Temporal Cortex

5

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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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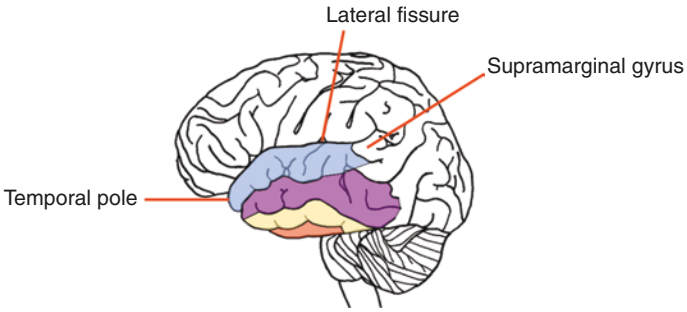

Fig. 5.1 The temporal lobe observed from the sagittal view. From this perspective, the dorsal-most structure is the superior temporal gyrus (blue), with the middle temporal gyrus (purple) and Inferior Temporal Gyrus (yellow) ventral to it. In some cases, the fusiform gyrus (orange), which runs along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

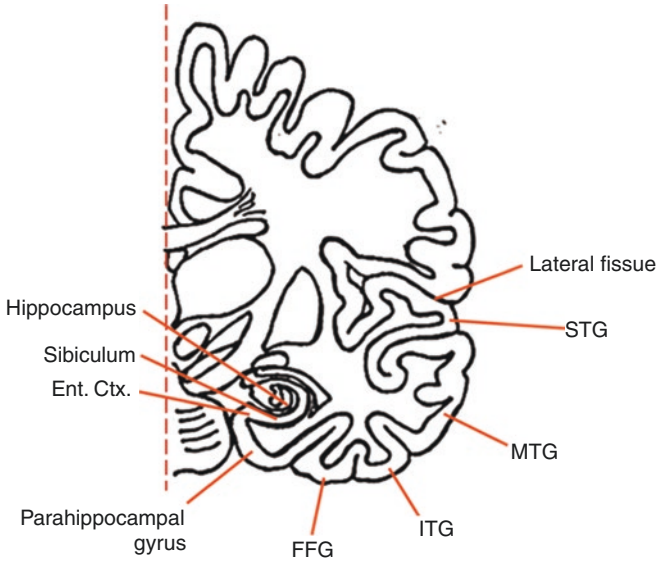

Fig. 5.2 A coronal cut through temporal lobe at the level of the hippocampus. *Ent. Ctx.* entorhinal cortex, *STG* superior temporal gyrus, *MTG* medial temporal gyrus, *ITG* inferior temporal gyrus, *FFG* fusiform gyrus. The lateral fissure is also known as the Sylvian fissure

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

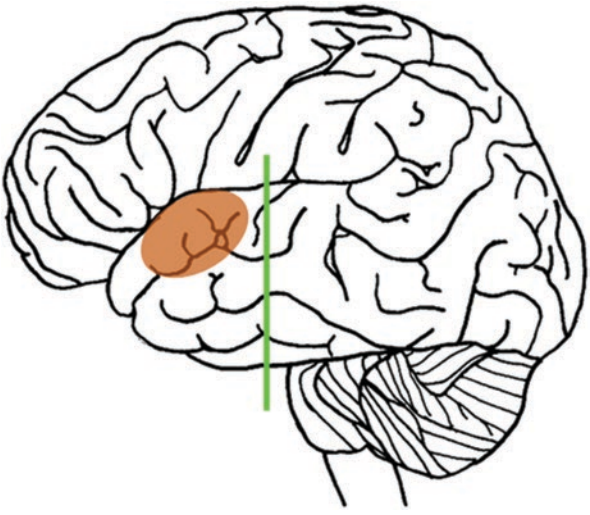

Fig. 5.3 Sagittal view illustrating a possible explanation for a lack of observed neuropathological cortical layer shrinkage in the temporal lobe in schizophrenia. The brown region roughly describes the reported areas of grey matter loss according to the structural imaging studies, whilst the green line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

