are found in the striatum

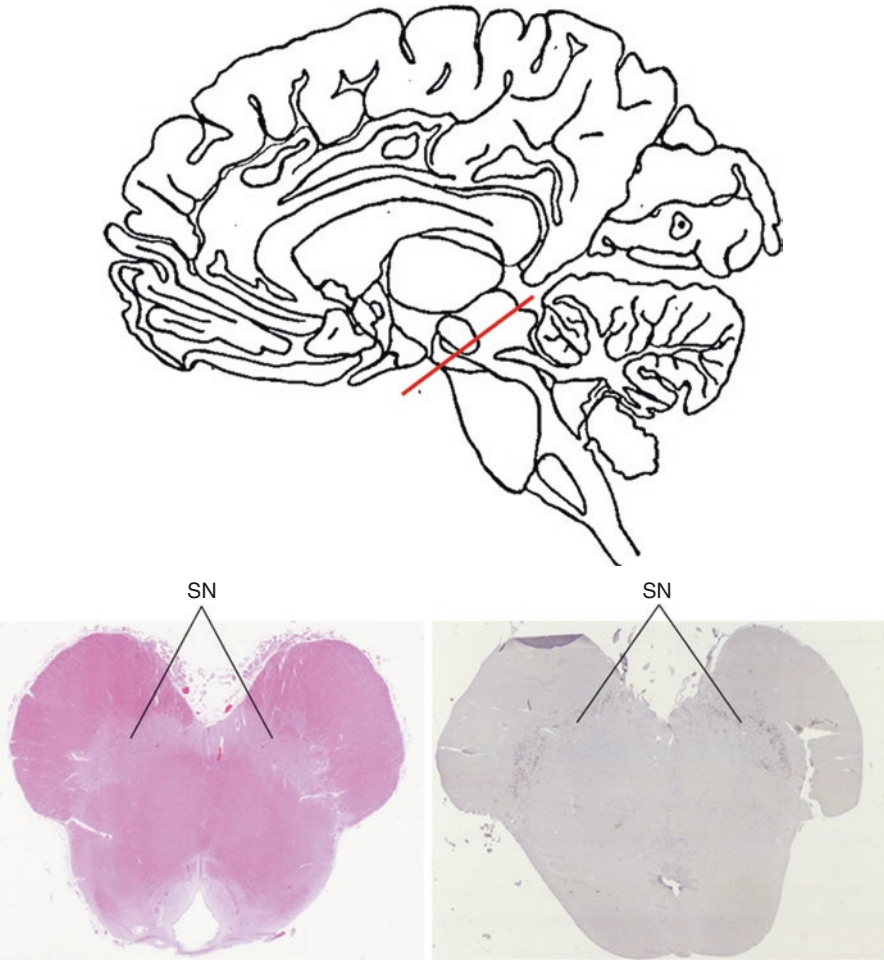

Fig. 9.4 Coronal cuts through midbrain at the level of the superior colliculus, cut indicated by red line on the upper image. Adjacent 10 μm slides stained with H&E (lower left) and cresyl-violet (lower right) histology both show the substantia nigra (SN) clearly by the presence of the large DA-producing neurons

where they modulate SN DA signal from the nigrostriatal pathway into the putamen. There is a strong correlation between therapeutic doses of antipsychotics and binding at the D_2 receptors [123, 124, 127], and D_2 antagonism can cause motor dysfunction such a pseudo-parkinsonism, which remained a problem with these early drug regimes. Second-generation antipsychotic drugs generally have lower rates of D_2 occupancy, decreasing the motor symptoms but often have better therapeutic outcomes. This is thought to be due to their dual action on the serotonin system, primarily through 5-HT_{2A} antagonism in addition to multiple reported sites of action other than dopamine D_2 receptors, including dopamine (D_1, D_3, D_4),

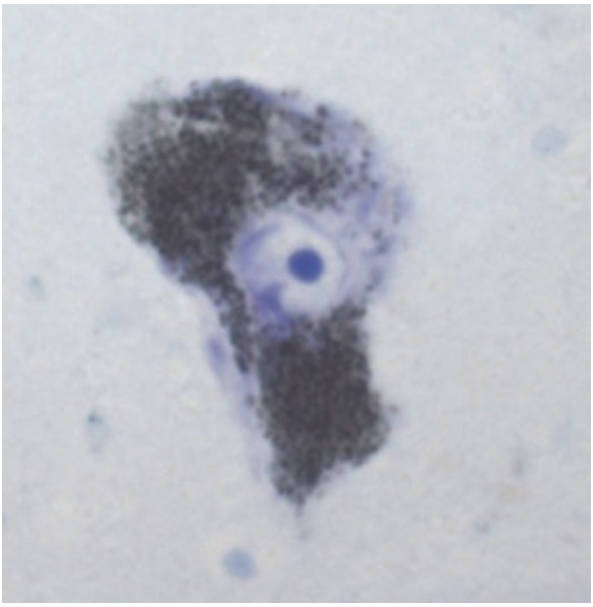

Fig. 9.5 Image of a large DA-producing SN neuron with light cresyl-violet staining. In addition to the clear nucleus and nucleolus, the neuromelanin can be clearly seen in the cytosol. Taken at ×400 magnification

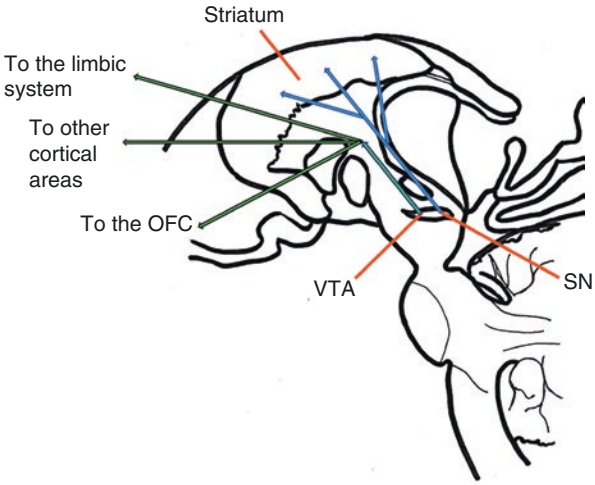

Fig. 9.6 Representation of the layout of the mesolimbic and mesocortical (green) and nigrostriatal (blue) pathways. These DA pathways have been heavily implicated in behavioural regulation, particularly in regard to antipsychotic medication action and addiction. *OFC* orbitofrontal cortex, *VTA* ventral tegmentum area, *SN* substantia nigra

serotonin (5-HT_{1A}, 5-HT_{2C}, 5-HT_6, 5-HT_7), muscarinic cholinergic and histamine receptors [128, 129]. In direct comparisons, there has been no difference in the efficacy of the first-generation antipsychotics and second-generation antipsychotics in acute therapy in schizophrenia at similar doses [130]. However, meta-analysis has shown some evidence that the second-generation antipsychotics may be better tolerated over time [131] and have a greater effect on negative symptoms than the first-generation antipsychotics [132, 133], primarily modulated by the serotonergic effects of the second-generation antipsychotics. Comparison of the effects of these

drugs on cognition have not yielded clear findings, although some mild improvement in cognitive symptoms with the second-generation antipsychotics have been reported [134–136]. As much of the basal ganglia DA system is involved with the motor system, the lack of effect of the first-generation antipsychotics on cognition may not seem surprising. But the causative pathway from elevated nigrostriatal DA to the cortical disruption leading to psychosis is not known, and clearly there are downstream effects from striatal DA-modulated changes critical in regulating cortical function.

In recent years, the SN has become more interesting to those who study psychotic disorders and schizophrenia as the DA hypothesis of schizophrenia has proposed subcortical DA dysfunction, presynaptic-DA dysfunction, underlies many symptoms [11, 137]. This model is based upon DA dysfunction in the striatum [138], and schizophrenia is associated with elevated striatal DA level and synthesis [139, 140]. One of the most interesting findings of recent years is that increased striatal dopamine synthesis capacity is evident in individuals with prodromal schizophrenia symptoms, suggesting that DA abnormalities predate the onset of first-episode psychosis [141]. By contrast, there is no similar elevation in non-psychotic depression [142] or in patients with persistent subclinical psychotic symptoms who have not developed a psychotic disorder, suggesting specificity to psychotic illness [12, 143, 144]. Whilst this focus has been on striatal DA, it should be reiterated that DA is synthesised in the SN and transported along the nigrostriatal pathway, meaning that the SN is the structure behind the extensive striatal DA changes. Direct examination of SN DA neurons suggests that excess DA synthesis is the cause of elevated DA, rather than insufficient DA breakdown. DA is synthesised from tyrosine via a two-step process, tyrosine hydroxylase (TH) converts tyrosine into dihydroxyphenyl-L-alanine, the rate-limiting step of DA synthesis, which is converted by aromatic acid decarboxylase into DA [145]. DA is broken down by two pathways: by dopamine-β-hydroxylase (DBH) to noradrenaline and by catechol O-methyltransferase (COMT) to 3-methoxytyramine. DBH is a vesicle-bound enzyme which has not been investigated well in mental illness, although has a strong role in addiction, whereas COMT exists in both intra- and extracellular forms, with the extracellular form often found in astrocytes, and astrocyte density has been reported to be decreased in the SN in schizophrenia [13]. However, no direct evidence has demonstrated that breakdown pathways have any role in SN DA function [146], in contrast to the PFC where COMT activity has been reported to have a role in working memory [147].

Post-mortem studies have found altered tyrosine hydroxylase mRNA levels, increased amount and variability of TH levels in the SN of schizophrenia patients [144, 148]. TH staining was significantly increased in nigral DA-neurons in schizophrenia, and this was not due to medication effects. These cells did not have elevated DA-mRNA, suggesting that this increases in regulated post-transcriptionally [12, 149], with these cells also having increased somal size, nuclear cross-sectional area and increased nucleolar volume compared with controls, in addition to decreased astrocyte density. Indeed, detailed examination of the DA neurons themselves suggests that their soma and nuclei are physically swollen in schizophrenia, suggesting a very substantial increase in DA synthesis [13].

Whilst we have much to learn about the regulation of the SN in schizophrenia and similar illnesses, the evidence so far suggests that excess SN-striatal DA may not be due to a fault within the SN itself but rather a regulatory issue that most likely originates elsewhere within the basal ganglia. As described above, the SN is part of a complex network which we are only now beginning to functionally examine piece by piece, and we hope that in the near future, the neurophysiology underlying these severe illnesses can be unravelled, and better therapies developed.

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The Thalamus

10

Matthew Williams

10.1 Structure and Location

The thalamus is a key diencephalic bilateral structure, roughly egg-shaped and composed of multiple nuclei which physically occupies around three-quarters of the diencephalon. It lies immediately adjacent to the lateral ventricles, bounded by the interventricular foramen, the transverse cerebral tissue and the floor of the lateral ventricles on the anterior end. It is superior to the midbrain allowing for cortical–cortical and cortical–subcortical connections globally. The thalamus forms the upper and lateral walls of the third ventricle whilst the dorsal surface is a part of the floor of the body of the lateral ventricle. Laterally, the thalamus limits with the posterior arm of the internal capsule. Anterolaterally it limits with the head of the caudate and ventral nucleus with the subthalamus and hypothalamus. The location of the thalamus in shown in coronal, sagittal and axial axes in Figs. 10.1, 10.2 and 10.3.

The two thalami are often connected by the interthalamic adhesion (ITA), a white matter structure crossing the midline. The ITA is not present in all cases though, and even where it is present very few axons cross from one hemisphere to another, mostly turning back upon themselves into the originating nucleus; therefore, it is not thought to be a critical structure for thalamic function.

The external and internal medullary laminae are white matter structures of thalamus, covering the lateral surface of the thalamus, and the internal medullary laminae (IML) divide the thalamic nuclei into its anterior, medial and lateral nuclear groups [1].

The thalamus has a large number of sub-nuclei, some sources reporting up to 60 definable structures [2], that make up key parts of many cortical–cortical, subcortical–subcortical and cortical–subcortical networks, and has been neuropathologically

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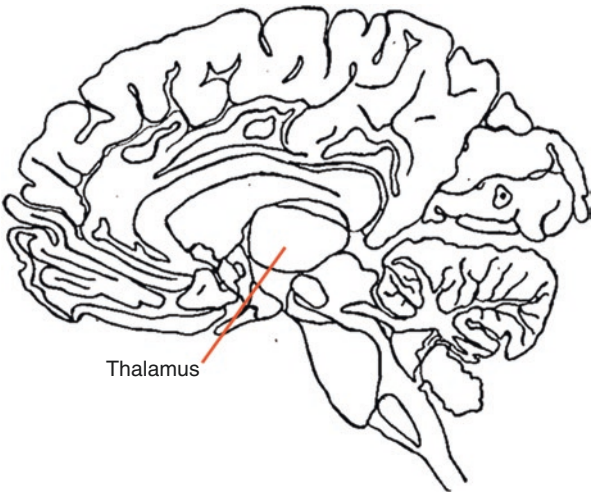

Fig. 10.1 Location of thalamus in sagittal view

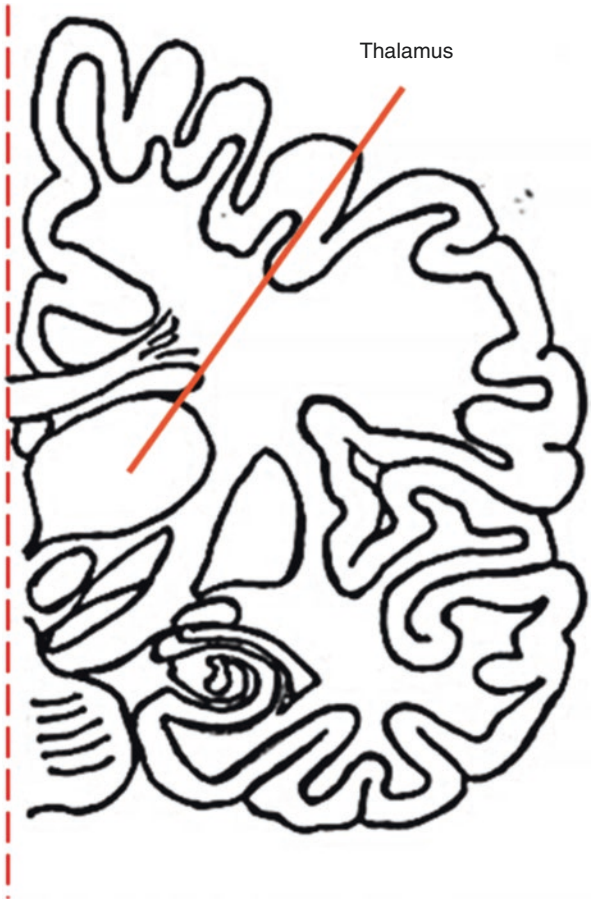

Fig. 10.2 Location of thalamus in coronal view. Dotted red line represents midline of brain

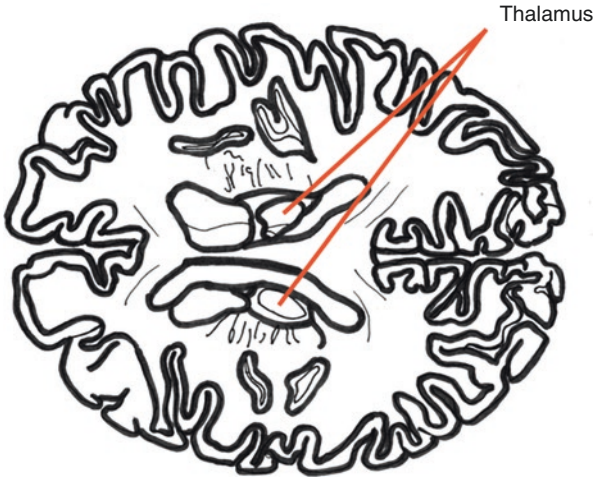

Fig. 10.3 Location of thalamus in axial view

studied in schizophrenia more than any other deep subcortical structure, although this focus has tended to be focused on specific nuclei such as the mediodorsal thalamus (mdTh).

The nuclei of the thalamus are generally split into medial and lateral groups, divided by the IML. Towards the anterior end of the thalamus, the IML splits to enclose the anterior nuclear group (ANG) on either side. It is this which borders on the intraventricular foramen. Similarly, the medial nuclear group is composed of a single large nucleus, the mdTh. The lateral nuclei are the largest thalami group, with the lateral posterior nucleus continuous with the pulvinar, often referred to as the pulvinar-lateral posterior complex, sharing similar connections with the rest of the brain. A summary of thalamic sub-nuclei is shown in Table 10.1.

Due to the complexity of the thalamus and its multiple sub-nuclei, it is not practical to examine all defined structures within or whether, like the amygdala, a more reasonable functional assessment should be made for future neuropathological research. The complexity of thalamic structure means that the terminology varies between papers and reviews. The terminology used in this chapter follows structural anatomy as far as can be with descriptions and abbreviations of nuclei shown in Table 10.1, with primary afferents and efferents illustrated in Figs. 10.4 and 10.5, which will inevitably deviate from some published descriptions. For a comprehensive review of the problems with thalamic anatomy and terminology, see Mai and Majtanik [3].

The reticular nucleus forms a capsule around the thalamus laterally. This nucleus does not project to the cerebral cortex, instead its function is to process information it receives from other thalamic nuclei. The reticular nucleus also receives disinhibitory input from the globus pallidus allowing for the initiation of voluntary movement. The lateral geniculate nucleus of the thalamus receives visual sensory information from the retina to route to the visual cortex of the occipital lobe. The medial geniculate nucleus receives auditory sensory information from inferior

Table 10.1 List of thalamic nuclear groups and sub-nuclei with abbreviations

Nuclear group	Nucleus	Abbr.	Notes
Medial	Mediodorsal thalamus	mdTh	The mdTh is often split into magnocellular and parvocellular parts dependent on the cell type
Midline (MNG)	Paratenial nucleus Paraventricular thalamic nucleus Nucleus reuniens	PN PVT NR	The PVT should not be confused with the paraventricular nucleus of the hypothalamus The NR is located within the interthalamic adhesion
Lateral (LNG)	Ventral anterior nucleus Ventral lateral nucleus Ventral posteromedial nucleus Ventral posterolateral nucleus Pulvinar	VAN VLN VPm VPl Pul	The LNG contains the ventral nuclear group (VNG)
Anterior (ANG)	Anterior nucleus	ANTh	The ANG is bounded medially and laterally by the IML and is formed of three sub-nuclei: The anteroventral, the anterodorsal and anteromedial
	Lateral geniculate nucleus	LGN	Thalamic relay for visual information
	Medial geniculate nucleus	MGN	Thalamic relay for auditory information

colliculus and projects it to the primary auditory cortex in the temporal lobe. The VPl of the thalamus is subdivided, with the spinothalamic tract is the sensory pathway for pain, temperature and touch that rises from the spine into the ventral posterolateral nucleus of the thalamus for further processing, whilst the VPm nucleus receives sensory information about the face from the trigeminal nerve.

