The Papez circuit in schizophrenia 1: Neuropathological changes

DR. MATTHEW WILLIAMS[1]

[1]Visiting Research Associate, Department of Medicine, Imperial College London, Hammersmith Hospital, W12 0NN, UK.
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Abstract

The Papez circuit was first described in 1937 as a potential enclosed system within the brain for emotional regulation. Since then the emotional role of the circuit has not received good support from laboratory investigation, the circuits roles in memory has become clear. As the clinical presentation of schizophrenia often includes symptoms related to the relevant functional roles of the constituent structures and also various memory problems this first paper reviews the neuropathological evidence for change in the constituent neurological structures of the Papez circuit, with additional information from modern imaging sciences.

KEYWORDS: PAPEZ, THALAMUS, HIPPOCAMPUS, CINGULATE, MAMILLARY, SCHIZOPHRENIA

Corresponding author: Matthew Williams - matthew.r.williams@imperial.ac.uk

The Papez Circuit

The Papez circuit is one of the first larger-scale brain circuits that students of neuroscience learn. It was first proposed by James Papez in 1937 in a landmark paper entitled, "A proposed mechanism of emotion" in the journal Archives of Neurology and Psychiatry (Papez 1937, Papez 1995). He wrote,

"The central emotive process of cortical origin may be conceived of as being built up in the hippocampal formation and as being transmitted to the mammillary body and then to the tract of Vicq d' Azir (mammillothalamic tract) and thence through the anterior thalamic nuclei to the cortex of the gyrus cinguli… Radiation of the emotive process from the gyrus cinguli to other regions in the cerebral cortex would add emotional colouring to psychic processes occurring elsewhere… It is evident that the proposed mechanism of emotion will have to stand the test of experiment and clinical experience if it is to be useful in science… The hypothalamus, the anterior thalamic nucleus, the cingulate gyrus, the hippocampus and their interconnections, constitute a harmonious mechanism which may elaborate the functions of central emotion as well as participate in the emotional expression."

From Papez (1937).

Whilst Papez was the first to describe this circuit in detail, it was built in turn on the earlier suggestion of Christfried Jakob who suggested the existence of a visceral brain that related in emotional systems in a brain-within-a-brain model (reviewed in Triarhou 2008). Papez believed that the circuit he described in 1937 was involved with emotion, writing,

"The cingulate cortex projects to the hippocampus, and

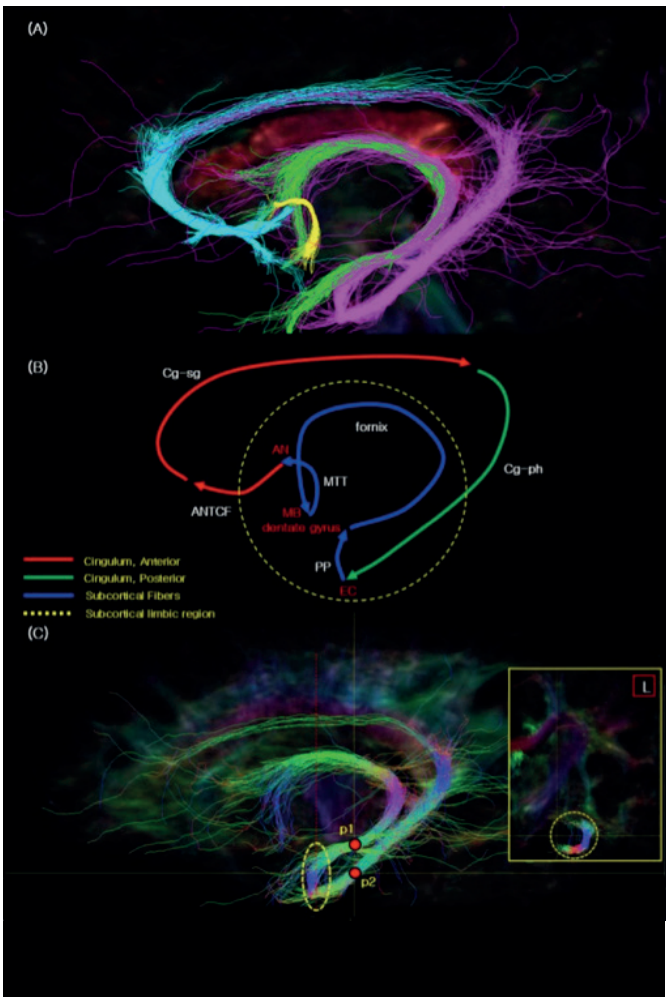

Figure 1. The seed tracking result of the complete Papez circuit. A The resulted fibre tracks of the Papez circuit showing the cyan: ANTCF, Cg-sg; magenta: Cg-ph, PP area, fornix; green: fornix; yellow: mammillothalamic tract (MTT). B The resulted flow lines of the Papez circuit showing the red: ANTCF, Cg-sg; green: Cg-ph; blue: PP area, fornix, and MTT. The names of nerve fibre in the image are indicated with the white colour, and other landmarks were red. C The seed tracking result of the PP in the EC area with the directional colour. This main sagittal image presents the two seed points (p1 and p2) with red points, and yellow dot circle which indicate the connectivity areas with the PP. Red dot line in the sagittal image indicate the coronal section line of the small yellow box in the right side. The coronal section image in the right shows the seed tracking results which illustrate the connectivity in the EC. EC - entorhinal cortex; MB, mammillary body, PP - perforant path (Choi, Kim et al. 2019).