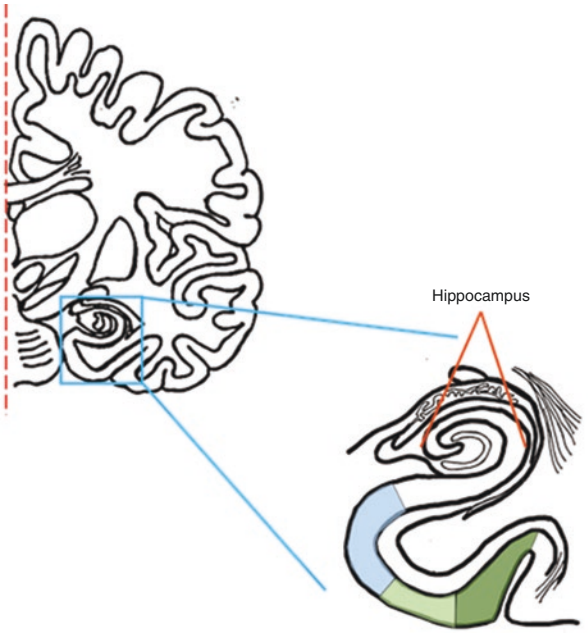

Fig. 5.4 The anatomical subdivisions of the parahippocampal gyrus and entorhinal cortex seen in coronal section. The parahippocampal gyrus is split into three main divisions. Green represents an area referred to as the parahippocampal cortex, often subdivided into medial (dark green) and lateral (pale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

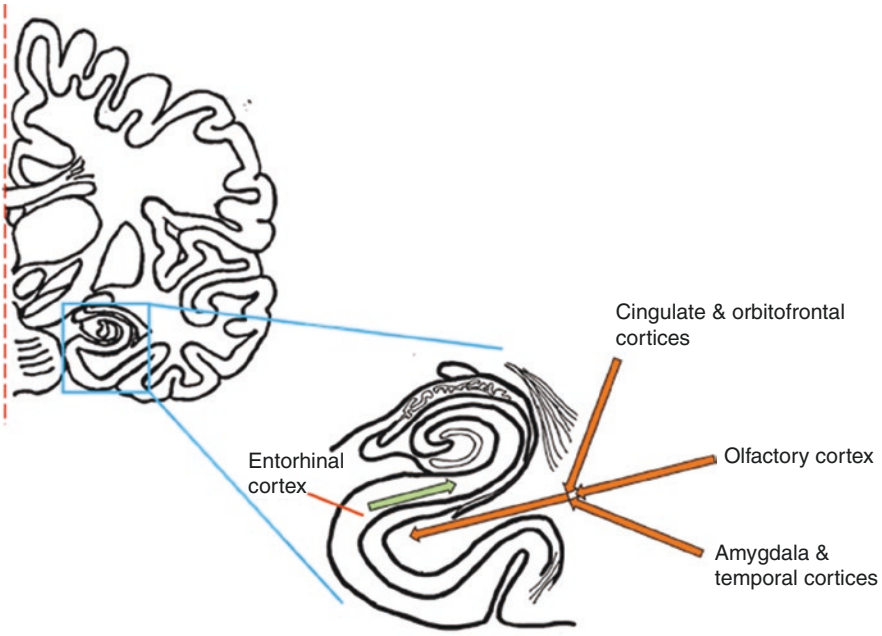

Fig. 5.5 The location and primary connections of the entorhinal cortex seen in coronal section. The inputs (orange) and hippocampal output (green) are shown. Dotted red line shows the midline of the brain

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.