Detailed examination of thalami from nine normal human brains according to cytoarchitectonic criteria shows that thalamic areas with multiple projections to the cerebral cortex are mostly symmetric. Thalamic areas that have projections to clearly defined cortical receptor fields reflected the asymmetry of the cortical fields to which they project. Hence, the MGN showed a slight right-sided bias, and the VPl, related to the asymmetric inferior parietal lobule, showed a significant left-sided bias in eight of the nine brains measured. This suggests that the idea of the thalamus as a whole having any lateralised biases may be too simple and that individual nuclear groups may be the better focus of asymmetry studies [4].

10.2 The Thalamus in Schizophrenia

With the central role of the thalamus in schizophrenia being suggested for some time, first proposed as far back as 1957, it has been neuropathologically studied in schizophrenia more than any other deep subcortical structure [5, 6].

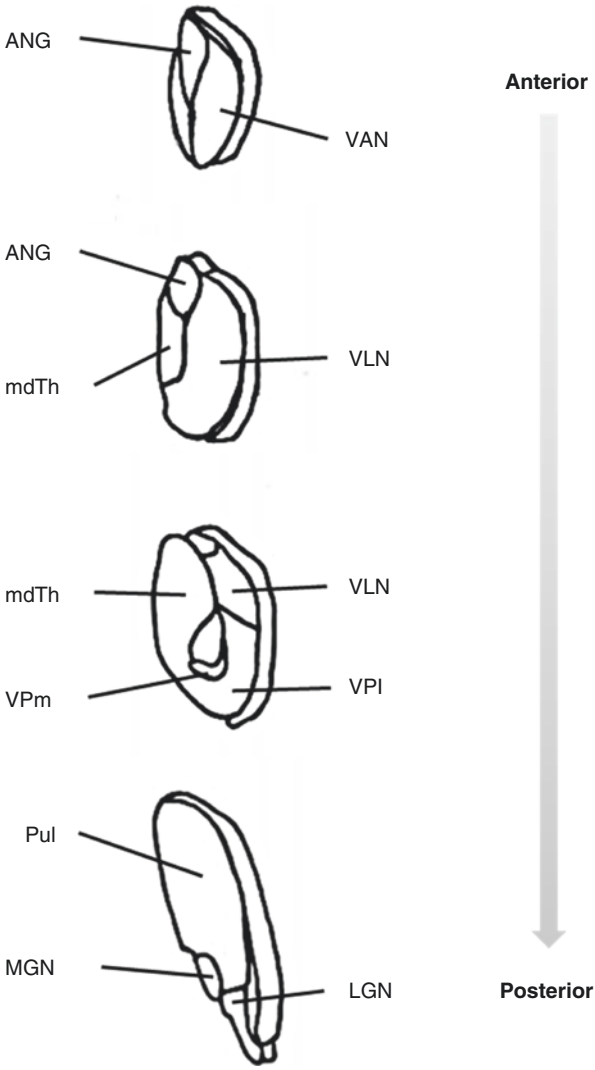

Fig. 10.4 Key thalamus sub-nuclei in coronal section from anterior to posterior through the structure. This is section through the left thalamus, with the midline of the brain to the left of the diagrams. *ANG* anterior nuclear group, *VAN* ventral anterior nucleus, *mdTh* mediodorsal thalamus, *VLN* ventral lateral nucleus, *VPm* ventral posteromedial nucleus, *VPl* ventral posterolateral nucleus, *Pul* pulvinar, *MGN* medial geniculate nucleus, *LGN* lateral geniculate nucleus

The thalamus has been reported to have reduced mean volume in schizophrenia in some neuropathological reports [7–10], with other studies suggesting no volume changes ([11–16]. Concordant twin pairs displayed significantly reduced thalamic volume compared with control twins, even when covarying for effects of whole-brain volume, age and sex. There was a significant linear decrease in thalamic volume, where the control cases were more discordant non-schizophrenic twins which in turn were greater than discordant schizophrenic twins greater than concordant. In all groups, the right thalamus was larger than left thalamus. There was no difference across groups in the frequency of the ITA [17, 18].

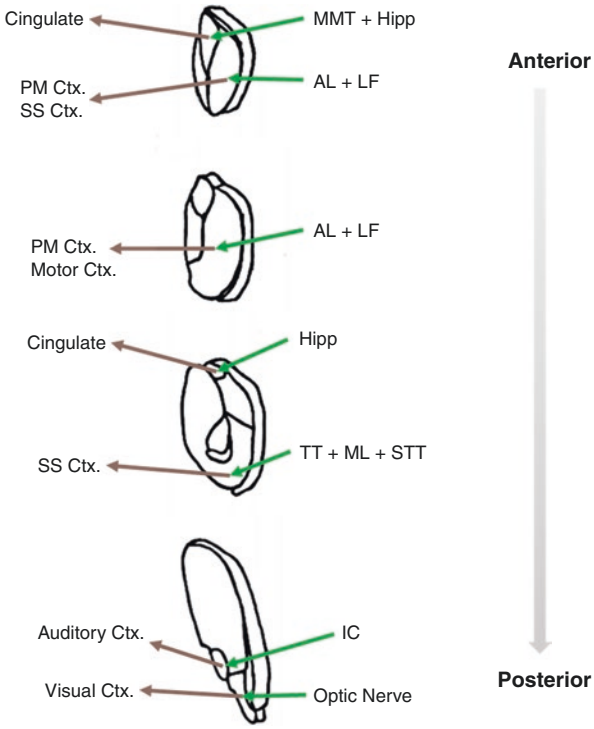

Fig. 10.5 Major inputs and outputs of thalamic relay sub-nuclei. Brown line indicates inputs, green lines indicate outputs. *MMt* mammilothalamic tract, *Hipp* hippocampus, *PM Ctx.* premotor cortex, *SS Ctx.* somatosensory cortex, *AL* ansa lenticularis, *LF* lenticular fasciculus, *TT* trigeminal tract, *ML* medial lemniscus, *STT* spinothalamic tract, *IC* inferior colliculus

Two studies have reported a reduction of the synaptic protein Rab3a from the thalamus, particularly the left thalamus, in schizophrenia post-mortem tissue, with one also reporting decreased synaptophysin compared with controls [19, 20]. Whilst not conclusive, there is scope for further examination [21, 22]. However, rather than examination of the thalamus as a whole, more useful perhaps are the changes in thalamic sub-nuclei due to their specific functional roles.

10.3 Medial Nuclear Group

The key thalamic region investigated in schizophrenia has been the mdTh, a structure implicated with a key role in cognition and memory. The mdTh has multiple separate connections to the PFC and receives inputs from several subcortical structures, but most prominently the basal ganglia [23]. The human brain has large areas of association cortex, most prominently the frontal cortex, anterior to the motor regions of the frontal lobe (often termed the prefrontal cortex as discussed Chap. 4). These regions are functionally connected to the mdTh which has been suggested to have a key role in higher cognitive functions such as foresight. Afferents into the mdTh are also present from the amygdala, suggesting a role in affect. It is because

of these higher cognitive involvements that neuropathological studies have examined the mdTh. The dlPFC-mdTh and OFC-lateral circuits are summarised in Figs. 10.6 and 10.7.

As with many other regions, these neuropathological investigations have produced conflicting results. The mdTh has been reported to have reduced mean volume and decreased total neuron number in schizophrenia in both the magnocellular and parvocellular regions [5, 7–10], but in contrast also shows no changes reported in volume, neuron density, number or size in the mdTh by stereological investigation ([11–16] or by MRI [31]. As imaging has suggested that the thalamus is erratically deformed in schizophrenia, it may be that these findings are not as inconsistent as they first appear [32].

MRI volumetric examination of a large cohort of 58 schizophrenia patients with 44 controls showed significantly smaller volumes of the bilateral mdTh in schizophrenia, although a larger study of 71 schizophrenic cases against 75 controls found

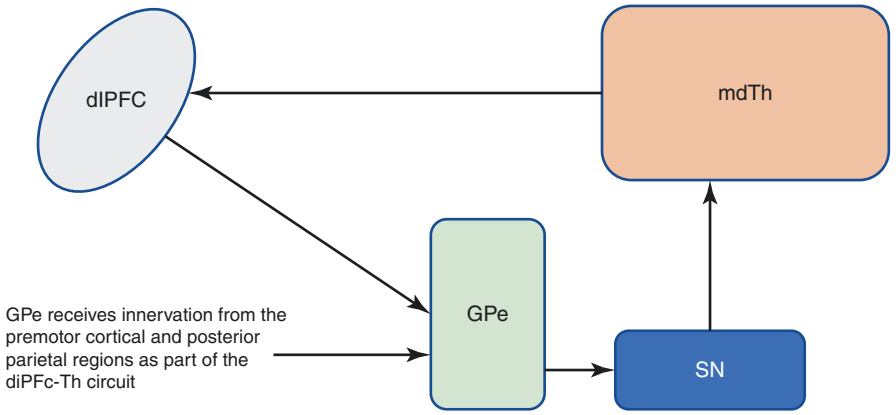

Fig. 10.6 The mdTh in the dlPFC circuit. *mdTh* mediodorsal thalamus, *dlPFc* dorsolateral prefontal cortex, *GPe* globus pallidus external, *SN* substantia nigra [24–29]

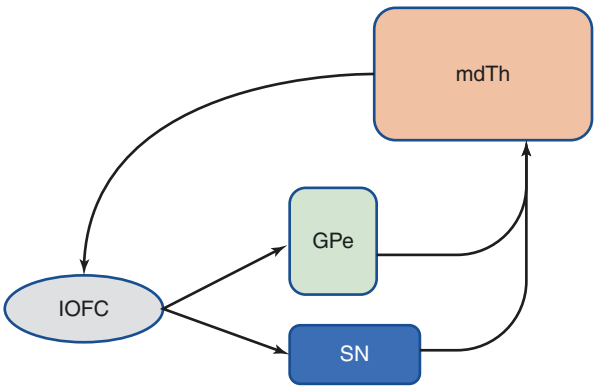

Fig. 10.7 The mdTh in the OFC lateral circuit. *mdTh* mediodorsal thalamus, *GPe* globus pallidus external, *SN* substantia nigra, *lOFc* lateral orbitofrontal cortex [24, 29, 30]

only non-significant trend in the medial thalamus, although with altered microstructure integrity reported across the thalamus in schizophrenia, which the authors conclude is the results of altered cytoarchitecture [33].

10.4 Lateral Nuclear Group

The LNG is the largest group of thalamic nuclei, containing all structures lateral of the IML and the lateral and ventral sub-nuclei as well as the pulvinar [2]. The ventral thalamus is composed primarily of three nuclei named by their anatomical organisation as the ventral anterior, ventral lateral and ventral posterior nuclei of the thalamus. These nuclei can be further subdivided as required (see Buren, [34] for a comprehensive review of human thalamic structure). Connections from the spine via the spinothalamic tract and the face via the trigeminal nerve enter the thalamus via the ventral nucleus, itself subdivided by function. The ventral nucleus of the thalamus appears to be primarily associated with sensory input from the body, relaying this to the appropriate part of the sensory cortex for neuronal processing. It is also associated with pathological tremors, suggesting motor involvement. Another key area of cortex in relation to the thalamus is the parietal-occipital-temporal association cortex which is broadly located in the grey matter surrounding the primary visual, auditory and somatosensory areas, discussed in Chap. 8. This region is similarly interconnected with the pulvinar and lateral-posterior nuclei, although the connections and functions of this network are less well understood than that of the mdTh.

Immunohistochemical study of the VAN has shown the majority of thalamocortical projection neurons in VAN were identified by parvalbumin-immunoreaction. Significantly reduced densities of thalamocortical projection neurons were reported bilaterally in schizophrenic subjects, as were decreased neuron density, though none of these were correlated with illness duration [35].

Stereological investigation of the VPl has shown that the global brain volume was not correlated to VPl volume. Both the overall volume and the total neuron number of the left VPl were decreased by around 25% in schizophrenia, although there were no significant changes in nuclear volume, neuron density and total neuron number in the right VPl, and no significant correlations between length of illness and the nuclear volume, neuron density and total neuron number in bilateral VPl [36].

Examination of volumes of the pulvinar in the right thalamus samples showed this was significantly smaller in the schizophrenic subjects. Additionally, neuronal number in the pulvinar was significantly lower. Although a small study with only 14 schizophrenia cases with eight controls, and seven cases between them having confounding Alzheimer pathology, this study does specifically suggest cytostructural disruption in the association nuclei but not the motor relay nuclei [7].

10.5 Anterior Nuclear Group

The ANG is most famous as a part of the Papez circuit. Damage to either the medial temporal lobe or the medial diencephalon often results in anterograde amnesia. Extensive hippocampal-ANG interconnections support the idea that these structures constitute a brain network crucial for memory and cognition [37–39]. As such, the ANG is the main relay for the limbic system, receiving the MMT and hippocampal afferents and projecting to the cingulate gyrus, the anterior part of which has been strongly implicated in the symptomatology of schizophrenia (discussed in Chap. 7). This network connection system is illustrated in Fig. 10.8.

Examination of the left thalami of eight male schizophrenia brains and eight male matched controls has suggested that the ANG has decreased total neuron number (−16%) [10]. A much larger imaging study of 60 schizophrenia cases and 44 controls revealed deformation of the ANG in schizophrenia, although it did not correlate to reported negative syndrome score as in the mdTh and pulvinar [47].

10.6 Geniculate Nuclei

Immediately posterior to the ventral area of the LNG, adjacent to the pulvinar, two structures are involved in the relay and processing of sensory inputs: the LGN as a part of the visual system and the MGN is a critical relay in the auditory pathway.

Use of stereology to examine the lateral geniculate nucleus (LGN), a relay between the optic nerves and the occipital lobes, has suggested that cell number and

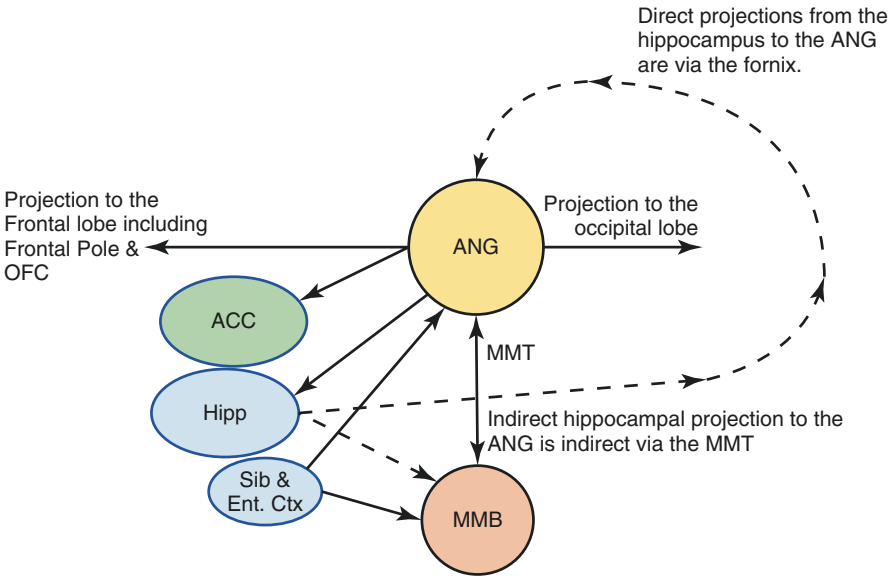

Fig. 10.8 The main connections of the anterior nuclear group. *ANG* anterior nuclear group, *ACC* anterior cingulate cortex, *Hipp* hippocampus, *Sib.* subiculum, *Ent. Ctx.* entorhinal cortex, *MMB* mamillary body, *MMT* mammilothalamic tract, *OFC* orbitofrontal cortex [37–46]

overall LGN volume in schizophrenic subjects were is not altered, although it has been reported that the volume of both LGN parvocellular and magnocellular layers is decreased with age [48].

Individuals with 22q11.2 micro-deletion syndrome have a very high chance of developing schizophrenia with auditory hallucinations and also have smaller MGNs, as well as hyper-connectivity between thalamus and cortical areas devoted to the primary processing of hearing and Wernicke's area, which is highly significant for understanding language. The authors suggests that, as this is common in unaffected children but not adults, this represents a lack of maturation of the neuronal system and is related more broadly to the neurodevelopmental process underlying the disorder [49, 50].

10.7 Summary

Early work suggests a likely significant role for the thalamus in schizophrenia. The tantalising results reported from neuropathological studies, in conjunction with the circuits described above, indicate that thalamic sub-nuclei involved with specific functions very likely play a critical role in the illness. Given the role of thalamus in many major circuit networks in the brain, this may not be surprising. However, the specific deficits and changes reported in structures such as the mdTh and the ANG appear to have a strong relationship with many of the classic schizophrenia symptoms, and a more detailed and precise investigation of these change could be vital in our understanding of the neuropathology of schizophrenia.