References

1. Van Hoesen GW. Anatomy of the medial temporal lobe. Magn Reson Imaging. 1995;13(8):1047–55.
2. Muñoz-López M, Insausti R, Mohedano-Moriano A, Mishkin M, Saunders RC. Anatomical pathways for auditory memory II: information from rostral superior temporal gyrus to dorsolateral temporal pole and medial temporal cortex. Front Neurosci. 2015;9:158.
3. Patel A, Biso G, Fowler J. Temporal lobe neuroanatomy. Treasure Island, FL: StatPearls Publishing; 2020.
4. Streitfeld BD. The fiber connections of the temporal lobe with emphasis on the rhesus monkey. Int J Neurosci. 1980;11(1):51–71.
5. Herzog AG, Van Hoesen GW. Temporal neocortical afferent connections to the amygdala in the rhesus monkey. Brain Res. 1976;115(1):57–69.
6. Kravitz DJ, Saleem KS, Baker CI, Ungerleider LG, Mishkin M. The ventral visual pathway: an expanded neural framework for the processing of object quality. Trends Cogn Sci. 2013;17(1):26–49.
7. Mohedano-Moriano A, Pro-Sistiaga P, Arroyo-Jimenez MM, Artacho-Pérula E, Insausti AM, Marcos P, Cebada-Sánchez S, Martínez-Ruiz J, Muñoz M, Blaizot X, Martinez-Marcos A, Amaral DG, Insausti R. Topographical and laminar distribution of cortical input to the monkey entorhinal cortex. J Anat. 2007;211(2):250–60.
8. Suzuki WA, Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. J Comp Neurol. 1994a;350(4):497–533.
9. Suzuki WA, Amaral DG. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. J Neurosci. 1994b;14(3 Pt 2):1856–77.
10. Amaral DG, Insausti R, Cowan WM. Evidence for a direct projection from the superior temporal gyrus to the entorhinal cortex in the monkey. Brain Res. 1983;275(2):263–77.
11. Markowitsch HJ, Emmans D, Irle E, Streicher M, Preilowski B. Cortical and subcortical afferent connections of the primate's temporal pole: a study of rhesus monkeys, squirrel monkeys, and marmosets. J Comp Neurol. 1985;242(3):425–58.

12. Qin S, Duan X, Supekar K, Chen H, Chen T, Menon V. Large-scale intrinsic functional network organization along the long axis of the human medial temporal lobe. Brain Struct Funct. 2016;221(6):3237–58.
13. Palejwala AH, O'Connor KP, Milton CK, Anderson C, Pelargos P, Briggs RG, Conner AK, O'Donoghue DL, Glenn CA, Sughrue ME. Anatomy and white matter connections of the fusiform gyrus. Sci Rep. 2020;10(1):13489.
14. Casanova MF. The temporolimbic system theory of paranoid schizophrenia. Schizophr Bull. 1997;23(3):513–5.
15. Ebert A, Bär KJ. Emil Kraepelin: a pioneer of scientific understanding of psychiatry and psychopharmacology. Indian J Psychiatry. 2010;52(2):191–2.
16. Kendler KS, Jablensky A. Kraepelin's concept of psychiatric illness. Psychol Med. 2011;41(6):1119–26.
17. Kraepelin E. Dementia praecox and paraphrenia. Edinburgh: Livingstone; 1919.