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The Neuropathology of White Matter in Schizophrenia

11

Natalya Uranova

11.1 Deep White Matter Changes in Major Lobes

The white matter (WM) of the CNS consists mostly of axon bundles unsheathed by the processes of oligodendrocytes, the myelin-forming glial cells. Myelin is formed by lipid-rich membrane layers wrapped around axons. Myelin functions as electrical insulation for axons, which maintains the amplitude and conduction velocity of the propagating action potential during saltatory conduction. Oligodendrocytes are metabolically active and functionally connected to the subjacent axon via cytoplasmic-rich myelinic channels for movement of macromolecules to and from the internodal periaxonal space under the myelin sheath [1]. The dynamic communication between axons and their myelin-forming oligodendrocytes includes activity-dependent signaling from axon to myelin [2]. Oligodendrocytes support the long-term integrity of myelinated axons. Myelin is involved in normal cognitive function, learning, and IQ; it is modifiable by experience, and it affects information processing by regulating the velocity and synchrony of impulse conduction between distant cortical regions [3]. Myelinated axons have higher conduction velocities than unmyelinated axons of the same caliber. Damage of myelinated axons can result in conduction delays and in a dyssynchrony between the activities of neuronal network. Even small changes in conduction velocity due to small changes in myelin thickness or nodal structure could have profound effects on neuronal network function in terms of spike-time arrival, oscillation frequency, oscillator coupling, and propagation of brain waves [4]. Myelination is a dynamical, activity-dependent process, and action potentials influence development of myelin sheaths ([5] for review). Oligodendrocytes and its precursors receive the signal from electrically active neurons and differentiate, proliferate, and myelinate the axons to modulate the activity of neuronal circuits, thus affecting behavior [6]. Myelin remodeling occurs in the course of life and adapts to the neuronal activity. Myelin plasticity varies from the

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generation of new myelinating oligodendrocytes to more subtle changes in myelin sheath length, thickness, and distribution along axons [7, 8]. WM contains oligodendrocytes, astrocytes, microglial cells, and neurons. Altered interneuronal connectivity is a main basis for the disruption of information processing in SZ. Growing evidence from neuroimaging and postmortem studies supports the notion that altered neuronal connectivity in SZ is associated with disturbed myelination in different fiber tracts [9, 10] and disruptions of WM organization and integrity.

11.2 Neuroimaging Evidence for WM Abnormalities in SZ

Diffusion tensor imaging (DTI), magnetic resonance in vivo technique, is sensitive to WM integrity disruptions and to fiber myelination abnormalities. Fractional anisotropy (FA), a quantitative index of WM coherence and integrity, is the most frequently used measure to evaluate water diffusion in WM. The FA difference is mainly a reflection of alteration of WM macromolecule structures, which might be related to axonal and myelination disruption [9, 11]. As an outcome parameter of DTI, FA is determined by a combination of factors including fiber orientation, axonal packing density, membrane permeability, and to a lesser extent the degree of myelination [12, 13]. DTI outcome parameters also include axial diffusivity (AD) (diffusion in the principal direction of an axon bundle) and radial diffusivity (RD) (diffusion perpendicular to the direction of an axon bundle). AD has been shown to be modulated by axonal degeneration, whereas RD is more specifically related to changes in the myelin sheath [14, 15]. These disruptions include reduced FA in the corpus callosum (CC), arcuate fasciculus, the internal capsule (IC) and the cingulum bundle (CB), uncinate fasciculus (UF), as well as parietal, prefrontal, and occipital lobes in SZ patients (see [16] for review). Results of the FA analyses suggest widespread neuronal connectivity abnormalities in SZ. Reduced FA in the UF has been reported in SZ [17, 18]. Miyata et al. [19] have found abnormal asymmetry of WM integrity in SZ revealed by voxelwise DTI.

Another MR technique that is sensitive to axonal and myelin density, and enables the detection of abnormalities in WM structure, is magnetization transfer imaging. This imaging technique provides an index of axonal/myelin density, called magnetization transfer ratio (MTR) [10].

DTI studies in early SZ suggest that structural dysconnectivity may be already present in recent-onset and drug-naïve patients, as well as in individuals clinically at high risk for developing the disease. Frontal, fronto-temporal, and fronto-limbic connections, with tracts including the superior longitudinal fasciculus (SLF), CB, UF, and CC are affected [20]. SZ is characterized by insufficient or ineffective communication associated with WM abnormalities. Resting-state functional MRI (rsfMRI) showed decreased amplitudes of low-frequency oscillation and increased functional connectivity in the superficial perception-motor networks in SZ [21]. This method also detected loss of connectivity between several thalamic subdivisions (superior-anterior, ventromedial, and dorsolateral part of the thalamus) and the sensorimotor system, anterior cingulate cortex, and cerebellum in patients with

SZ. Altered connectivity was negatively correlated with symptom scores and duration of illness [22].

Abnormalities in FA in SZ patients are associated with cognitive impairment and negative and positive symptoms (see [23, 24] for review). Holleran et al. [25] in the ENIGMA Consortium study provide evidence that cognitive ability is associated with global structural connectivity, higher FA associated with higher IQ independent of diagnosis. SZ patients tended to have lower FA and lower IQ than healthy controls. FA reduction in different WM tracts is associated with impairments in working memory [26, 27] and executive function (see [23] for review). These changes were observed in individuals with prodromal symptoms who were at very high risk for SZ and patients in early stage of their illness [28]. On the other hand, higher fractional anisotropy was associated with better cognitive functioning for individuals at ultra-high risk for psychosis, but not for the healthy controls [29]. Fronto-striatal disconnectivity in adolescent-onset SZ was also associated with cognitive deficits [30]. Zeng et al. [31] have reported in drug-naive first-episode SZ patients lower FA, higher AD, and RD versus controls in forceps, left SLF, inferior fronto-occipital fasciculus, left corticospinal tract, left UF, left anterior thalamic radiation, and bilateral inferior longitudinal fascicule (ILF). FA values in SZ patients were correlated with negative symptoms and cognitive impairment. A significantly reduced FA values in UF, and a positive correlation of attention, spatial memory, sensorimotor dexterity, and emotion with FA compared to controls have been reported in SZ [32]. Knöchel et al. [33] demonstrated that the fornix fiber tracking scores (FA, tract volume, length, and number (in a key fronto-limbic connection to hypothalamus) were associated with cognitive performance in SZ. In SZ patients with recent onset psychosis, lower FA in the bilateral UF was correlated significantly with greater severity of negative symptoms (alogia and affective flattening), and worse verbal learning/memory functioning. In addition, higher FA in the inferior fronto-occipital fasciculus was correlated significantly with greater severity of delusions and hallucinations [17]. Reduced FA between left amygdala and insular cortex in SZ compared with controls was negatively correlated with avolition/apathy but not with expressive deficit scores [34]. Auditory verbal hallucinations are accompanied by decreased FA and increased RD compared to the healthy control group in multiple WM tracts including the CC, SLF, inferior fronto-occipital fasciculus, UF, cingulum, external capsule, and anterior limb of the IC [35]. In first-episode SZ patients, N-acetyl aspartate (NAA) in the centrum semiovale WM was significantly correlated with performance on processing speed, visual, and working memory [36].

In drug-naïve first-episode SZ patients, FA in the right anterior thalamic radiation was correlated with positive symptoms. The ROI analyses showed significant associations between positive symptoms and FA of the frontal fasciculi, specifically the right arcuate fasciculus and right SLF. Antipsychotic-naive patients with SZ displayed subtle deficits in WM, and psychotic symptoms appeared specifically associated with frontal fasciculi integrity. Six weeks of amisulpride treatment normalized WM [37]. Wu et al. [38] using an automatic tractography-based analysis method detected in first-episode patients with SZ seven tracts exhibited significant

differences between the SZ and control groups; they included the right arcuate fasciculus, bilateral fornices, left SLF, and fibers of the CC to the bilateral dorsolateral prefrontal cortices (DLPFC), bilateral temporal poles, and bilateral hippocampi. Post hoc between-group analyses revealed that the connection of the callosal fibers to the bilateral DLPFC was significantly decreased in chronic patients but not in first-episode patients. In a stepwise regression analysis, the decline of the tract connection was significantly predicted by the duration of illness. In contrast, the remaining six tracts showed significant alterations in both first-episode and chronic patients and did not associate with clinical variables. In conclusion, reduced WM connectivity of the callosal fibers to the bilateral dlPFC may be a secondary change that degrades progressively in the chronic stage, whereas alterations in the other six tracts may be inherent in the disease. Reduced integrity of the left arcuate fasciculus is specifically associated with auditory verbal hallucinations in SZ [39].

Frontal lobe and the prefrontal cortex demonstrated disruption in WM integrity in SZ patients associated with clinical symptoms. The frontal lobe controls emotion, motivation, attention, and its dysfunctions may cause negative symptoms in schizophrenia [40]. DTI studies of WM in SZ have reported the reduction in FA in frontal lobe and the relationships between WM abnormalities and symptoms of the disorder [17, 41, 42]. Neuroimaging studies have shown reduced WM volume in the prefrontal cortex in SZ [43]. SZ subjects with high negative symptom scores had significantly smaller bilateral WM volumes than those with low negative symptom scores [44]. Decrements in prefrontal WM were related to higher levels of negative symptoms [45, 46]. Inferior frontal WM FA was significantly inversely correlated with the SANS global ratings of negative symptoms [47]. Cheung et al. [48] have reported in never-medicated first-episode SZ patients the reduction in FA and positive correlation between FA scores and positive symptoms scores in frontotemporal tracts, including left fronto-occipital fasciculus and left ILF. Metabolic abnormalities in fronto-striatal-thalamic WM tracts (lower lactate and alanine levels) have been reported in SZ as compared to controls [49]. Based on [(18)F]fluorodeoxyglucose PET and MRI study, patients with SZ have higher glucose metabolic rates in the frontal WM, CC, SLF, IC, and WM of the temporal lobe [50]. Mitelman et al. [51] using 18-fluorodeoxyglucose PET showed increased metabolic rates in IC, CC, and WM in the frontal and temporal lobes. The highest metabolic increases in both disorders were seen in the prefrontal WM and anterior limb of the IC. Leroux et al. [52] in fMRI and DTI study have shown that the disturbance in the integrity of the left fronto-temporal tracts might be one origin of the functional disconnectivity in the language-comprehension network in SZ. A new non-tensor-derived diffusion method measuring fiber density (FD) detects subtle changes in the WM [53]. Using tract-based spatial statistics (TBSS), the authors found reduced FD in SZ patients as compared to normal controls in the left and right thalamic radiation, SLF, CC, and corticospinal tract without FA differences between groups. Also FD values in the thalamic radiation were negatively correlated with the severity of positive symptoms and medication dose. Csukly et al. [54] detected decreased coupling strength

from anterior cingulate cortex to left thalamus that correlated with the PANSS total positive syndrome score and with delusion score.

The inferior fronto-occipital fasciculus (IFOF) forms the main connection between the fusiform and lingual gyri and the prefrontal cortex [55]. Disruption of the left IFOF is associated with cognitive deficits [56], with poorer outcomes and more negative symptoms [57]. In SZ patients, lower FA value of the left inferior longitudinal fasciculus (ILF) and left IFOF was significantly correlated with worse processing speed, as well as verbal learning and visual learning abilities [58]. Epstein et al. [59] used DTI and tractography methods to examine FA of SLF, ILF, and IFOF. Lower FA in these tracts may disrupt functioning of ventral visual and language streams, producing domain-specific neurocognitive deficits that interfere with higher-order cognitive abilities. Recent DTI study [60] showed that WM microstructure in patients with SZ interacts with cognitive abilities with a large effect size.

Reduced FA has been reported in the right SLF, the major WM tract that connects prefrontal and parietal cortical regions and frontal WM in the deficit SZ patients [61]. Lei et al. [62] have reported that WM disruption was prominent in deficit SZ (DSZ) compared to controls; the DSZ group had lower volumes in the cerebellum, bilateral extra-nuclear and bilateral frontoparietal regions, and lower FA in the body of CC, posterior (SLF) and UF. The DSZ group also had lower volume in bilateral extranuclear regions compared to non-DSZ, and the volume of these clusters was negatively correlated with deficit symptom ratings. Non-DSZ patients however had no significant volume alterations and limited disruption of microstructural integrity compared to controls. First-degree relatives of those with DSZ shared volume abnormalities in right extranuclear WM. Thus, WM pathology in SZ is most evident in the deficit condition, and lower extranuclear WM volumes in both DS patients and their relatives may represent a brain structural "endophenotype" for DSZ.

The Cingulum Bundle (CB) is a fiber tract 5–7 mm in diameter that interconnects all parts of the Limbic System. It is a major fiber tract in the limbic system. It underlies cingulate cortex and is located longitudinally over the corpus callosum. The connections of CB play a major role in emotional expression, motivation, and cognitive functions (attention, working memory). The CB has connections with regions associated with memory and executive functioning including the thalamus, amygdala, hippocampus, and dorsolateral and dorsomedial prefrontal cortex [63]. Reduced DTI in the CB WM is associated with working memory impairment [63] and executive functioning [64]. CB may be involved in the etiology of delusions [65, 66]. Lowered FA bilaterally in the CB has been reported in the SZ patients [67]. FA reductions in CB are also associated with hallucinations [68].

The anterior limb of the IC serves as a bridge between the thalamus, cingulate, and prefrontal cortices and thus plays an important role in motivation, reward, and emotion [69]. The association of anterior limb of the IC and SLF with a pleasure/motivation domain of negative symptoms has been reported [70]. Reduced FA in the

anterior limb of IC was found in the SZ patients with auditory verbal hallucinations and in healthy voice-hearers [71]. FA in IC was correlated with processing speed, attention/working memory, and executive functioning in first-episode psychosis [72]. In SZ, negative symptoms were inversely correlated with FA in the IC, anterior thalamic radiation, parietal portion of the SLF, FOF, and CC [73, 74]. Positive correlation with negative symptoms in SZ was also found in the area near right insula [38], left cingulum, and left SLF [75] (see [65] for review).

Gray matter volume in the bilateral PFC and WM volume in the right frontal and left CC were reduced in the SZ patients. Prefrontal cortex volume was significantly and inversely associated with both auditory verbal hallucinations and depression severity [76]. A DTI tractography study [77] showed that SZ patients having auditory verbal hallucinations have longer left arcuate fasciculus fiber tracts. SZ patients with auditory hallucinations had lower FA values in bilateral SLF and arcuate fasciculi as compared to healthy controls and those without auditory hallucinations [78]. On the contrary, the SZ subjects with auditory verbal hallucinations had higher FA in the left long segment within the perisylvian language network as compared with the healthy controls [79]. Interestingly, SZ patients younger than 40 years old with auditory verbal hallucinations and healthy voice hearers showed overlapping FA deficits in the genu and splenium of the corpus callosum and in the anterior limbs of the IC [66]. Gurholt et al. [80] using the free-water imaging method to model the diffusion signal demonstrated that positive symptoms were associated with localized increased free-water and negative symptoms with localized decreased free-water corrected FA and increased RD.

Childhood trauma is a major risk factor for SZ. In the review of Cancel et al. [81] in SZ patients, the association between childhood trauma, decreased total cerebral gray matter, particularly in the prefrontal cortex and alterations of WM integrity in the inferior and SLF, the IFOF, and the forceps major have been detected. Caprihan et al. [82] found that FA correlated positively with positive symptom severity in genu, body and splenium of CC, anterior and superior corona radiata, superior longitudinal and inferior fronto-occipital fasciculi, and IC. The FA/symptoms relationships corresponded with opposite correlations between RD and positive symptoms. On the other hand, recent study of acute psychosis vs. remission [83] showed that at baseline, the SZ patients with first-episode psychosis presented reductions of FA in comparison with healthy controls affecting fronto-limbic WM and associative, projective, and commissural fasciculi. After symptom remission, patients showed FA increase in the right anterior thalamic radiation, right UF/IFOF, and left IFOF/ILF. FA increases were significantly correlated with the reductions in PANSS scores. The largest coordinated study of diffusion tensor imaging (DTI) data and meta-analyzed effects across studies of WM microstructural differences in SZ [84] provided a widespread WM abnormalities in SZ patients. The anterior corona radiata and CC showed greatest effect sizes. Interactive three-dimensional visualization of the results is available at www.enigma-viewer.org. Thus, neuroimaging studies provide evidence for the widespread disruption of WM integrity in SZ associated with cognitive dysfunction, negative, and positive symptoms of SZ.

11.3 Changes in Glial Cells

11.3.1 Histopathological and Ultrastructural Studies of Oligodendrocytes and Myelin in WM in SZ

Oligodendrocytes, the myelin forming cells in the CNS, are essential for the propagation of action potentials along axons and additionally serve to support neurons by producing neurotrophic factors. Myelination of appropriate brain regions coincides with the development of specific cognitive functions, such as reading, development of vocabulary, and proficiency in executive decision-making [3]. To identify a structural basis for the WM changes observed by brain imaging in vivo, oligodendrocytes and myelin have become the most important focus of interest. Myelin and oligodendrocyte abnormalities have been reported in SZ in neuroimaging, neurocytochemical, microarray, and morphometric studies [9, 10].

In most of the postmortem stereological studies the numerical density (Nv) of oligodendrocytes was estimated in the WM. Morphometric studies of Nissl-stained sections revealed a deficit of oligodendrocytes in WM of different brain regions in SZ. Hof et al. [85] detected in the superior frontal gyrus lower oligodendrocyte density in SZ cases compared to controls both in the gray matter (−22%) and the WM (−20%) underlying DLPFC (BA9). Later, Hof et al. [86] found in the same gyrus 28% decrease in total numbers (or densities) of cortical layer III oligodendrocytes and a 27% decrease in the WM in SZ compared with controls based on CNPase immunostaining. The spatial distribution of oligodendrocytes in the WM exhibited a less clustered arrangement in SZ cases. Vostrikov et al. [87] have reported 12% reduction in the Nv of oligodendrocytes in the WM underlying the prefrontal cortex (BA10). Farkas et al. [88] have found reduced Nv of ADAM12 immunoreactive oligodendrocytes in the WM of the anterior cingulate cortex in SZ patients. However, others have shown no significant changes in oligodendrocyte density and distribution in the CB [89], in the WM underlying BA9 of the DLPFC [90]. In the WM underlying BA9 of the DLPFC, Hercher et al. [91] have reported no differences in Nissl-stained sections in oligodendrocyte nuclear area and diameter and oligodendrocyte density between the SZ and control groups. In contrast to these studies, Bernstein et al. [92] have demonstrated that in SZ the Nv of prohibitin-expressing oligodendrocytes was significantly increased in the right dorsolateral WM area. Recently, Mauney et al. [93] found that the density of NG2-immunoreactive cells was unaltered, but the density of oligodendrocyte transcription factor 2 (OLIG2)-immunoreactive cells was significantly decreased in subjects with SZ, consistent with the notion that oligodendrocyte precursor differentiation impairment may contribute to oligodendrocyte disturbances and thereby myelin deficits in SZ.

In postmortem studies, Highley et al. [94, 95] have reported decreased fiber number and density in the anterior commissure and the CC in women but not in men with SZ. The UF was found to be asymmetrical in both sexes, being 27% larger and containing 33% more fibers in the right than the left hemisphere [96]. The first stereological study estimated the length of myelinated nerve fibers in the whole brain, as well as in the prefrontal cortex of subjects with SZ, did not find significant

differences from normal controls [97]. Regenold et al. [98] by the Kluver-Barrera method of myelin staining have reported that mean deep WM myelin staining was less intense in SZ and mood disorders compared to controls. Altered intracortical myelin staining with Luxol® fast blue (reduced optical tissue attenuation) has been reported in the frontal cortex in SZ [99]. Williams et al. [100] using standard high-resolution oil-immersion light microscopy examined the density of myelinated axons and the cross-sectional area of the nerve fibers and the axonal myelin sheath in the genu of the CC. No significant change in the density of myelinated axons and no changes in the fornix have been found in this study.

Electron microscopic study of myelinated fibers (MF) in the WM of the prefrontal cortex (BA10) underlying layer VI [101] has revealed six types of pathological MF in both gray and WM in SZ subjects and rather rarely in controls (Figs. 11.1 and 11.2). Figure 11.1 demonstrates the ultrastructure of MF from the control brain. Pathological MF of type 1 (P1) was characterized by focal lysis of myelin sheath lamellae, sometimes with the formation of concentric lamellar bodies. This type of pathology often appeared in close apposition to astrocytic processes or inside them (Fig. 11.2a). Fibers of type 2 (P2) exhibited the presence of myelin-like figures of unknown origin in swollen periaxonal oligodendroglial processes though myelin sheaths looked well preserved (Fig. 11.2b). Type 3 (P3) fibers demonstrated swelling of periaxonal oligodendroglial processes, atrophy of inner axon, and preserved myelin sheath. These types of alterations of MF were seen mostly in MF of small caliber, containing few myelin sheath lamellae (Fig. 11.2c). Besides, three types of degenerating MF were rarely seen in gray matter and were common in the WM in SZ and controls. They demonstrated degeneration of myelin sheaths: splitting and decompaction of myelin sheath lamellae (type 4, P4) (Fig. 11.2d), inclusions of dense cytoplasm with vacuoles resembling the cytoplasm of microglial cell between myelin sheath lamellae (type 5, P5) (Fig. 11.2e) and dark degeneration of MF (type 6, P6) (Fig. 11.2f). Importantly to note is that all these types of pathological alterations of MF demonstrated deformations of MF (Fig. 11.2). P4–6 fibers were seen mostly in WM, in gray matter they were observed rarely in SZ and in controls, so they were counted only in WM. Thus, abnormalities of MF in SZ include altered oligodendrocyte/axon interaction and myelin/axon integrity, axonal atrophy, damage of myelin sheaths in gray matter and in WM, and degeneration of myelinated

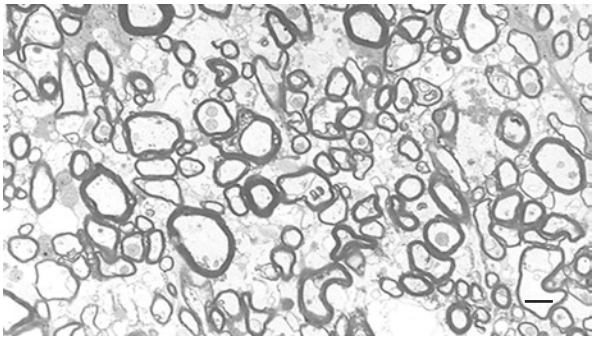

Fig. 11.1 Myelinated fibers in WM of the prefrontal cortex from the control brain. Scale bar = 2 μm

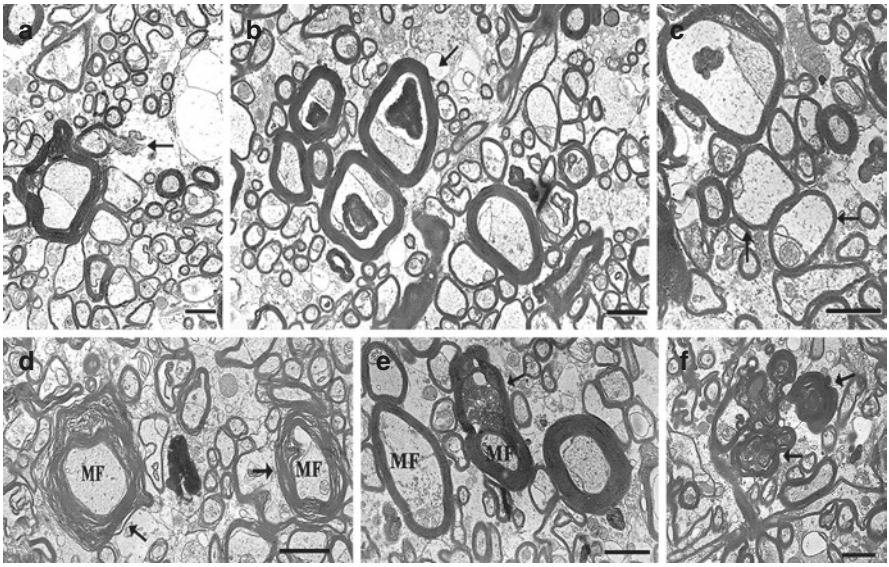

Fig. 11.2 Six types of pathological MF in WM. Description is in the text. Scale bars = 2 μm (from Uranova et al. Schizophr Res Treatment. 2011)

sheaths in WM. Degenerating myelin sheaths were found in medium and large-sized MF suggesting that cortico-subcortical and cortico-cortical fibers might be involved in degenerating process of MF in SZ. The frequency of all pathological MF and of P2 fibers was significantly increased in the subgroup of patients with predominantly positive symptoms. The frequency of P3 fibers was increased both in the subgroup with predominantly positive symptoms and in the subgroup with predominantly negative symptoms as compared to controls. A significant increase in the frequency of P5 and P6 MF was found in the subgroup with predominantly negative symptoms. Multiple regression analysis and analysis of covariance demonstrated that these changes could not be explained by the effects of postmortem delay, age, neuroleptic medication, or gender. The frequency of pathological MF in the WM correlated with duration of SZ (Fig. 11.3) but not with age [101].

The changes of MF were accompanied by prominent alterations of the ultrastructure of oligodendrocytes in SZ as compared to controls (Fig. 11.4). Electron lucent chromatin and small rim of cytoplasm were characteristic features of oligodendrocytes in control brains (Fig. 11.4a). In SZ subjects, oligodendrocytes demonstrated dystrophic changes (in the WM underlying the prefrontal cortex (BA10) in subjects with SZ looked swollen and vacuolated as compared to controls (Fig. 11.4b) [101].

Recent morphometric study of oligodendrocytes in the prefrontal WM (BA10) [102] has found oligodendrocyte swelling, vacuolation, paucity of ribosomes and mitochondria, and accumulation of lipofuscin granules in SZ as compared to controls. Morphometry detected a significant reduction in volume density (Vv) and the number (N) of mitochondria and the increase in Vv and N of lipofuscin granules and vacuoles in oligodendrocytes in the SZ group as compared to controls. Thus,

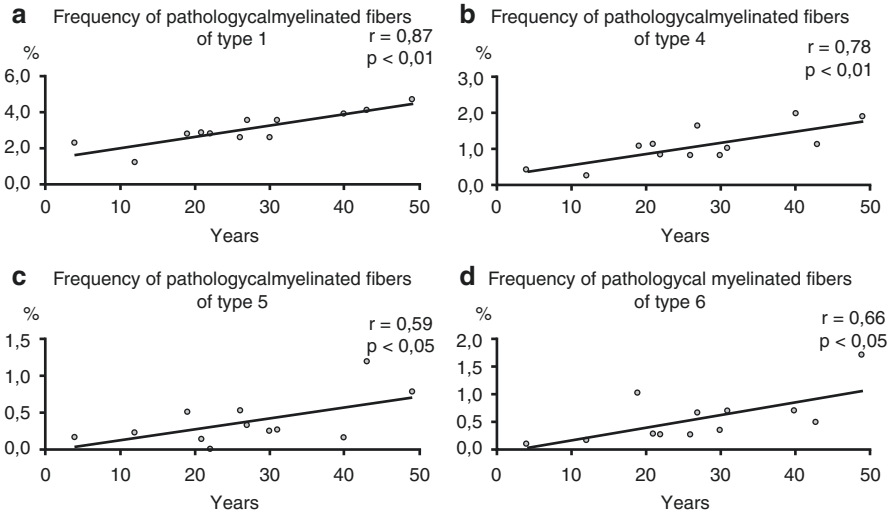

Fig. 11.3 The frequency of pathological MF in WM correlated with duration of SZ (from Uranova et al. Schizophr Res Treatment. 2011)

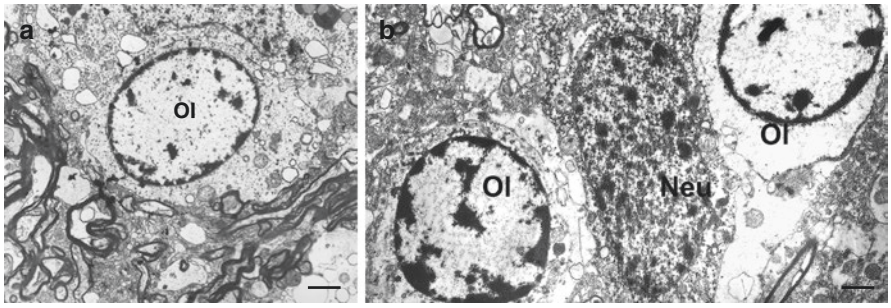

Fig. 11.4 Electron micrographs of oligodendrocytes in WM from control subject (**a**) and from SZ subject (**b**). Dystrophic alterations of oligodendrocytes (**b**). Scale bar = 0.5 μm

alterations of oligodendrocytes in SZ provide evidence for the disturbance of their energy, lipid, and protein metabolism in prefrontal WM. These data are in agreement with altered lipid composition reported in dorsolateral prefrontal WM in SZ [103]. Oligodendrocyte abnormalities might disturb axonal integrity and circuitry and contribute to the pathophysiology of SZ.

The prefrontal cortex and hippocampus are known to be critical for different aspects of cognitive and mnemonic processes [104]. They play a central role in the memory impairments exhibited in patients with SZ. Shaffer et al. [105] using fMRI have outlined evidence that the basal ganglia and the prefrontal cortex are associated with negative SZ symptoms. Kolomeets and Uranova [106] have found ultrastructural dystrophic changes of oligodendrocytes and an atrophy of part of MF in the hippocampal CA3 region in SZ as compared to normal controls. Uranova et al.

[107] performed electron microscopic morphometric study of MF in the prefrontal cortex (BA10), hippocampus (CA3 region), and caudate nucleus in 25 SZ cases and 25 normal controls. The ultrastructural damage of MF with the prevalence of atrophy of the axon due to the alteration of myelin sheath (P3) similar in all brain structures studied has been found. The highest frequency of this myelin pathology was detected in layer V of the prefrontal cortex, but it was also significantly higher than in the control group in the hippocampus and in the caudate nucleus in SZ as compared to controls. The frequency of this pathological MF correlated positively significantly in the prefrontal cortex with the frequency of the same pathological MF in the hippocampus and in the caudate nucleus in SZ but not in control brains. These data are in line with the neuroimaging data that demonstrated altered connectivity of the prefrontal cortex with the hippocampus and striatum associated with psychosis in SZ [108], and striatum contributes to cognitive dysfunctions in SZ [109]. There were no significant differences in area density of MF between control and SZ groups in the brain structures studied [107]. The results are in accordance with the data of Marner and Pakkenberg [97] which demonstrated that the length of MF in the whole brain as well as in the prefrontal cortex of subjects with SZ showed no significant differences with controls.

11.3.2 Oligodendrocyte/Myelin/Axon Disruption and Dysfunction in SZ

Together these data support the hypothesis of Mitterauer [110] that decomposition of the oligodendrocyte-axonic system may be responsible for the symptoms of incoherence (thought disorder, etc.) in SZ. Our study detected prominent dystrophic alterations of oligodendrocytes, including their swelling in both gray and WM in SZ. These data are in accordance with the most pronounced changes of P3 MF in SZ demonstrating swelling of periaxonal oligodendrocytic process and shrinkage of the MF inner axon. P3 MFs had small size and a thin myelin sheath. Thus, this type of pathological MF might belong mostly to associative fibers or to axons of interneurons. Together the data provide evidence for a widespread axonopathy due to injured oligodendrocyte–axon interactions in SZ brains. These data support the notion of the unique pathological process in myelin in SZ and a widespread brain pathology of myelin in this disease. The changes of MF might cause changes in conduction velocity and might lead to the atrophy of presynaptic axon terminals in SZ and contribute to altered connectivity in SZ [111]. This hypothesis is in accordance with the work of Brébion and coauthors [112], who have found that slowing in processing speed strongly predicts verbal memory performance in SZ. Tanaka et al. [113] have reported that mice with altered myelin proteolipid protein gene expression display cognitive deficits accompanied by abnormal neuron-glia interactions and decreased conduction velocities. Decreased FA implies disorganized WM tracts that can be caused either by disorganized oligodendrocyte/myelin/axon relationships or by dysmyelination. These direct data of altered ultrastructure of oligodendrocytes and MF provide evidence for oligodendrocyte abnormalities in

SZ. Since myelin is produced by oligodendrocytes, these data suggest that the pathology of MF in SZ might be due to oligodendrocyte abnormalities.

Haroutunian et al. [114] have reported that some of the genes affected in SZ are associated with the regulation of axoglial contacts, axon caliber, and the integrity of functional elements involved in signal propagation. In KCC3 knockout mice, an animal model of agenesis of the CC associated with peripheral neuropathy, some fibers accumulate fluid periaxonally. The swelling pathologies are followed by axon and myelin degeneration in adult nerves, leading to reduction in nerve conduction velocity [115]. To maintain axonal integrity, mammalian myelin-forming cells require the expression of some glia-specific proteins, including CNP, PLP, and MAG, as well as intact peroxisomes, none of which is necessary for myelin assembly. Loss of oligodendroglial support causes progressive axon degeneration and possibly local inflammation, both of which are likely to contribute to a variety of neuronal diseases in the central and peripheral nervous systems [116]. Axon–glial interactions underlie the clustering of ion channels and of cell adhesion molecules, regulate gene expression, and control cell survival. Rasband et al. [117] have reported that CNP1-null mice, lacking expression of the myelin protein cyclic nucleotide phosphodiesterase (CNP), have disrupted axon–glial interactions in the central nervous system.

11.3.3 Effects of Neuroleptic Treatment on WM

Potential effects of initiating acute antipsychotic treatment on WM microstructure in SZ patients remain poorly characterized. Kraguljac et al. [118] found no significant WM changes assessed microstructural (fractional anisotropy, mean diffusivity, and radial diffusivity) and macrostructural (radial fiber trophy) WM integrity after 6 weeks treatment with risperidone. On the contrary, FA decrease was found in patients after 6 weeks of treatment with the second-generation antipsychotic medications in corona radiata and posterior thalamic radiation as well as in IC and CC [119].

Xiao et al. [120] have reported that quetiapine increased the synthesis of myelin basic protein and facilitated myelination in rat embryonic cortical aggregate cultures; chronic administration of quetiapine to C57BL/6 mice prevented cortical demyelination and concomitant spatial working memory impairment induced by cuprizone, a neurotoxin. Quetiapine alleviates the cuprizone-induced WM pathology in the brain of C57BL/6 mouse [121]. Konopaske et al. [122] have found a nonsignificant lower oligodendrocyte number in parietal gray matter after chronic exposure of monkeys to haloperidol or olanzapine. However, protective effects of neuroleptics on oligodendrocytes [123] have been reported.

Wang et al. [124] have shown that haloperidol treatment for 3 weeks increased the number of NG2-expressing cells in the CC; haloperidol treatment for three and 6 weeks increased the numbers of Olig2-expressing cells in CC, hippocampus and cerebral cortex and increased the levels of Olig2 expression in the same brain regions. These results suggest that haloperidol treatment activates adult

oligodendrocyte precursors (OPC), which divide infrequently under normal conditions but respond to a variety of insulting factors by proliferation and differentiation. However, no changes in the number of mature oligodendrocytes and the amount of myelin basic protein in haloperidol-treated mice suggests that the drug treatment has no effect on the maturation of oligodendrocytes. In addition, haloperidol treatment did not increase the numbers of GFAP- and CD68-expressing cells, suggesting that no gliosis and inflammatory responses occurred while the drug activated the quiescent OPCs in adult brain. These results suggest that haloperidol treatment may target the development of oligodendrocytes.

Together with the postmortem data on oligodendrocyte and myelin abnormalities in SZ, these data suggest that the reduction in oligodendrocyte density in SZ is not attributable to neuroleptic exposure. The suggestion is in accordance with some neuroimaging studies demonstrated that chronic neuroleptic treatment may reverse a previous deficit associated with WM disruption. Ozcelik-Eroglu et al. [125] in DTI study via tract-based spatial statistics have found that 12 weeks of treatment with clozapine in two of the regions where FA had initially been lower in patients compared with controls (left inferior fronto-occipital fasciculus and superior parietal lobule), appeared to increase FA. An improvement in semantic fluency was correlated with the increase in FA value in the left IFOF. Bartzokis et al. [126] have demonstrated that long-lasting injection with risperidone may improve the trajectory of myelination in first-episode patients and have a beneficial impact on cognitive performance. Clozapine treatment led to reductions in caudate nucleus volume [127]. Halene et al. [128] demonstrated that chronic clozapine exposure in young adult macaque monkeys for 6 months increases the proportion of NeuN+ nuclei in frontal subcortical WM, without alterations in frontal lobe volumes or OLIG2 gene expression.

11.3.4 Biological Basis for Developmental and/or Progressive WM Changes in SZ

The underlying biological process of SZ has already been studying for many years. SZ has a characteristic onset during adolescence or young adulthood but also tends to persist throughout life. MRI studies indicate that brain abnormalities are present at disease onset, but longitudinal studies showed progressive brain change occurs in SZ, affecting both gray matter and multiple WM regions (total cerebral, frontal, temporal, parietal) [129].