18. Chance SA, Esiri MM, Crow TJ. Ventricular enlargement in schizophrenia: a primary change in the temporal lobe? Schizophr Res. 2003;62(1–2):123–31.
19. Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain. 1999;122(Pt 4):593–624.
20. Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry. 1998;172:110–20.
21. Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry. 1998;55(5):433–40.
22. Zipursky RB, Lambe EK, Kapur S, Mikulis DJ. Cerebral gray matter volume deficits in first episode psychosis. Arch Gen Psychiatry. 1998;55(6):540–6.
23. Takayanagi Y, Sasabayashi D, Takahashi T, Furuichi A, Kido M, Nishikawa Y, Nakamura M, Noguchi K, Suzuki M. Reduced cortical thickness in schizophrenia and schizotypal disorder. Schizophr Bull. 2020;46(2):387–94.
24. Widmayer S, Sowislo JF, Jungfer HA, Borgwardt S, Lang UE, Stieglitz RD, Huber CG. Structural magnetic resonance imaging correlates of aggression in psychosis: a systematic review and effect size analysis. Front Psych. 2018;9:217.
25. Raucher-Chéné D, Lavigne KM, Makowski C, Lepage M. Altered surface area covariance in the mentalizing network in schizophrenia: insight into theory of mind processing. Biol Psychiatry Cogn Neurosci Neuroimaging. 2020; https://doi.org/10.1016/j.bpsc.2020.06.020.
26. Williams MR, Chaudhry R, Perera S, Pearce RK, Hirsch SR, Ansorge O, Thom M, Maier M. Changes in cortical thickness in the frontal lobes in schizophrenia are a result of thinning of pyramidal cell layers. Eur Arch Psychiatry Clin Neurosci. 2013;263(1):25–39.
27. Pakkenberg B. Total nerve cell number in neocortex in chronic schizophrenics and controls estimated using optical disectors. Biol Psychiatry. 1993;34(11):768–72.
28. Turetsky B, Cowell PE, Gur RC, Grossman RI, Shtasel DL, Gur RE. Frontal and temporal lobe brain volumes in schizophrenia. Relationship to symptoms and clinical subtype. Arch Gen Psychiatry. 1995;52(12):1061–70.
29. Falkai P, Bogerts B, Greve B, Pfeiffer U, Machus B, Fölsch-Reetz B, Majtenyi C, Ovary I. Loss of sylvian fissure asymmetry in schizophrenia. A quantitative post mortem study. Schizophr Res. 1992;7(1):23–32.
30. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res. 2001;49(1–2):1–52.
31. Flaum M, O'Leary DS, Swayze VW 2nd, Miller DD, Arndt S, Andreasen NC. Symptom dimensions and brain morphology in schizophrenia and related psychotic disorders. J Psychiatr Res. 1995;29(4):261–76.
32. Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. Am J Psychiatry. 1990;147(11):1457–62.
33. Levitan C, Ward PB, Catts SV. Superior temporal gyral volumes and laterality correlates of auditory hallucinations in schizophrenia. Biol Psychiatry. 1999;46(7):955–62.