Some data suggest that neurodevelopmental problems might occur in oligodendrocytes and myelin in WM in SZ. Myelination is a highly dynamic process that continues well into adulthood in humans. Several recent gene expression studies have found abnormal expression of genes involved in myelination in the prefrontal cortex of brains from patients with SZ and other psychiatric illnesses [130]. Chavarria-Siles et al. [131] have shown that multiple genetic variants in myelination-related genes contribute to the observed correlation between SZ and decreased WM integrity as measured by FA. Defects in myelination could contribute to the

pathophysiology of psychiatric illness by impairing information processing as a consequence of altered impulse conduction velocity and synchrony between cortical regions carrying out higher level cognitive functions. Myelination can also be altered by impulse activity in axons and by environmental experience. Myelinogenesis in humans occurs postnatally and continues in young adulthood in the period where the incidence of SZ is at its peak [130]. Cetin-Karayumak et al. [132] analyzed the largest sample of carefully harmonized diffusion MRI data measured by FA and found three patterns of neuropathology in WM in SZ: developmental abnormalities in limbic fibers, accelerated aging and abnormal maturation in long-range association fibers and severe developmental abnormalities, and accelerated aging in callosal fibers. The data point out that WM in SZ is affected across entire stages of the disease. There is increasing evidence that oligodendrocyte and myelin related genes are genetically associated with SZ: *NRG1* gene and its receptor ERBB4 as well as *MAG* (playing important roles in myelination), *MOG*, *OLIG2* and *CNP1*, *PLP1*, *DISC1* genes are involved in oligodendrocyte development (see [15] for review). McCullumsmith et al. [133] found decreased expression of MAG, QKI, TF, and CNP transcripts in WM in SZ. The data support the hypothesis that myelination and oligodendrocyte function are impaired in SZ. However, Mitkus et al. [134] have reported that expression of MAG, CNP, OLIG2, and MOBP did not differ between patients with SZ and controls in the DLPFC WM.

Profound WM abnormalities have repeatedly been described in SZ, which involve the altered expression of numerous oligodendrocyte-associated genes. Transcripts of the disrupted-in-SZ 1 (*DISC1*) gene, a key susceptibility factor in SZ, have recently been shown to be expressed by oligodendroglial cells and to negatively regulate oligodendrocyte differentiation and maturation. Compared with controls and cases with undifferentiated/residual SZ, there was a significantly increased density of DISC1-expressing glial cells in the fronto-parietal WM in paranoid SZ, which unlikely resulted from neuroleptic treatment [135].

Some literature data support the heritability of WM phenotypes. Loci in genes intimately implicated in oligodendrocyte and myelin development, growth and maintenance, and neurotrophic systems are associated with WM microstructure [136]. de Leeuw et al. [137] found reduced FA in the tract connecting the left nucleus accumbens and left DLPFC that indicates a possible reduction of WM integrity, commonly associated with SZ. As both patients and unaffected siblings show reduced FA, this may represent a vulnerability factor for SZ.

Delayed myelination in the prefrontal cortex has been proposed in patients with SZ. The fact that the prefrontal cortex matures last and that myelination is not complete until late adolescence may be significant, as the timing coincides with the typical onset of symptoms in SZ. This suggests that a dysfunctional myelination process could underlie the pathogenesis of SZ. Lang et al. [138] found altered patterns of association between age and years of education and myelin water fraction in the anterior and posterior IC and the genu of the CC in first episode SZ patients compared to normal controls. This supports the notion that subtle disturbances in myelination may be present early in the course of psychosis. Combined WM imaging results suggest myelination defects in visual processing regions in SZ [139].

Cellular changes including abnormal cell cycle properties leading to WM abnormalities in SZ could include not only cell death but also delayed maturation of the progenitor cell population (see [140] for review).

Oligodendrocytes and their precursors are very vulnerable to conditions common to CNS injury and disease sites, such as inflammation, oxidative stress, and elevated glutamate levels leading to excitotoxicity. Tkachev et al. [141] have provided evidence for altered myelin synthesis and glutamatergic dysfunction in the prefrontal cortex in SZ. Oligodendrocyte/myelin dysfunction may lead to changes in glutamatergic and dopaminergic signaling (see [15]). Growing body of evidence coming from epidemiological, neuropathological, neuroimaging, and clinical studies suggest an important role of neuroinflammation in the pathogenesis of SZ. Exposure to infection, stress-induced inflammatory response, glial cell signaling, structural and functional brain changes, and therapeutic trials demonstrates the impact that inflammation has in the onset and progression of SZ [142]. Pasternak et al. [143] using diffusion MRI have found a significant increase in the extracellular volume in both white and gray matter, but significant signs of axonal degeneration were limited to focal areas in the frontal lobe WM. The authors suggest that neuroinflammation is more prominent than axonal degeneration in the early stage of SZ. Neuroinflammation, associated with WM pathology in people with SZ, may contribute to structural and functional disconnectivity, even at the first episode of psychosis [144].

In WM, significant correlations of the frequency of pathological MF changes with illness duration were found in SZ subjects. The results concurred with the progressive frontotemporal gray matter reduction and frontoparietal WM expansion in SZ associated with poor outcome during a chronic stage of illness [73]. Mori et al. [145] have reported in WM a significant negative correlation between FA and duration of illness. Progressive WM loss may be a consequence of chronic disease [146–148]. Thus, the changes found in WM in SZ may be a consequence of chronic illness including dystrophic and degenerative processes in oligodendrocytes and myelin sheaths. The frequency of altered MF in the WM in SZ subjects was increased significantly in elderly patients, in patients with predominantly negative symptoms and correlated with illness duration [101]. The data suggest progressive alterations of MF in WM in SZ. These data are in line with accelerated WM deterioration with age in SZ [149] and with progressive deterioration of connectivity in SZ [147, 150].

Vostrikov and Uranova [151] revealed the age-related increase in the Nv of oligodendrocytes in layer VI and adjacent WM of BA10 and BA9 in normal controls but not in SZ, bipolar disorder and major depressive disorder. The absence of normal increase in the number of oligodendrocytes in gray and WM with age in SZ and mood disorders suggests that age-related process of oligodendrocyte increase is dysregulated in SZ and mood disorders. This is consistent with neuroimaging data. Tracts between the frontal lobe and other brain regions, but not temporal, occipital and interhemispheric tracts, showed a differential aging pattern in control subjects and SZ patients indicating that the WM pathology in these regions is not stable between the onset and the chronic state in SZ [152]. Kochunov et al. [153] used

multimodal WM imaging to investigate CC and have reported reduced FA and its accelerated decline with age in SZ. Increased rate of age-related WM FA decline in SZ and a significant age-related decline in WM blood perfusion have been recently reported [154]. The authors suggest that potential causes of accelerated decline in FA values may include loss of axonal myelination and/or loss of glial cell density. The accelerated aging of the WM in SZ could be the product of gene × diagnosis × age interaction.

Uranova et al. [101] have demonstrated that in gray matter, the frequency of pathological fibers was increased significantly in the subgroup of patients with predominantly positive symptoms. On the contrary, in WM, the frequency of MF containing degenerating myelin sheaths was increased significantly in subjects with predominantly negative symptoms. It is important to note that according to our previous data, cases with predominantly negative symptoms showed significant increase in the volume fraction of heterochromatin in layer VI [155]. Our data are in accordance with the results of neuroimaging studies that prefrontal WM FA correlated with negative symptoms, impulsiveness, and aggressiveness [47, 156]. Cognitive deficit in SZ is associated with the dysfunction of the prefrontal cortex, and negative symptoms may involve disruption of frontal-subcortical connections [157].

Our study detected positive correlation between age and the frequency of degenerating myelin sheaths in the WM in SZ group (P6 MF), similar to those described in monkey during aging and correlated with cognitive impairment [158], though the effect of illness duration was more pronounced. Thus, degeneration of myelin sheaths in WM found in the present study might be associated with cognitive impairment in SZ. It is possible that defects in myelin might lead to some breakdown in the insulation and affect conduction. It is proposed that age-related correlations between frequency of myelin alterations and impairments in cognition occur because the conduction velocity along the affected nerve fibers is reduced, so that the normal timing sequences within neuronal circuits break down [159–161].

Therefore, multiple lines of evidence from brain imaging, postmortem research, and genetic studies have implicated oligodendrocyte and myelin dysfunction in SZ. Impaired cell maturation and altered gene expression of myelin/oligodendrocyte-related genes may in part explain WM abnormalities and disturbed inter- and intrahemispheric connectivity, which are characteristic signs of SZ. Altered energy and lipid metabolism, reduced number of oligodendrocytes in WM, disrupted oligodendrocyte/axon interaction and myelin/axon integrity, axonal atrophy, damage, and progressive degeneration of myelin sheaths in WM might be a structural basis for diverse pathological changes that occur in neuroimaging studies in the WM of patients with SZ. Alterations of MF and oligodendrocytes in SZ might contribute abnormalities of neuronal connectivity in SZ. Activation of microglial cells apposed to oligodendrocytes and myelin and neuroinflammation might contribute to oligodendrocyte and myelin abnormalities in SZ patients. WM changes of oligodendrocytes and myelin in SZ might be of developmental origin, and they progress in the course of disease. Together, these data suggest that oligodendrocytes and myelin

abnormalities might be among the major components of the neurobiology of SZ and may be a basis to create new therapeutic strategies directed to myelin abnormalities in SZ.

11.3.5 Astrocytes in WM in SZ

Astrocytes provide metabolic support of neurons and play a key role in the synaptic metabolism of glutamate, GABA, monoamines, and purins. Astrocyte dysfunction may contribute to certain aspects of disturbed neurotransmission in SZ (see [162] for review). Astrocytes respond to all forms of CNS insults through reactive astrogliosis, which has become a pathological hallmark of structural lesions. However, there are rather few studies that examined astrocytes in WM in SZ. Falkai et al. [163] have found a trend toward decreased astrocyte density in premotor WM in the SZ groups as compared to the healthy controls. Williams et al. [164] have reported a significant decrease in density of GFAP-labeled astrocytes in the cingulate gray and WM and in the midline of the CC in SZ compared with normal controls, but not in bipolar disorder. Williams et al. [165] using GFAP immunohistochemistry for astrocyte identification classified astrocytes as fibrillary or gemistocytic based on staining and morphometric criteria and have found that only fibrillary astrocytes were decreased in the base of the cingulate WM in SZ. Since fibrillary astrocytes regulate synaptic glutamate, this morphological change may relate to dysregulation of function of the subgenual cingulate cortex. Hercher et al. [91] have demonstrated decreased GFAP area fraction and increased astrocyte cell clustering in both SZ and bipolar disorder samples in the dorsolateral WM, which is indicative of a more clustered distribution of GFAP-positive astrocytes in the psychiatric groups. Increased astrocyte clustering could result in disruption of structural support of axons in individuals with SZ and bipolar disorder. Reduced GFAP area fraction could be due to the less complex or atrophied astrocyte processes, decreased astrocyte density, downregulation of GFAP expression, or a combination of these factors (see [156] for review). Postmortem electron microscopic study revealed swollen and vacuolated astrocytes in the prefrontal WM in SZ cases as compared to normal controls. In WM, astrocytic cell processes were involved in the phagocytosis of degenerating myelin sheaths in SZ [101].

In the WM of anterior cingulate cortex, the mean GFAP mRNA levels were nonsignificantly decreased in individuals with SZ and bipolar disorder as compared with the unaffected controls [166]. Katsel et al. [167] studied the mRNA expression of nine specific markers known to be localized to astrocytes in the anterior cingulate gray and WM. The expression of astrocyte markers was not altered in the superficial layers or the underlying WM of the cingulate cortex of persons with SZ. Barley et al. [168] reported that GFAP and aldehyde dehydrogenase 1 family member L1 had higher mean expression levels across regions in SZ and major depressive

disorder in IC and CC relative to normal controls. Haloperidol and olanzapine produced significant reductions in S100B-IR astrocyte numbers in the parietal gray matter cortex that might affect cortical glutamate and glutamine levels [122].

Thus, the data on astrocyte changes in WM in SZ are few and inconsistent. Nasrallah et al. [169] using semiquantitative ratings of gliosis, based on the identification of astrocytes and glial processes by a neuropathologist, showed significantly greater gliosis in the CC of late-onset SZ subjects compared to early-onset schizophrenics as well as the control group. However, most studies showed no evidence for astrogliosis in brains of patients with SZ vs. healthy controls [163, 170]. Therefore, neurodegeneration is unlikely to be the main neuropathological mechanism in SZ brains.

11.3.6 Microglia in WM in SZ

Microglia, the resident immune defenders of the central nervous system, play important roles in the development and protection of neurons, but can contribute to injury under pathological conditions. Activation of microglia and macrophages is a key event in response to pathological changes in the CNS. Postmortem studies provide evidence of an association between SZ and microglial activation, particularly in the WM [144, 171, 172].

Microgliosis encompasses morphological changes, cell proliferation, and modifications in the synthesis and secretion of both pro- and anti-inflammatory substances. When activated ramified microglia take on an ameboid shape and increased size. There is an increasing evidence for the significance of neuroinflammation in SZ. Some evidence for microglial activation in WM in SZ have been reported. HLA-immunoreactive microglial density in the dorsolateral prefrontal and superior temporal gray and WM was significantly increased in subjects with SZ [173]. Fillman et al. [174] have reported a 9% increase in microglial density in frontal WM and a significant positive correlation between microglial density and interleukin-1β (IL-1β) mRNA expression in the dorsolateral prefrontal WM among SZ subjects. Recently, Fu et al. [175] demonstrated that inflammation might play a regulatory role in microstructural WM in SZ. Peripheral IL-10 levels were higher and a significant reduction of FA and AD, and increase of RD and mean diffusivity (MD) were observed in SZ. Also peripheral IL-10 was negatively correlated with FA in the right posterior thalamic radiation and left IFOF and with MD in the right parietal arcuate fasciculus and body of the CC in SZ, while not in healthy controls. Thus, peripheral IL-10 levels were associated with the disruption of microstructural WM integrity in SZ.

Fung et al. [176] have revealed that orbitofrontal WM neuronal density was increased in SZ cases exhibiting high transcription levels of pro-inflammatory cytokines relative to those exhibiting low transcription levels and to controls. However, some authors [91] did not find significant difference in the density of IBA1-immunoreactive in the dorsolateral prefrontal WM in SZ subjects as compared to controls. Wierzba-Bobrowicz et al. [177, 178] have reported degeneration of microglial cells in frontal and temporal lobes in SZ. Some studies have found associations between the magnitude of microglia ligand binding and SZ symptom

severity [179, 180]. Busse et al. [181] have reported that there was a significant difference in microglial density between cases with paranoid versus residual schizophrenia.

Ultrastructural analysis from an electron microscopic study revealed "activated" microglia adjacent to dystrophic oligodendroglia (cytoplasmic swelling and vacuolation), demyelinating axons in the prefrontal WM in subjects with SZ but not in controls. Activated microglia containing numerous vacuoles in WM in SZ brains often located in close apposition to swollen astrocytic process containing myelin debris. In WM, both astrocytic cell processes and microglial cells were involved in the phagocytosis of degenerating myelin sheaths in SZ (Fig. 11.5) [101]. Groups of activated microglial cells (containing invaginated nuclei and vacuolated cytoplasm) were also located in close apposition to swollen dystrophic oligodendrocytes in the SZ brain (Fig. 11.6b) in contrast to the controls (Fig. 11.6a) [102]. Ultrastructural analyses also demonstrated activated microglial cells and processes located between myelin sheath lamellae in the prefrontal WM specimens of subjects with SZ but not in those of controls (Fig. 11.7).

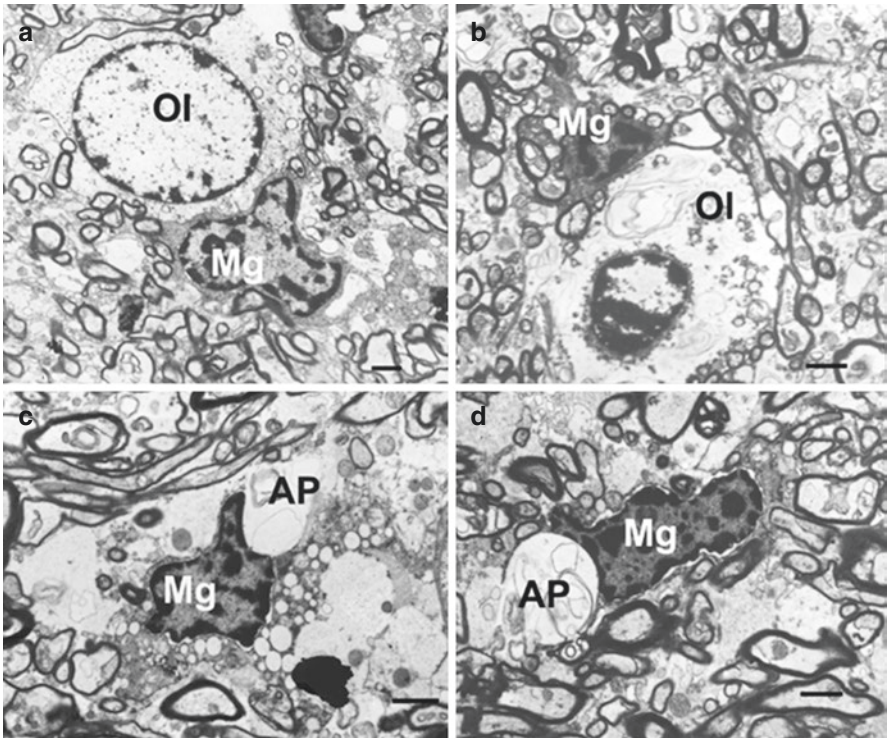

Fig. 11.5 Electron micrographs of oligodendrocytes (Ol) and microglia (Mg) in WM from control subjects (**a**) and from subjects with schizophrenia (**b**–**d**). Dystrophic changes of oligodendrocyte (**b**). Activated microglia in close apposition to swollen astrocytic process (Ap) containing myelin debris in schizophrenia brain (**c**). Microglial cell participates in phagocytosis of myelin membranous debris in schizophrenia (**d**). Scale bars = 2 μm (from Uranova et al. Schizophr Res Treatment 2011)

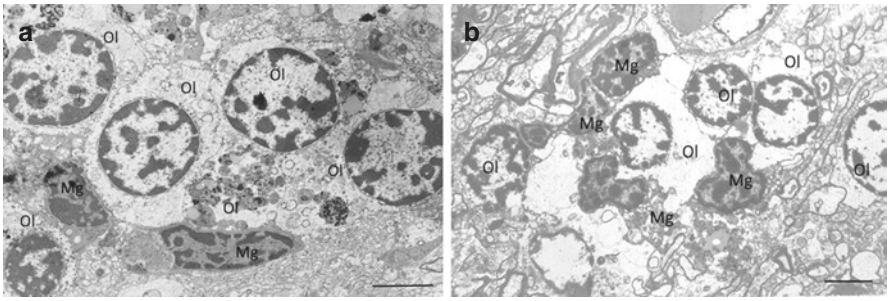

Fig. 11.6 These micrographs from the prefrontal WM demonstrate groups of oligodendrocytes in close apposition to microglial cells in the control brain (**a**) and in the SZ brain (**b**). B - Dystrophic changes of oligodendrocytes (the cytoplasm is almost empty of organelles) and activated microglial cells (they contain invaginated nuclei and vacuolated cytoplasm). *Ol* oligodendrocyte, *Mg* microglia. Scale bar = 2.5 μm (from Vikhreva et al. Schizophr Res 2016)

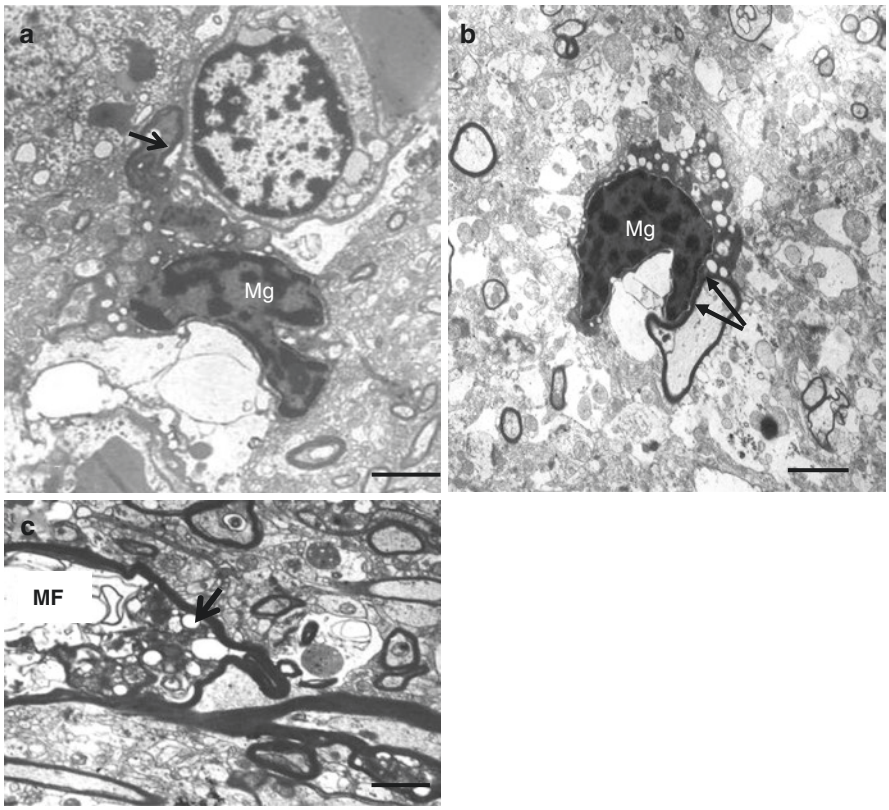

Fig. 11.7 Microglial cell processes (arrows) were detected between myelin sheath lamellae in prefrontal WM in SZ samples. Scale bars = 2 μm. *Mg* microglia

Previously Vostrikov et al. [87] reported that numerical density (Nv) of oligodendrocytes decreased significantly in layer VI of the prefrontal cortex (BA 10) (−25%) and in adjacent WM (−12%) in SZ as compared to controls. Age-related increase in Nv of oligodendrocytes in gray matter and WM in control is dysregulated in SZ [151]. The frequency of pathological MF in WM correlated with the duration of disease [101]. Together with the data described above, these data suggest that microglial activation might be involved in the pathology of oligodendrocytes and of MF in SZ. The results are in agreement with the data of the attenuation of proliferation in oligodendrocyte precursor cells by activated microglia [182]. Glutamate excitotoxicity might contribute to microglial activation in the WM in SZ since premyelinating oligodendrocytes are highly vulnerable to death caused by glutamate, free radicals, and proinflammatory cytokines [183] and IL-1β expression promotes oligodendrocyte death through glutamate excitotoxicity from activated microglia [184, 185]. These data suggest a detrimental cytotoxic demyelinating and progressive effects of microglial activation on myelinated fibers in SZ patients.

An in vivo PET study with new radioligand [18F]-FEPPA [172] in patients with SZ having ongoing psychotic symptoms and healthy volunteers found no significant differences between the groups, suggesting that neuroinflammatory processes either may take place early in disease progression or are affected by antipsychotic treatment. Recent neuroimaging studies provide no evidence for microglial activation at early stage of SZ. Hafizi et al. [186] have reported no significant differences between first episode SZ patients and healthy volunteers in microglial activation, as indexed by [18F] FEPPA VT, in either the DLPFC or the hippocampus. Van der Doef et al. [187] have found no significant difference in the PET tracer (R)-[(11)C]PK11195 BPND between SZ patients at early stage of disease and controls in total gray matter as well as in frontal cortex, temporal cortex, parietal cortex, striatum, and thalamus. These findings suggest that microglia activation is not present in recent onset psychosis or that it is a subtle phenomenon that could not be detected using the designs of these studies.

Prasad et al. [188] found in MRI study that serum IL-6 and C-reactive protein (CRP) levels were negatively correlated with the FA in the forceps major, the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus in SZ patients but not in a healthy controls. The authors suggest that the IL-6 and CRP contribute to impaired anisotropy of water diffusion in selected pathways that have been previously associated with SZ, suggesting differential susceptibility of selected neural pathways to immune mediators. Recently, researchers began to directly investigate how neuroinflammation might link neurodevelopmental abnormalities to progressive WM pathology/disconnectivity in SZ [140, 189]. The inhibitory effects of some typical and/or atypical antipsychotics on the release of inflammatory cytokines and free radicals from activated microglia have been reported ([189] for review). The treatment through the inhibition of microglial activation may shed new light on therapeutic strategies in SZ.

Neuroinflammation is associated with WM pathology in people with SZ and may contribute to structural and functional disconnectivity [144]. However, neuroinflammation is associated not only with SZ but also with autoimmune demyelinating multiple sclerosis, Alzheimer's disease, Parkinson disease, and amyotrophic lateral sclerosis.

11.3.7 Neurons in WM in SZ

Interstitial WM neurons (IWMN) are located among WM tracts of the human and rodent brain. One of the more consistent pathological abnormalities in MF is an increased density of IWMN in prefrontal, temporal [190, 191], and parietal lobe WM [192]. Eastwood and Harrison [193] have shown increased density of IWMN and decreased expression of reelin in superficial temporal WM in SZ. Kirkpatrick et al. [194] have reported increased density of IWMNs in the DLPFC in the deficit SZ group compared with the non-deficit as well as the control groups, suggestive of different pathophysiology for deficit and non-deficit SZ. A maldistribution of IWMN has been reported in the WM of the lateral temporal lobe in patients with SZ compared to controls [195].

Many studies of WM neuronal density in SZ used three markers, nicotinamide-adenine dinucleotide phosphatediaphorase (NADPH), microtubule-associated protein-2 (MAP 2), and neuronal nuclear antigen (NeuN). Multiple WM neuronal populations are affected in SZ. Increased density of microtubule-associative protein (MAP 2)-immunoreactive neurons in the prefrontal WM were found in SZ compared to controls [196]. A twofold increase in NeuN+ density have been reported in cingulate WM [197]. Neurons defined by immunoreactivity for MAP 2 and NeuN—which include primarily glutamatergic (MAP 2) or a mixed (NeuN) population of cells—are affected by a generalized increase in density in the subcortical WM (see [198] for review). However, Beasley et al. [199] have reported that WM neurons immunoreactive for MAP-2 in the frontal lobe in SZ and affective disorders did not differ significantly between the control and psychiatric groups. It is important to note that a prominent increase in the densities of the WM neurons has been detected in approximately 30% of SZ subjects [191].

Yang et al. [200] have found that density of NeuN+IWMN and somatostatin-expressing neurons is significantly increased in superficial WM in SZ subjects compared with control subjects. Increased IWMN density is correlated with a gray matter interneuron deficit, suggesting that migration of interneurons from WM to the cortex may be deficient in some patients with SZ. The hypothesis of deficient migration of interneurons is supported by the study of developmental patterns of doublecortin expression and WM neuron density in the postnatal primate prefrontal cortex and SZ [201]. Joshi et al. [202] reported higher GABA-ergic interneuron density in the superficial WM of orbital frontal cortex in SZ. Electron microscopy and immunofluorescence studies demonstrated myelination of fast-spiking PV interneurons [203]. The authors proposed that myelination of fast-spiking parvalbumin (PV) interneurons could be an important locus of pathophysiology of SZ.

The abnormal migration of cortical inhibitory interneurons during the second or early third trimester of pregnancy and apoptosis of embryonic sub-plate neurons in SZ cortex due to inflammation-induced early WM injury is supposed as a mechanism of these abnormalities (see [198] for review). High WM neuron density with elevated cortical cytokine expression in SZ has been recently reported [176]. The authors demonstrated that the density of neuronal nuclear antigen (NeuN)-immunoreactive orbitofrontal WM neurons was significantly higher in SZ subjects with high expression of interleukin (IL)-6, IL-8, IL-1β and SERPINA3 compared with controls and with low-inflammation SZ. The density of glutamic acid decarboxylase 65/67 kDa (GAD65/67)-immunoreactive orbitofrontal, but not dorsolateral prefrontal, WM neurons was significantly higher in both high-inflammation and low-inflammation subgroups compared with controls; however, there was no statistically significant difference between the high-inflammation and low-inflammation subgroups. Among the high-inflammation subgroup, a significant negative correlation was also observed between the densities of NeuN-immunoreactive WM neurons and GAD67-immunoreactive gray matter neurons in the dorsolateral prefrontal region [176]. Increased WM neuron density in a rat model of maternal immune activation has been reported [204]. Beasley et al. [205] have performed a cytoarchitectural study of the WM adjacent to the planum temporale (PT), an auditory association between regions located within the superior temporal gyrus, in subjects with SZ and affective disorders using two-dimensional measures. Neuronal density, neuronal size, and glial nuclear size did not differ between groups. No significant difference in neuronal clustering was observed in the patient groups. But glial density was lower in SZ as compared to normal controls. McFadden et al. [206] have recently reported the absence of differences in IWMN densities in the DLPFC in SZ in cresyl-violet sections using stereological principles.

A number of SZ susceptibility genes at other loci, including *DISC1*, *NRG1*, and *RELN*, are known to play a critical role in neuronal migration and positioning in developing brain and could contribute to the observed increase of WMN observed in SZ [198]. Fetal sub-plate neurons and surviving postnatal IWMN are important modulators of cortical functions in both normal and SZ cerebral cortices. Since IWMN play a role in migration of neurons during brain development, and they are indirectly involved in forming connections between brain regions, these data support neurodevelopmental theories of SZ.

11.3.8 Corpus Callosum in SZ

Morphological, electrophysiological, and neurophysiological studies suggest that the CC, which is the largest portion of WM in the human brain and responsible for inter-hemispheric communication, is altered in SZ patients [207]. The CC is the largest fiber bundle in the mammalian brain. It connects equivalent association between cortical regions across hemispheres of the brain. In human brain, the CC genu and splenium connect association areas of the prefrontal and temporo-parietal cortices, whereas the callosum body and isthmus connect visual, auditory, and

somatosensory areas [208]. The CC mediates sensory-motor coordination [209]. Morphological, electrophysiological, and neurophysiological studies suggest that the CC, which is responsible for inter-hemispheric communication, is altered in SZ patients. Proteomes quantified by label-free spectral counting have shown that among the differentially expressed proteins in CC in SZ are those associated with cell growth and maintenance, such as neurofilaments and tubulins, cell communication and signaling, such as 14–3-3 proteins, and oligodendrocyte function, such as myelin basic protein and myelin-oligodendrocyte glycoprotein [207].

The neuropathology of the CC was studied mostly by neuroimaging methods. Structural magnetic resonance imaging (MRI) studies have provided evidence for CC abnormalities. The first MRI study suggested alterations in CC size and shape [210]. A meta-analysis showed that the CC is smaller in SZ, especially in patients with first-episode SZ [211]. Structural MRI studies have demonstrated smaller CC [147, 212–214] and alterations of CC shape [215–217]. Whitford et al. [218] reported geometric abnormalities in the prefrontal callosal fibers in SZ patients. Chaim et al. [219] in MRI study found volume reduction of the CC and its relationship with deficits in interhemispheric transfer of information in recent-onset psychosis. WM volume reductions in the right frontal and left corpus were found from high-resolution T1 structural images in the SZ patients. WM volume alterations were related to alogia, anhedonia, and delusions [76]. Two-tensor tractography showed decreased FA_t corrected for free water and increased trace and radial diffusivity (RD_t) in the five CC subdivisions in first-episode SZ patients compared to healthy controls associated with larger lateral ventricles volume [220]. The authors suggest possible de- or dysmyelination or changes in axonal diameters according to neurodevelopmental hypotheories of SZ. Collinson et al. [221] demonstrated that both area and volume of the CC were significantly reduced in SZ patients relative to controls but no significant differences in CC existed between genders in either patients or controls. Differences in area and volume of the CC were greatest in chronic patients with SZ relative to patients with a first episode and controls. The data suggest that morphological abnormalities in the CC may increase with illness progression.

Imaging studies have identified a widespread reduction of WM FA in the CC in adolescent onset SZ patients [222]. Patients 18–30 years old within 5 years of illness had lower FA and higher RD than controls in numerous WM tracts, including the CC and the SLF. Illness duration was associated with lower FA and higher RD, most prominently in the CC [223]. Balevich et al. [224] have reported that both adult and adolescent SZ patients demonstrated reduced callosal FA, with the adolescents exhibited reductions mostly in anterior regions while the reductions were more prominent in posterior regions of the adults. Callosal maldevelopment during adolescence due to reduced axonal density or myelination could affect interhemispheric communication in SZ. Reduced fiber density has recently been found in the CC in the SZ patients using a new non-tensor-derived diffusion method measuring fiber density that detects subtle changes in the WM [52]. Ultra-high risk (UHR) subjects who later developed psychosis showed lower FA compared with healthy controls in the CC, the left SLF and ILF, the left IFOF and the forceps; RD

was significantly higher in the CC, the forceps, the anterior thalamic radiation bilaterally, and the CB. First-episode SZ patients, compared to healthy controls, showed a significant FA reduction in the CC, the SLF and ILF bilaterally, the IFO bilaterally, the corona radiate bilaterally, and the forceps; while RD was found to be significantly increased in the left SLF. Ultra-high risk subjects who later developed psychosis had WM abnormalities affecting brain pathways that are crucial for intra- and inter-hemispheric connections [225]. Kim et al. [226] have reported increased FA in the genu of subjects at genetically high risk for SZ compared to controls, which may be an indicator of compensatory alteration in WM integrity, whereas SZ patients showed significantly decreased FA in the splenium.

Lower FA values has been found in the genu and body of CC in first-episode patients with SZ [227] and in patients at an early stage of SZ [228]. Zhang et al. [229] have recently reported FA reduction in several brain regions, including CC, brainstem, internal capsule, cingulate, and cerebellum and a significant positive correlation between the FA values in the CC in drug-naive patients with first-episode SZ. Spectroscopy detected a decrease of NAA level in the CC genu, indicating axonal lesion during the early stage of SZ. However, reduced FA in the CC, including the genu [75, 230, 231], and an FA decrease in splenium related to a longer illness duration [15] have been reported in chronic SZ patients compared with healthy controls. With voxel-based and fiber-tracking DTI techniques, significantly decreased FA values were identified in the genu of CC in patients with chronic SZ, but not first-episode SZ, compared with healthy controls [232]. Ellison-Wright et al. [230] using Tract-Based Spatial Statistics (TBSS) detected significantly lower FA in the genu, body, and splenium of the CC and the left anterior limb of the IC.

CC abnormalities are related to SZ clinical symptoms. Cognitive impairment in SZ is associated with abnormal glucose metabolism. Patients with SZ demonstrated greater fasting plasma levels of glucose and insulin and poorer cognitive scores, as well as reduced FA values in five brain areas, including left and right CC [233]. Hubl et al. [234] found anterior callosal microstructure disruption in SZ patients with auditory hallucinations. FA deficits in the genu and splenium of the CC were associated with auditory verbal hallucinations [71]. Whalley et al. [235] showed that FA values within the CC correlated significantly with positive psychotic symptom severity. The FA value of the anterior part of the CC was negatively correlated with the avolition score on the SANS scale [74]. Patients with deficit SZ had reduced FA in the body of the CC [236]. Lowered FA in the CC was associated with treatment resistance in SZ [237]. FA reduction was also found in the mid-body of the CC in first-episode SZ patients after acute antipsychotic treatment [119]. Never-treated patients demonstrated lower amplitude of low-frequency fluctuations in splenium of CC as compared to treated patients and controls [238]. Postmortem study showed less neurofilament heavy protein in the CC in SZ than in the normal controls [239]. The CC is crucial for the development of structural brain asymmetry. Whitford et al. [240] have reported a variety of diffusion abnormalities in the CC in patients with SZ, which were related to the severity of psychotic symptoms. Taken together, these imaging studies provide strong evidence that inter-hemispheric connectivity plays a key role in the pathophysiology of SZ. Recently, Savadjiev et al. [241] have reported

a reversal of normal sexual dimorphism in callosal WM geometry consistent with recent results in adolescent onset SZ. This pattern may be indicative of an error in neurogenesis and a possible trait marker of SZ.