34. Marsh L, Harris D, Lim KO, Beal M, Hoff AL, Minn K, Csernansky JG, DeMent S, Faustman WO, Sullivan EV, Pfefferbaum A. Structural magnetic resonance imaging abnormalities in men with severe chronic schizophrenia and an early age at clinical onset. Arch Gen Psychiatry. 1997;54(12):1104–12.
35. Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N Engl J Med. 1992;327(9):604–12.
36. Ohi K, Matsuda Y, Shimada T, Yasuyama T, Oshima K, Sawai K, Kihara H, Nitta Y, Okubo H, Uehara T, Kawasaki Y. Structural alterations of the superior temporal gyrus in schizophrenia: detailed subregional differences. Eur Psychiatry. 2016;35:25–31.
37. Taylor JL, Blanton RE, Levitt JG, Caplan R, Nobel D, Toga AW. Superior temporal gyrus differences in childhood-onset schizophrenia. Schizophr Res. 2005;73(2–3):235–41.
38. Matsumoto H, Simmons A, Williams S, Hadjulis M, Pipe R, Murray R, Frangou S. Superior temporal gyrus abnormalities in early-onset schizophrenia: similarities and differences with adult-onset schizophrenia. Am J Psychiatry. 2001;158(8):1299–304.
39. Gaser C, Nenadic I, Volz HP, Büchel C, Sauer H. Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. Cereb Cortex. 2004;14(1):91–6.
40. Kim GW, Kim YH, Jeong GW. Whole brain volume changes and its correlation with clinical symptom severity in patients with schizophrenia: a DARTEL-based VBM study. PLoS One. 2017;12(5):e0177251.
41. Garey LJ, Von Bussmann KA, Hirsch SR. Decreased numerical density of kainate receptor-positive neurons in the orbitofrontal cortex of chronic schizophrenics. Exp Brain Res. 2006;173(2):234–42.
42. Radewicz K, Garey LJ, Gentleman SM, Reynolds R. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. J Neuropathol Exp Neurol. 2000;59(2):137–50.
43. Rajarethinam RP, DeQuardo JR, Nalepa R, Tandon R. Superior temporal gyrus in schizophrenia: a volumetric magnetic resonance imaging study. Schizophr Res. 2000;41(2):303–12.
44. Lee CU, Shenton ME, Salisbury DF, Kasai K, Onitsuka T, Dickey CC, Yurgelun-Todd D, Kikinis R, Jolesz FA, McCarley RW. Fusiform gyrus volume reduction in first-episode schizophrenia: a magnetic resonance imaging study. Arch Gen Psychiatry. 2002;59(9):775–81.
45. Takahashi T, Wood SJ, Yung AR, Soulsby B, McGorry PD, Suzuki M, Kawasaki Y, Phillips LJ, Velakoulis D, Pantelis C. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch Gen Psychiatry. 2009;66(4):366–76.
46. Eastwood SL, Harrison PJ. Hippocampal and cortical growth-associated protein-43 messenger RNA in schizophrenia. Neuroscience. 1998;86(2):437–48.
47. Steiner J, Brisch R, Schiltz K, Dobrowolny H, Mawrin C, Krzyżanowska M, Bernstein HG, Jankowski Z, Braun K, Schmitt A, Bogerts B, Gos T. GABAergic system impairment in the hippocampus and superior temporal gyrus of patients with paranoid schizophrenia: a post-mortem study. Schizophr Res. 2016;177(1–3):10–7.
48. Highley JR, McDonald B, Walker MA, Esiri MM, Crow TJ. Schizophrenia and temporal lobe asymmetry. A post-mortem stereological study of tissue volume. Br J Psychiatry. 1999;175:127–34.
49. Onitsuka T, Shenton ME, Salisbury DF, Dickey CC, Kasai K, Toner SK, Frumin M, Kikinis R, Jolesz FA, McCarley RW. Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. Am J Psychiatry. 2004;161(9):1603–11.
50. Guo W, Hu M, Fan X, Liu F, Wu R, Chen J, Guo X, Xiao C, Quan M, Chen H, Zhai J, Zhao J. Decreased gray matter volume in the left middle temporal gyrus as a candidate biomarker for schizophrenia: a study of drug naive, first-episode schizophrenia patients and unaffected siblings. Schizophr Res. 2014;159(1):43–50.
51. Hu M, Li J, Eyler L, Guo X, Wei Q, Tang J, Liu F, He Z, Li L, Jin H, Liu Z, Wang J, Chen H, Zhao J. Decreased left middle temporal gyrus volume in antipsychotic drug-naive,