Imaging techniques such as DTI suggest that some of the callosal alterations in SZ are driven by alterations to WM microstructure, through either disrupted myelination or altered axonal structure or organization. However, there are very few postmortem neuropathological studies of the CC in SZ. Casanova et al. [242] have reported that there was no significant difference in the total number or density of fibers in the CC between SZ patients and controls. But Highley et al. [95] have shown decreased total fiber number and fiber density in genu, midbody, isthmus, and splenium of the CC in women with SZ.

Williams et al. [164] measured oligodendrocyte and astrocyte density using systematic anatomical distinctions and randomized counting methods. Astrocytes were identified by GFAP immunohistochemistry. A significant decrease in astrocyte density was observed in SZ compared with normal controls in the cingulate gray matter, cingulate WM, and the midline of the CC. Bipolar disorder and major depression cases showed no significant changes in astrocyte density. Oligodendrocytes did not show any changes between diagnostic groups. These data are in line with consistent evidence that astrogliosis is absent among individuals with SZ. Williams et al. [100] using standard high-resolution oil-immersion light microscopy examined the density of myelinated axons and the cross-sectional area of the nerve fibers and the axonal myelin sheath in the genu of the CC. There was no significant change in the density of myelinated axons. Major depression cases had significantly greater mean myelin cross-sectional area and myelin thickness per axon than in control or SZ groups. Steiner et al. [243] reported the downregulation of S100B in the nuclear proteome of the CC from SZ patients compared to mentally healthy controls using mass spectrometry and Western blot. There is a paucity of information about the effects of neuroleptic treatment on the CC. Wang et al. [124] showed that haloperidol treatment for 3 weeks increased the number of NG2-expressing cells, a specific marker for oligodendroglia precursor cells, in the CC. Taken together, the data demonstrated that the CC is implicated as a region of dysfunctional connectivity in SZ.

11.4 Conclusion

Both imaging and postmortem studies on patients with SZ have shown a widespread disruption of WM integrity as a consequence of the pathology of oligodendrocytes and of myelinated fibers. Postmortem studies provide evidence for morphological basis of oligodendrocyte and myelin abnormalities in SZ that might disturb intra- and interhemispheric axonal integrity and neuronal connectivity in SZ patients. These abnormalities are accompanied by the activation of microglial cells, signs of neuroinflammation, decreased density of astrocytes and increased density of interstitial WM neurons in SZ as compared to controls. The data might be useful for better understanding of the pathophysiology and pathogenesis of SZ, for the interpretation of neuroimaging data and to develop new WM neuroimaging techniques

and to create new therapeutic strategies directed to precise WM abnormalities in SZ. Future studies should use multi-modal imaging methods to integrate them with clinical, neurochemical, neuroimmunological, and genetic approaches. Multi-parametric methods are required to estimate the relationships between neurons and glial cells, between microglia, oligodendrocytes, myelinated fibers and astrocytes to determine what kind of cellular type show the most robust changes in disease and the association of these changes with other cell types. Clinical-pathological correlates including antipsychotic treatment, age, gender, onset, duration of disease, phase, and course of illness are necessary to make progress in better understanding the pathogenesis and altered neuroplasticity in schizophrenia to determine new treatment strategy.

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Glial Cells

12

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12.1 Introduction

Rudolf Virchow made the first description of glial cells in the mid-nineteenth century when he described a neuroglia connective tissue ('nervenkitt') that embedded and maintained nerve cell structure [1]. Otto Dieters reported the first description and of an astrocyte [2], and after the invention of appropriate histological staining by Santiago Ramon y Cajal, Camilo Golgi, and Pio del Rio Hortega, it became possible to describe the morphology of astrocytes and begin to unravel their diversity and morphological states [3]. The term astrocyte, derived in English from Astrocyten, was from Michael von Lenhossek, who suggested that the star-shaped glial cells should be named either spider or star cells to describe the shape they made with multiple processes emanating from their centre [4]. Astrocytes are typically detected by antibodies to GFAP or s100β. Neither of these stain all astrocytes present and so we are likely not witnessing the total behaviour of these cells in schizophrenia and associated disorders. Furthermore, we are now seeing the further separation of these types in function subtypes, such as reactive or fibrillary astrocytes and non-reactive or gemistocytic astrocytes (see Figs. 12.1, 12.2 and 12.3), and seeing how these subtype changes may be responsible for the changes observed [5–7]. In oligodendrocytes, we have additional problems as a reliable antibody for oligodendrocyte identification in formaldehyde-fixed tissue has been elusive, although recently

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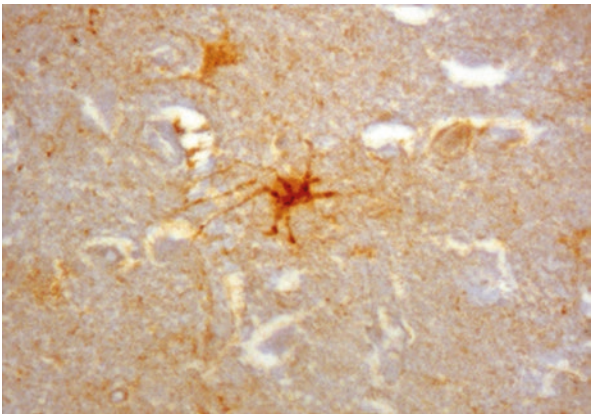

Fig. 12.1 A GFAP-immunohistochemical stained fibrillary or reactive astrocyte observed at x400 magnification. The multiple processes projecting from the cell body can clearly be observed

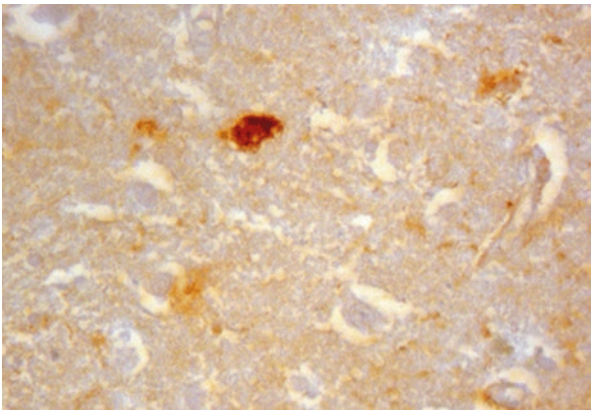

Fig. 12.2 A GFAP-immunohistochemical stained gemistocytic or reactive astrocyte observed at x400 magnification. The dark staining in the cell body is clear, with no processes observed. A gemistocytic astrocyte may sometimes have a single, large, darkly stained process

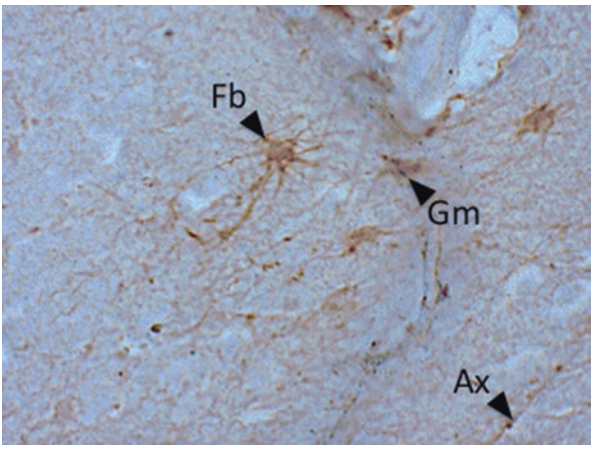

Fig. 12.3 GFAP-labelled section showing multiple stained astrocytes. Gemistocytic astrocytes are identified by the deep cell body stain, oval or rectangular shape and either no processes or a single, thick process. Fibrillary astrocytes are characterised by a clearly stained cell body with multiple, thinner processes. *Gm* gemistocytic, *Fb* fibrillary, *Ax* GFAP-reactive axon

ADAM-12 has been reported to have some success in this respect [8]. The conflicting findings described previously in dorso-lateral prefrontal cortex (dlPFC) white matter using different stains suggest this could be a key issue in the future of neuropathological investigation of schizophrenia. Microglia have not been shown to have a substantial role in schizophrenia using pathological methods, although some PET studies have suggested an elevation globally in cortical grey matter, although some studies have suggested an increase in subcortical microglia associated with acute psychosis [9–12]. More recent theoretical models of schizophrenia, including a link between microglia and oligodendrocytes in maintenance of white matter axons [10, 13–15], suggest the role of microglia in this disorder may be subtler than previously thought. This is demonstrated clearly in the white matter microglia density studies described previously, as it is suggested that neuroinflammation in schizophrenia may be associated with white matter pathology by linkage with axonal degradation, myelin phagocytosis and oligodendrocyte density.

Therefore, it is not functionally useful to pay attention to combined total glial but rather to separate into the glial types described. As the results of studies on neuropathological findings on glia cells populations have been described by anatomical location in previous chapters, here we examine a specific factor in each glial cell type biology that is related to the pathology of schizophrenia.

12.2 Astrocytes

Many symptoms of schizophrenia and associated psychosis have been suggested to have a biological cause originating in the cortex [16], although competing pathological and imaging studies are renowned for showing a complex mixture of results. In recent years, the link between cortical glutamate (GLU) and psychosis has been strongly supported by experimental evidence.

As glial cells have received more attention in research, it has become clear that the role of astrocytes in neuronal function is more diverse and critical than was originally assumed. Astrocytes were first described in 1893 by Michael von Lenhossek, the name reflecting the star-like structure of their fibrillary morphological form and are now understood to have many roles in normal neuronal function. They are thought to make up to 30% of CNS cells in the mammalian brain [17, 18], although they seem to be rarer in non-mammalian animals [19–23]. A critical function of astrocytes is the regulation of GLU, an amino acid and the most prevalent excitatory neurotransmitter in the brain [24]. GLU is released in the cortex by excitatory interneurons, found predominantly in cortical layers II and IV, and is a key neurotransmitter in most aspects of normal brain operation such as cognition, memory and learning and several biological processes including the control of synaptic plasticity, cell migration, differentiation and cell death. GLU is released from vesicles in presynaptic terminals by a Ca^{++}-dependent mechanism that involves N- and P/Q-type voltage-dependent Ca^{++} channels, and GLU-neurotransmission is mediated or affected by metabotropic and ionotropic GLU receptors. These receptors are each subdivided into three groups. Group I metabotropic glutamate receptors (mGluR1 and mGluR5) are mainly

post-synaptic, and groups II (mGluR2 and mGluR3) and III (mGluR4, mGluR6, mGluR7 and mGluR8) are primarily presynaptic and modulate neurotransmitter release. Ionotropic GLU receptors are amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA) [25].

High activation of GLU receptors is dangerous as GLU is toxic in high concentrations inducing cell death. The mammalian nervous system has an evolutionarily conserved mechanism to regulate GLU uptake, with homeostasis of GLU maintained by synaptic release from glutamatergic cells and uptake to glial cells through GLU absorption. To regulate extracellular GLU levels, the CNS has a complete family of high-affinity excitatory amino acid transporters (EAAT1–5). EAAT1 and EAAT2 are expressed in glial cells and EAAT3 expressed peri-synaptically on neurons, possibly playing a more central role in regions where astrocytes are less dense such as in the hippocampus, or in situations where there is an excess of GLU such as ischemia. EAAT3 also transports cysteine, contributing to the synthesis of intracellular glutathione, an important antioxidant providing an additional neuroprotective effect especially in early CNS development [26]. EAAT4 and EAAT5 found mainly in the cerebellum and retina, respectively, are also expressed peri-synaptically on neurons and can act as uncoupled Cl ion channels providing a physiological clamp on membrane potential and may act more like inhibitory GLU receptors [27]. They have a much higher affinity for GLU than EAAT1, EAAT2 or EAAT3 but are situated much further away from synaptic junctions and are therefore thought to be involved in 'mopping up' excess GLU [28, 29]. The five trans-membrane GLU-transporters are encoded by solute carrier family SLC1 genes crucial in the regulation of GLU homeostasis in neurons in the brain and other organs (detailed in Table 12.1). The transporters are ATPase-coupled ion transporters; the influx of GLU coupled with 3Na+/1H and the efflux of 1K+ where it is converted to glutamine by glutamine-synthase and recycled to the pre-synaptic neuron. The transporters can also act as uncoupled chloride ion channels, typically in response to the build-up of extracellular K+, and so help to maintain the membrane potential at physiological levels [30–32].

GLU transporters form a transmembrane protein of eight helices with distinct regions involved in ion transport and an associated scaffold domain [33]. Functional transporters exist in the membrane as homo-trimers although there is some evidence that EAAT2 and EAAT3 can form hetero-trimers in the membrane. This alternative configuration has been shown to alter receptor localisation within the membrane, without appearing to affect functionality [34].

EAAT1 and EAAT2 are expressed at different levels in different brain regions and is selectively expressed in astrocytes in the brain [35]. EAAT1 is highly present in specialised glial cells such as the Bergmann glia of the cerebellum [36], the Müller cells of the retina and supporting glia in the vestibular end organ, inner ear [37]. EAAT1 is regulated in multiple levels with the results of important changes in the EAAT1 expression on the plasma membrane. All these changes are dependent on the phosphorylation status of EAAT1, which is regulated by several kinases. EAAT2 is the most abundant GLU transporter, so is also highly expressed in astrocytes in all parts of the brain and spinal cord.

Table. 12.1 The five primary glutamate transporters encoded by solute carrier family 1 (*SLC1*) genes crucial in the regulation of glutamate homeostasis in neurons in both the brain and other organs

Gene	Human gene locus	Gene size (bp)	Exons	Introns	Splice variants	Post-transcriptional modification	Protein name	Protein size	Isoforms	Substrate	Distribution in CNS
SLC1A1	9q24	97,043	14	13	3	Glycosylated (acetylation, phosphorylation, ubiquitination)	EAAC1 EAAT3	524 AA 57,100 Da	2	L-Glu, D/L-Asp L-Cys	Neurons
SLC1A2	11p13-p12	168,859	16	18	8	Glycosylation (acetylation, ubiquitination, sumoylation, palmitoylation, phosphorylation)	GLT-1 EAAT2	574 AA 62,104 Da	2–5	L-Glu, D/L-Asp	Astrocytes (some neuronal)
SLC1A3	5P13	81,980	12	17	12	Glycosylation Ubiquitination	GLAST EAAT1	542 AA 5972 Da	2–9	L-Glu, D/L-Asp	Astrocytes (some neuronal)
SLC1A6	19	72,957	15	19	9	Glycosylation (acetylation, dimethylation, phosphorylation)	EAAT4	564 AA 61,565 Da	2–5	L-Glu, D/L-Asp	Neurons (cerebellum, Purkinje cells)
SLC1A7	1p	55,435	13	11	4	Glycosylation	EAAT5	50 AA 60,658 Da	4	L-Glu, D/L-Asp	Neurons, glia (retina)

Once taken up by the astrocyte GLU is metabolised to glutamine- the GLU precursor. The GLU-glutamine pathway can occur in neurons but recent evidence shows it may primarily be a glial-determined process, mainly conducted by astrocytes around the synaptic cleft. This proximity allows fast GLU uptake and efficient recycling of astrocytic glutamine back to the neuron [38], and also regulate the diffusion of GLU into the extracellular space [39, 40].

EAAT dysfunction has been implicated in a variety of neurodegenerative and neurological diseases, with a very special downregulation of EAAT2 in amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, ischemia and epilepsy. The perturbation of glutamatergic neurotransmission by a decrease/loss of GLU transporter activity/expression can be regarded as a major cause for a number of neurological disorders and to be crucial for distinct neurodegenerative diseases. However, GLU abnormalities may also disturb brain function and underpin psychotic symptoms and cognitive impairments.

Genetic depletion in EAAT1 & EAAT2 double knockout mice has shown they are both required for brain development through regulation of extracellular GLU concentration [41]. EAAT2 deletion in mice has shown a very important reduction of GLU uptake activity, increased levels of extracellular GLU and induce hyperactive, epileptic phenotype accompanied by moderate mild sensorimotor impairment, hyperlocomotion lower anxiety, better learning of cue-based fear conditioning [36]. EAAT1 deletion in mice has shown insufficient GLU uptake in all region where EAAT1 is the predominant transporter, and display poor nesting behaviour, abnormal sociability and impaired learning, proposing that gene deletion of EAAT1 could be the source of select abnormalities related to the negative and cognitive symptoms of schizophrenia [42]. In humans the reduced expression of EAAT1 and EAAT2 have been correlated with impaired cognitive functions in schizophrenia patients [43]. GLU transporter expression and function are regulated both pre- and post-transcriptionally via a variety of mechanisms which have been widely characterised for EAAT2 and EAAT 1 in both rodents and humans both in vivo and ex vivo; less is known about the regulatory mechanisms of EAAT3, 4 and 5. The most basic regulatory mechanism is via a physiological feedback loop as glutamate transporter function optimally at normal membrane potentials [31].

Transcriptional upregulation of EAAT1 and EAAT2 resulting in increased protein expression and/or function has been documented in response to a variety of growth factors including oestrogen, TGF-alpha [44], IGF-1 [45], EGF [46] and PACAP [47]. The SLC genes contain promoter regions in the 5′ region that contain consensus sites to numerous nuclear transcription factors such as NFκB, CREB, c-Jun and mTOR. These can be activated by growth factors via downstream receptor signalling pathways such as PI3K/AKT, ERK/MAPK or Protein Kinase A, resulting in increased gene transcription. Growth factors such as TGF-alpha have also been shown to bind directly to regulatory transcription factor binding sites within the gene additionally promoting transcription.

Downregulation of the SLC genes is less well characterised; however, manganese is known to decrease the function, localisation and expression of transporters and is thought to act via the Protein Kinase C-induced activation of the novel

Transcription Factor YY1 [44, 48]. TNF-alpha and IL-1 beta have also been shown to down regulate transcription although the pathways remain unclear [44].

Post-transcriptional regulation has been shown to occur via alternative splicing of the gene and epigenetic modification. Multiple splice variants of EAAT1 and EAAT2 have been characterised (Genecard: GC05P036606 and GC11M035272) [33, 49]. Functionally these splice variants are not different, but they have been shown to have differential localisation within neurons and astrocytes which may affect function.

Histone acetylation has been shown to increase/stabilise GLU transporter mRNA whilst DNA methylation has differential effects on protein expression [50]. Hypo- and hyper-methylation have been associated with both increased and decreased EAAT2 expression in vivo, a discrepancy that may be due to the specific site being modified by methyl-transferase within the gene. MicroRNA is usually associated with the destabilisation of mRNA and decreased translation, although miR-124a has been shown to consistently increase EAAT2 protein expression [51]. miR-124a can transfer the astrocytes from the neuron via exosomes which precipitate direct interaction with mRNA. Whilst the exact mechanism remains unclear, this indirect interaction could explain this unusual effect. All GLU transporters are post-translationally glycosylated within the endoplasmic reticulum to allow insertion into the plasma membrane and formation of homotrimers. EAAT2 has also been shown to be additionally palmitoylated and sumoylated [50]. EAAT1, EAAT2 and EAAT3 also undergo ubiquitination. These modifications effect membrane cycling and therefore regulate cell surface expression and function. Ubiquitination and sumoylation both result in the retention of glutamate transporters intracellularly and subsequent degradation [52] [50]. Ubiquitination has been shown to be promoted by Protein Kinase C which also has a role in transcriptional downregulation.

The number of transporters in the plasma is a key regulatory mechanism, their subsequent localisation also affecting function. EAAT2 and to a lesser extent EAAT1, EAAT3 and EAAT4 are associated with cholesterol-rich lipid rafts found on both neurons and glia [33, 53]. This could aid in the effective formation of homotrimers or concentrate receptors in the synaptic cleft during nerve transmission. Membrane cholesterol depletion has been shown to result in decrease GLU uptake suggesting a regulatory function.

Electron microscopy shows EAAT1 and EAAT2 is found in astrocytic soma and processes, specifically in small astrocytic processes adjacent to axon terminals forming asymmetric GLU synapses. Whilst EAAT2 labelling was most prevalent in these astrocytic processes, EAAT1 labelling was also present in neuronal processes including the soma, axons and dendritic spines, showing the dual, but weighted, regulatory pathways involved in cortical GLU regulation [54]. Direct immunohistochemical examination of mouse cortex shows co-localisation of EAAT4 with cellular GFAP, a classic astrocytic marker [55].

C6 cell lines, astrocyte-like cells obtained from rat gliomas, are often used to study cellular functions such as GLU uptake and glutamine synthetase activity. Treatment of C6 cells with Riluzole, an approved drug for the treatment of amyotrophic lateral sclerosis, has shown to stimulate GLU uptake and augmented the

expression of the GLU EAAT1, directly supporting the role of astrocyte-type cells in regulating GLU [56]. RT-PCR analysis has also demonstrated mRNA expression of EAAT4 in astrocyte cultures [55], with additional cell culture studies demonstrating that EAAT1 and EAAT2 are expressed by morphologically distinct glial-fibrillary-acid-protein (GFAP)-positive astrocytes following their transformation from gemistocytic to fibrillary type [56, 57], and their expression correlates with the status of neuron differentiation, maturation and activity [57]. Up-regulation of lipocalin-2 (LCN2) marker has also been reported in reactive astrogliosis, although not to the same extent as GFAP. The function of this is not clear, as LCN2 is more typically involved in immune regulation, although this has not been shown to be its endogenous function in astrocytes [58, 59].

Activation of reactive astrogliosis is a complex process not well understood. Extracellular nucleotide binding to astrocytic P2 purinergic receptors (P2Y) has been shown to be a key trophic signalling pathway, particularly for the induction of stellation—the astrocyte formation of the long processes distinctive in the fibrillary state. Nucleotide binding to P2Y acts mainly through mitogen-activated protein kinase (MAPK) cascades, with trophic signal activated via the extracellular signal-regulated protein kinases (ERK) pathways, and mediating signals regulated via stress-activated pathways c-Jun N-Terminal kinases (JNKs) and p38 [60]. The trophic signals, after activation via ERKs, are transmitted through c-Fos, Elk1, STAT3 and GSK-3β pathways within the astrocyte to regulate cell behaviours such as stellation and movement. Nucleotides can also act in concert with polypeptide trophic factors such as glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) to magnify trophic signalling on astrocytes [61].

Functional differences linked to astrocyte morphology have been described in astroglial scars, as the astrocytes within derive almost entirely from newly proliferated cells with elongated shapes, fitting the description of gemistocytic astrocytes [62]. Fibrillary astrocytes are identified by the presence of many visibly stained processes emanating from a single cell body, although more recent findings suggest there may be two distinct populations of fibrillary astrocytes that could exist either in a continuous heterogeneous state or in multiple distinct activation states [63].

In contrast, gemistocytic astrocytes have substantially larger more-swollen cell bodies, often with a rectangular or cylindrical shape, and either no visible processes or a single, thicker process. With clear staining and microscopy, these can be distinguished clearly by eye. Astrocytes that become activated and undergo a series of morphological and functional changes termed astrogliosis. Morphologically, the continuous process of transformation, causing a relatively high intra-group heterogeneity, means that there can be individual cells which can be difficult to classify, although fractal analysis has suggested there are three types of astrocyte morphology [64], the difference is only detectable using detailed mathematical analysis and not visible to the eye, and therefore is of no use to researchers or clinicians using pathological methods. Astrocytes have also been found to have distinct ‘domains’ in pathological samples, with only the most distal ends of the processes overlapping between adjacent cells. The overlap of the process tips shows connecting gap

junctions when examined using ultrastructural methods, allowing cell–cell communications. This organisation has been shown in grey and white matter and means that the entire brain is covered in a continuous network of astrocytic processes [65, 66].

There are also methodological issues, such as astrocyte staining in frozen a formalin-fixed tissue requiring different antibodies and protocols. Astrocytes are typically identified using S100β and glial fibrillary acid protein (GFAP) antibodies in pathological samples, although neither antibody binds to even a majority of target cells S100β 10–30% of astrocytes, GFAP 25% [18, 67]. This distinction is potentially functionally important as S100β, a member of an EF-hand-type family of Ca2+−binding proteins found diffused throughout the cytoplasm, cytoskeleton and in cell membranes, has been implicated in the regulation of the morphological state of astrocytes [68]. Similarly, GFAP is likely involved in control of astrocyte morphology and movement [69].

Reports go back some decades of an increase in fibrillary gliosis using Holzer's stain in the periventricular structures of the diencephalon, the periaqueductal region of the mesencephalon, the basal forebrain, hypothalamus, midbrain tegmentum, and substantia innominata in schizophrenia cases [70], although subsequent analysis has suggested that this may well be a result of schizophrenia cases having a concurrent disorders with their own neuropathologies [71–73]. More recently, morphological astrocyte change in the human brain has been directly reported in the subgenual cingulate cortex in schizophrenia with psychosis where fibrillary, but not gemistocytic, astrocytes were decreased [5, 7], and in the dorsolateral prefrontal cortex where astrocyte morphology is changed in schizophrenia along with density [74]. As both these structures are heavily implicated in schizophrenia symptomatology, these pathological findings do support the hypothesis presented. This suggests that not only astrocytes are critical in the pathophysiology of psychosis via the GLU pathway but that the different morphological states observed correspond to very different functional roles, an under-examined area of pathology for some time [75]. Whilst this research is at an early stage, we would suggest that future studies should attempt to take morphological state into account along with cell numbers, clustering and density as is currently a normal practice.

12.3 Oligodendrocytes

Oligodendrocytes are highly specialised glia whose primary role is the wrapping of the axon in a myelin sheath to aid action potential conduction [76], a process conducted by mature oligodendrocytes spiral-wrapping plasma membrane extensions around axon internodes [77, 78]. They were discovered by Pío del Río Hortega (1882–1945) along with microglia [79].

Research into oligodendrocytes has been less consistent than other glial cell types. The main role of oligodendrocytes has always been thought to be in myelinating CNS axons [76, 79, 80], and as schizophrenia is not a typically demyelinating disorder, these cells may have less relation to the causes of the illness than

astrocytes or immune cells. The underlying mechanisms behind oligodendrocyte are still poorly understood, but to maintain axonal integrity, mammalian myelin-forming cells require the expression of some glia-specific proteins, such as CNP, PLP and MAG, as well as intact peroxisomes. None of these are necessary for myelin assembly. Loss of glial support causes progressive axon degeneration and possibly local inflammation, both of which are likely to contribute to a variety of neuronal diseases in the central and peripheral nervous systems [80].

Secondly, there are practical staining problems. Oligodendrocytes are more routinely identified using immunohistochemistry, with probes such as Olig1, NOGO, MOG and CPNase used by research groups and tissue banks worldwide. However, they are only effective in frozen tissue, and obtaining good-quality well-matched frozen tissue for schizophrenia research has been an insurmountable block for many research groups. Overwhelmingly, histopathological research is performed on formalin-fixed paraffin-embedded tissue which has so far proved resistant to antibodies for labelling oligodendrocytes.

Even with these experimental limitations, oligodendrocytes have shown to be disrupted in schizophrenia in the prefrontal cortex, cingulate and deep white matter (see Chaps. 4, 7 and 11).

There has been considerable interest in one oligodendrocyte-specific protein, 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP) has been implicated in the maintenance of axonal integrity and is essential in generating and maintaining cytoplasm within the myelin compartment. CNP directly organises the actin cytoskeleton, providing an intracellular scaffold that acts to resist membrane compaction by myelin basic protein (MBP). A system of cytoplasmic channels within the growing myelin sheath enables membrane trafficking to the leading edge. The majority of these channels close as development progresses but can be reopened in adults by experimentally raising phosphatidylinositol-(3,4,5)-triphosphate levels, a phospholipid found in the plasma membrane, which has the effect of reinitiating myelin growth, suggesting the assembly of myelin as a multi-layered structure [77, 78, 81–83].

There is evidence that the exonic single-nucleotide polymorphism rs2070106 is associated with CNP expression, with under-expression of CNP mRNA in schizophrenia and with the lower-expressing A allele significantly associated with schizophrenia [84]. Prior studies have found decreased mRNA expression of oligodendrocyte-associated genes in the dlPFC of patients with schizophrenia. However, it is unclear which specific genes are affected and whether the changes occur in the cortical white or grey matter. Examination of mRNA expression levels of four oligodendrocyte-related genes, myelin-associated basic protein (MOBP), myelin-associated glycoprotein (MAG), CNP and oligodendrocyte-lineage transcription factor 2 (OLIG2) in dlPFC white and grey matter using quantitative-PCR and high-risk polymorphisms in CNP and OLIG2 on mRNA levels of these genes revealed changes between schizophrenia and control cases. Genetic polymorphisms in CNP (rs2070106) and OLIG2 (rs1059004 and rs9653711), previously linked with schizophrenia, predicted low expression. Expression of MAG, CNP and OLIG2 between schizophrenia and controls in the grey or white matter, and MOBP

and CNP protein in the white matter was unchanged between the experimental groups [85]. This is of particular interest as OLIG2 targets chromatin remodellers to enhancers to initiate oligodendrocyte lineage progression and maturation [86].

Even if this field is still in an early stage, there is compelling evidence that common single-nucleotide polymorphisms with alleles associated with schizophrenia have a distinct role in the development and function of oligodendrocytes and that this may have a similar effect in their morphology. The difficulty of using oligodendrocyte morphology in neuropathology studies in this field has been discussed in several papers in various contexts [7, 74, 87–96], although recent ultrastructural examination of oligodendrocytes in the dlPFC by morphometry and electron microscopy showed oligodendrocyte swelling, vacuolation, paucity of ribosomes and mitochondria and accumulation of lipofuscin granules in the schizophrenia as compared to controls. Morphometry detected a significant reduction of mitochondria and the increase in lipofuscin-granules and vacuoles in oligodendrocytes in the schizophrenic group as compared to controls [97]. Given these findings, it may be worth future neuropathological studies refocusing their attention on these glial cells to identify consistent morphology traits that could be linked with schizophrenia.

12.4 Microglia and Macrophages

Macrophages were first discovered late in 1884 by Ilya Metchnikoff. They are an evolutionarily conserved phagocytic cell type thought to have been present for over half a billion years [98, 99]. Whilst the idea that all macrophages in body tissues are derived from the blood has now been superseded by the understanding that many tissue types have their own resident macrophage populations [100–105], microglia have been termed the tissue-specific ‘macrophages of the brain’, and what neuroscientists call macrophages are those larger immune cells that move from the blood population [106, 107]. Microglia are extremely active cells within the CNS. Even in their resting state, microglia are mobile with the most active processes of any cell in the central nervous system, which may call into question the term ‘resting’ used to describe them [108], and have been found to have an active role in supporting synaptic activity via the microglia projections in a manner similar to astrocytes [109].

Microglia were first identified a few decades later and categorised around 1920 by the same histopathologist who classified oligodendrocytes in 1922, Rio Hortega, using silver carbonate staining [79]. They typically exist in a quiescent state in the healthy CNS, becoming activated immune cells upon injury or infection [110]. Microglia also play a role in synapse refinement by cell–cell interaction, notably in synapse function by means of ligand–receptor groups already well characterised in immune function (reviewed in [111]), including key complement receptors CR1, CR3 and CR4 [112]. Unfortunately, it is particularly difficult to interpret the role of microglia morphology and activity in psychiatric disorders in neuropathology as they have been shown to remain active and remodel their process for up to 10 h after death, long before the majority of human post-mortem samples are taken [113–115].

Blood-resident monocytes infiltrate the brain parenchyma and differentiate into monocyte-derived macrophages which express receptors to detect exogenous risk chemical signals for pathogens, as well as endogenous inflammatory signals, such as cytokines, ATP and glucocorticoids. In many neurological diseases, binding and activation of these receptors lead to an altered phenotype and the induction of inflammatory responses ([116–124].

Monocyte-derived macrophages generated from 15 schizophrenia patients and 15 healthy controls exposed to pro-inflammatory and anti-inflammatory stimuli (LPS, R848, IL-4 and dexamethasone). One genes of interest, P2RX7, belongs to a family of purinoceptors for ATP (location: 12q24.31), and is implicated as a potential treatment for schizophrenia via two antipsychotics drugs, prochlorperazine and trifluoperazine, which may inhibit human P2X7 receptor function [125]. P2X7 is significantly reduced in expression in schizophrenia [126], but no other measured changes in monocyte-derived macrophages were reported [111].

The decreased synapse density in post-mortem cortical tissue discussed in previous chapters in schizophrenia has been suggested to be a result of increased synapse elimination. Controlled study of this process using a reprogrammed in vitro model of microglia-mediated synapse engulfment demonstrates increased synapse elimination in patient-derived neural cultures and isolated synaptosomes. This excessive synaptic pruning reflects abnormalities in both microglia-like cells and synaptic structures. Additionally, schizophrenia risk-associated variants within the human complement component 4 locus are associated with increased neuronal complement deposition and synapse uptake. As useful as these findings are, they do not fully explain the observed increase in synapse uptake [127].

The density of cells expressing immune markers as well as expression of some pro-inflammatory cytokines is increased in post-mortem brain tissue in schizophrenia [128, 129]. Immunological pathways have repeatedly been implicated in schizophrenia. Single-nucleotide polymorphisms (SNPs) in immune genes have been linked with the illness [130, 131], and the prevalence of immune-related disorders is higher in patients and their family members [132]. As discussed in Chap. 3, immunological markers have been found to be altered in blood, cerebrospinal fluid and post-mortem brain tissue in schizophrenia [129, 133].

One recent study investigated possible association between SNPs and the expression levels of 190 serum proteins in 149 schizophrenia patients and 198 matched controls. The results suggested that the effect of these SNPs on the expression of the respective proteins varies with diagnosis with a total of 21 SNPs showing significant interactions for 19 proteins. This also demonstrated that in both schizophrenia and the control group there were seven SNPs and seven proteins statistically linked with the diagnosis (Factor-VII [rs555212], Alpha-1-Antitrypsin [rs11846959], Interferon-Gamma Induced Protein 10 [rs4256246] and von-Willebrand-Factor [rs12829220] in the control group; Chromogranin-A [rs9658644], Cystatin-C [rs2424577] and Vitamin K-Dependent Protein S[rs6123]), as well as two SNPs associated with two proteins in both the control and schizophrenia groups [134].

The interleukin-6 receptor (IL-6r) gene has been investigated extensively, with a reported significant association of rs2228145 C-allele with schizophrenia [135], and although the Ala allele of Asp358Ala was significantly associated with higher levels

of both IL-6 and sIL-6, whilst IL-6 levels were significantly elevated in schizophrenic patients, the specific association of rs2228145 was not replicated [136]. However, schizophrenia patients homozygous for this SNP allele had significantly higher levels of IL-6r protein compared to controls homozygous for the wild-type allele, suggesting a possibility of differential regulation of protein expression in schizophrenia patients based on allele copy number of rs7553796 [134].

Also studied in this area is Chromogranin-A (CgA), a protein widely expressed in secretory granules in the CNS which is co-released with several neurotransmitters, notably catecholamines. CgA acts as a neuromodulator via calcium binding and has a key role in the regulation of microglial activity, neurotoxicity mediated through the secretion of glutamate, TNFα and NO, inducing mitochondrial stress and apoptosis. CgA has been found decreased in the PFC cortical layer III–V in schizophrenia, and plasma CgA and derived peptides are now commonly used as diagnostic and prognostic markers or to monitor the response to pharmacotherapeutic intervention [137–142].

For some time there was hope that an immune-marker would allow a blood test for schizophrenia. The peripheral benzodiazepine receptor (PBR) was targeted by a probe known as PK11195 and was reported to have decreased platelet-binding in schizophrenia [143–146], as well as increased PBR levels associated with the degree of demyelination and temporal activation of glial cell types in different anatomical regions [147]. Despite some discussion over PBR playing a significant role in the pathogenesis of several neurodegenerative disorders, such as Alzheimer's disease, multiple sclerosis, Parkinson's disease and HIV-associated dementia, brain injury and neuroinflammation [148–150], follow-up studies have not validated this as an accurate predictor of schizophrenia diagnosis, and so this has largely been abandoned as a potential diagnostic route.

With greater understanding of the roles and biology of glial cells, it is gratifying to see the increasing focus on their role in neurodevelopment, normal brain function and illnesses such as schizophrenia. However, as a field we still have a way to go to integrate measures of glial morphology, density and clustering as part of routine studies, as well as the deficits in including neuropathology research alongside molecular, biochemical and imaging studies, where different approaches often yield results that complement one another and so yield increased biologically useful information generated from research.

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