first-episode schizophrenia patients and their healthy unaffected siblings. Schizophr Res. 2013;144(1–3):37–42.
52. Akbarian S, Viñuela A, Kim JJ, Potkin SG, Bunney WE Jr, Jones EG. Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. Arch Gen Psychiatry. 1993;50(3):178–87.
53. Thompson PM, Sower AC, Perrone-Bizzozero NI. Altered levels of the synaptosomal associated protein SNAP-25 in schizophrenia. Biol Psychiatry. 1998;43(4):239–43.
54. Mizukami K, Ishikawa M, Hidaka S, Iwakiri M, Sasaki M, Iritani S. Immunohistochemical localization of GABAB receptor in the entorhinal cortex and inferior temporal cortex of schizophrenic brain. Prog Neuro-Psychopharmacol Biol Psychiatry. 2002;26(2):393–6.
55. McDonald B, Highley JR, Walker MA, Herron BM, Cooper SJ, Esiri MM, Crow TJ. Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: a postmortem study. Am J Psychiatry. 2000;157(1):40–7.
56. Zhang W, Wang J, Fan L, Zhang Y, Fox PT, Eickhoff SB, Yu C, Jiang T. Functional organization of the fusiform gyrus revealed with connectivity profiles. Hum Brain Mapp. 2016;37(8):3003–16.
57. Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Carson RE, Herscovitch P, Schapiro MB, Rapoport SI. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. Proc Natl Acad Sci U S A. 1991;88(5):1621–5.
58. Sergent J, Ohta S, MacDonald B. Functional neuroanatomy of face and object processing. A positron emission tomography study. Brain. 1992;115(Pt 1):15–36.
59. Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci. 1997;17(11):4302–11.
60. McCarthy G, Luby M, Gore J, Goldman-Rakic P. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. J Neurophysiol. 1997;77(3):1630–4.
61. Puce A, Allison T, Asgari M, Gore JC, McCarthy G. Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. J Neurosci. 1996;16(16):5205–15.
62. Kanwisher N, Tong F, Nakayama K. The effect of face inversion on the human fusiform face area. Cognition. 1998;68(1):B1–11.
63. Spiridon M, Kanwisher N. How distributed is visual category information in human occipitotemporal cortex? An fMRI study. Neuron. 2002;35(6):1157–65.
64. Tong F, Nakayama K, Moscovitch M, Weinrib O, Kanwisher N. Response properties of the human fusiform face area. Cogn Neuropsychol. 2000;17(1):257–80.
65. Andrews TJ, Schluppeck D, Homfray D, Matthews P, Blakemore C. Activity in the fusiform gyrus predicts conscious perception of Rubin's vase-face illusion. NeuroImage. 2002;17(2):890–901.
66. Hasson U, Hendler T, Ben Bashat D, Malach R. Vase or face? A neural correlate of shape-selective grouping processes in the human brain. J Cogn Neurosci. 2001;13(6):744–53.
67. Tsao DY, Livingstone MS. Mechanisms of face perception. Annu Rev Neurosci. 2008;31:411–37.
68. Addington J, Addington D. Facial affect recognition and information processing in schizophrenia and bipolar disorder. Schizophr Res. 1998;32(3):171–81.
69. Amminger GP, Schäfer MR, Klier CM, Schlögelhofer M, Mossaheb N, Thompson A, Bechdolf A, Allott K, McGorry PD, Nelson B. Facial and vocal affect perception in people at ultra-high risk of psychosis, first-episode schizophrenia and healthy controls. Early Interv Psychiatry. 2012;6(4):450–4.
70. Edwards J, Pattison PE, Jackson HJ, Wales RJ. Facial affect and affective prosody recognition in first-episode schizophrenia. Schizophr Res. 2001;48(2–3):235–53.
71. Gabrovska VS, Laws KR, Sinclair J, McKenna PJ. Visual object processing in schizophrenia: evidence for an associative agnosic deficit. Schizophr Res. 2003;59(2–3):277–86.

72. Gruzelier JH, Wilson L, Liddiard D, Peters E, Pusavat L. Cognitive asymmetry patterns in schizophrenia: active and withdrawn syndromes and sex differences as moderators. Schizophr Bull. 1999;25(2):349–62.
73. Gur RE, McGrath C, Chan RM, Schroeder L, Turner T, Turetsky BI, Kohler C, Alsop D, Maldjian J, Ragland JD, Gur RC. An fMRI study of facial emotion processing in patients with schizophrenia. Am J Psychiatry. 2002;159(12):1992–9.
74. Habel U, Gur RC, Mandal MK, Salloum JB, Gur RE, Schneider F. Emotional processing in schizophrenia across cultures: standardized measures of discrimination and experience. Schizophr Res. 2000;42(1):57–66.
75. Herniman SE, Allott KA, Killackey E, Hester R, Cotton SM. The effect of comorbid depression on facial and prosody emotion recognition in first-episode schizophrenia spectrum. J Affect Disord. 2017;208:223–9.
76. Johnston PJ, Stojanov W, Devir H, Schall U. Functional MRI of facial emotion recognition deficits in schizophrenia and their electrophysiological correlates. Eur J Neurosci. 2005;22(5):1221–32.
77. Kohler CG, Bilker W, Hagendoorn M, Gur RE, Gur RC. Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. Biol Psychiatry. 2000;48(2):127–36.
78. Penn DL, Combs D. Modification of affect perception deficits in schizophrenia. Schizophr Res. 2000;46(2–3):217–29.
79. Phillips ML, David AS. Facial processing in schizophrenia and delusional misidentification: cognitive neuropsychiatric approaches. Schizophr Res. 1995;17(1):109–14.
80. Shasteen JR, Pinkham AE, Kelsven S, Ludwig K, Payne BK, Penn DL. Intact implicit processing of facial threat cues in schizophrenia. Schizophr Res. 2016;170(1):150–5.
81. Whittaker JF, Deakin JF, Tomenson B. Face processing in schizophrenia: defining the deficit. Psychol Med. 2001;31(3):499–507.
82. Wölwer W, Streit M, Polzer U, Gaebel W. Facial affect recognition in the course of schizophrenia. Eur Arch Psychiatry Clin Neurosci. 1996;246(3):165–70.
83. Onitsuka T, Niznikiewicz MA, Spencer KM, Frumin M, Kuroki N, Lucia LC, Shenton ME, McCarley RW. Functional and structural deficits in brain regions subserving face perception in schizophrenia. Am J Psychiatry. 2006;163(3):455–62.
84. Onitsuka T, Shenton ME, Kasai K, Nestor PG, Toner SK, Kikinis R, Jolesz FA, McCarley RW. Fusiform gyrus volume reduction and facial recognition in chronic schizophrenia. Arch Gen Psychiatry. 2003;60(4):349–55.
85. Yan J, Cui Y, Li Q, Tian L, Liu B, Jiang T, Zhang D, Yan H. Cortical thinning and flattening in schizophrenia and their unaffected parents. Neuropsychiatr Dis Treat. 2019;15:935–46.
86. Yasuda Y, Okada N, Nemoto K, Fukunaga M, Yamamori H, Ohi K, Koshiyama D, Kudo N, Shiino T, Morita S, Morita K, Azechi H, Fujimoto M, Miura K, Watanabe Y, Kasai K, Hashimoto R. Brain morphological and functional features in cognitive subgroups of schizophrenia. Psychiatry Clin Neurosci. 2020;74(3):191–203.
87. Tanaka K. Inferotemporal cortex and object vision. Annu Rev Neurosci. 1996;19:109–39.
88. Di Rosa E, Crow TJ, Walker MA, Black G, Chance SA. Reduced neuron density, enlarged minicolumn spacing and altered ageing effects in fusiform cortex in schizophrenia. Psychiatry Res. 2009;166(2–3):102–15.
89. Drevets WC, Price JL, Simpson JR, Todd RD, Reich T, Vannier M, Raichle ME. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997;386(6627):824–7.
90. Ongür D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci U S A. 1998;95(22):13290–5.
91. Rosoklija G, Toomayan G, Ellis SP, Keilp J, Mann JJ, Latov N, Hays AP, Dwork AJ. Structural abnormalities of subicular dendrites in subjects with schizophrenia and mood disorders: preliminary findings. Arch Gen Psychiatry. 2000;57(4):349–56.
92. Sweet RA, Bergen SE, Sun Z, Marcsisin MJ, Sampson AR, Lewis DA. Anatomical evidence of impaired feedforward auditory processing in schizophrenia. Biol Psychiatry. 2007;61(7):854–64.

93. Kivisaari S, Probst A, Taylor K. fMRI – basics and clinical applications. The perirhinal, entorhinal, and parahippocampal cortices and hippocampus: an overview of functional anatomy and protocol for their segmentation in MR images. Berlin: Springer-Verlag; 2013.
94. Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. J Neural Transm. 1986;65(3–4):303–26.
95. Jakob H, Beckmann H. Circumscribed malformation and nerve cell alterations in the entorhinal cortex of schizophrenics. Pathogenetic and clinical aspects. J Neural Transm Gen Sect. 1994;98(2):83–106.
96. Akil M, Lewis DA. Cytoarchitecture of the entorhinal cortex in schizophrenia. Am J Psychiatry. 1997;154(7):1010–2.
97. Bernstein HG, Krell D, Baumann B, Danos P, Falkai P, Diekmann S, Henning H, Bogerts B. Morphometric studies of the entorhinal cortex in neuropsychiatric patients and controls: clusters of heterotopically displaced lamina II neurons are not indicative of schizophrenia. Schizophr Res. 1998;33(3):125–32.
98. Arnold SE, Ruscheinsky DD, Han LY. Further evidence of abnormal cytoarchitecture of the entorhinal cortex in schizophrenia using spatial point pattern analyses. Biol Psychiatry. 1997;42(8):639–47.
99. Arnold SE, Lee VM, Gur RE, Trojanowski JQ. Abnormal expression of two microtubule-associated proteins (MAP2 and MAP5) in specific subfields of the hippocampal formation in schizophrenia. Proc Natl Acad Sci U S A. 1991;88(23):10850–4.
100. Schultz CC, Koch K, Wagner G, Roebel M, Nenadic I, Schachtzabel C, Reichenbach JR, Sauer H, Schlösser RG. Complex pattern of cortical thinning in schizophrenia: results from an automated surface based analysis of cortical thickness. Psychiatry Res. 2010a;182(2):134–40.
101. Schultz CC, Koch K, Wagner G, Roebel M, Schachtzabel C, Nenadic I, Albrecht C, Reichenbach JR, Sauer H, Schlösser RG. Psychopathological correlates of the entorhinal cortical shape in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2010b;260(4):351–8.
102. Heinsen H, Gössmann E, Rüb U, Eisenmenger W, Bauer M, Ulmar G, Bethke B, Schüler M, Schmitt HP, Götz M, Lockemann U, Püschel K. Variability in the human entorhinal region may confound neuropsychiatric diagnoses. Acta Anat (Basel). 1996;157(3):226–37.
103. Krimer LS, Herman MM, Saunders RC, Boyd JC, Hyde TM, Carter JM, Kleinman JE, Weinberger DR. A qualitative and quantitative analysis of the entorhinal cortex in schizophrenia. Cereb Cortex. 1997a;7(8):732–9.
104. Krimer LS, Hyde TM, Herman MM, Saunders RC. The entorhinal cortex: an examination of cyto- and myeloarchitectonic organization in humans. Cereb Cortex. 1997b;7(8):722–31.
105. Akil M, Edgar CL, Pierri JN, Casali S, Lewis DA. Decreased density of tyrosine hydroxylase-immunoreactive axons in the entorhinal cortex of schizophrenic subjects. Biol Psychiatry. 2000;47(5):361–70.
106. Daubner SC, Le T, Wang S. Tyrosine hydroxylase and regulation of dopamine synthesis. Arch Biochem Biophys. 2011;508(1):1–12.
107. Howes OD, Williams M, Ibrahim K, Leung G, Egerton A, McGuire PK, Turkheimer F. Midbrain dopamine function in schizophrenia and depression: a post-mortem and positron emission tomographic imaging study. Brain. 2013;136(Pt 11):3242–51.
108. Kaushik P, Gorin F, Vali S. Dynamics of tyrosine hydroxylase mediated regulation of dopamine synthesis. J Comput Neurosci. 2007;22(2):147–60.
109. Williams MR, Galvin K, O'Sullivan B, MacDonald CD, Ching EW, Turkheimer F, Howes OD, Pearce RK, Hirsch SR, Maier M. Neuropathological changes in the substantia nigra in schizophrenia but not depression. Eur Arch Psychiatry Clin Neurosci. 2014;264(4):285–96.
110. Powell HW, Guye M, Parker GJ, Symms MR, Boulby P, Koepp MJ, Barker GJ, Duncan JS. Noninvasive in vivo demonstration of the connections of the human parahippocampal gyrus. NeuroImage. 2004;22(2):740–7.
111. Altshuler LL, Casanova MF, Goldberg TE, Kleinman JE. The hippocampus and parahippocampus in schizophrenia, suicide, and control brains. Arch Gen Psychiatry. 1990;47(11):1029–34.

112. Bogerts B, Meertz E, Schönfeldt-Bausch R. Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage. Arch Gen Psychiatry. 1985;42(8):784–91.
113. Brown R, Colter N, Corsellis JA, Crow TJ, Frith CD, Jagoe R, Johnstone EC, Marsh L. Postmortem evidence of structural brain changes in schizophrenia. Differences in brain weight, temporal horn area, and parahippocampal gyrus compared with affective disorder. Arch Gen Psychiatry. 1986;43(1):36–42.
114. Colter N, Battal S, Crow TJ, Johnstone EC, Brown R, Bruton C. White matter reduction in the parahippocampal gyrus of patients with schizophrenia. Arch Gen Psychiatry. 1987;44(11):1023.
115. Falkai P, Bogerts B, Rozumek M. Limbic pathology in schizophrenia: the entorhinal region—a morphometric study. Biol Psychiatry. 1988;24(5):515–21.
116. Jeste DV, Lohr JB. Hippocampal pathologic findings in schizophrenia. A morphometric study. Arch Gen Psychiatry. 1989;46(11):1019–24.