the hippocampus projects to the hypothalamus by way of the bundle of axons called the fornix. Hypothalamic effects reach the cortex via a relay in the anterior thalamic nuclei."

Although this has been somewhat abandoned now, the circuit is strongly implicated in spatial and episodic memory and is still studied in some detail today for these reasons (Shibata 1992, Aggleton and Brown 1999, Vertes, Albo et al. 2001, Nishio, Hashimoto et al. 2011). A more detailed history of this circuit can be found in Bhattacharyya's excellent review (Bhattacharyya 2017).

Recent imaging studies have built upon the history of investigation to reveal a functional model of the circuit *in vivo* (Choi, Kim et al. 2019).

The classic Papez circuit is now known to have a crucial role in spatial memory, memory retrieval and verbal memory functions that are affected in schizophrenia (Baumann, Griffa et al. 2016). To examine the potential role and alterations of the Papez circuit in schizophrenia we must first examine reported changes from post-mortem and imaging studies in the structures that make up the circuit.

Cingulate Gyrus

The cingulate is largest region of the Papez circuit and has considerable neuroanatomical and functional variation across its regions. There has been considerable discussion and examination over the organisation of the cingulate sub-divisions, particularly Vogt's papers (Vogt, Pandya et al. 1987, Bogerts 1988, Vogt, Absher et al. 2000, Vogt, Berger et al. 2003, Vogt, Hof et al. 2004, Vogt 2005, Vogt, Vogt et al. 2005, Vogt, Vogt et al. 2006, Palomero-Gallagher, Mohlberg et al. 2008, Palomero-Gallagher, Zilles et al. 2013, Bzdok, Heeger et al. 2015, Vogt 2016), but it seems to be agreed upon that the target of the projections into the cingulate cortex terminate towards the caudal end rather than the rostral, although there is still some disagreement on whether this in the posterior cingulate cortex or the retrosplenial cortex. Figure 1 illustrates that the Papez circuit projects through much of the structure, looping through the subgenual region before following the anterior cingulate cortex to the posteriors and retrosplenial regions. Figure 2 summarises the standard modern arrangement of cingulate cortical regions implicated in the Papez circuit.

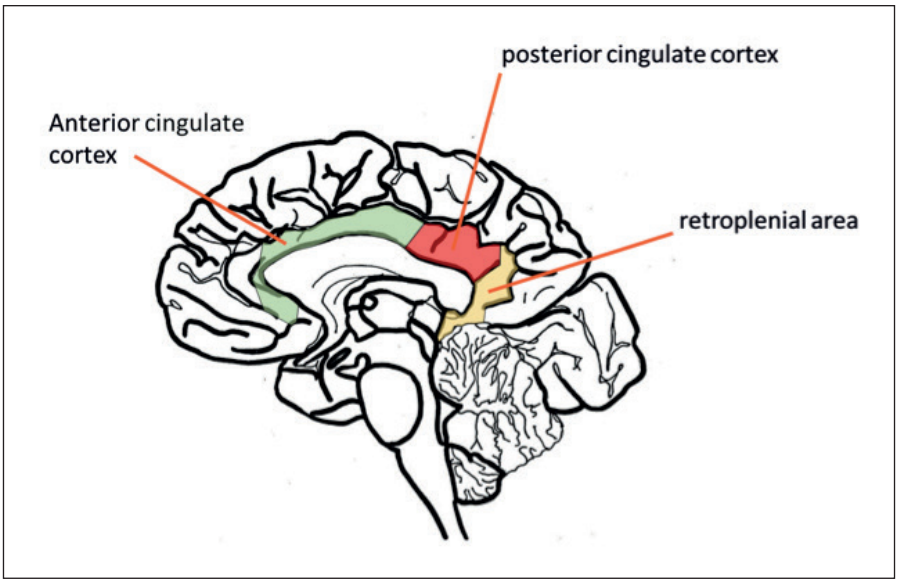

Figure 2. Main areas of the cingulate cortex shown in sagittal section. The green area is the anterior cingulate cortex (Brodmann areas 24 & 33), the red area shows the posterior ventral cingulate cortex (Brodmann areas 23 & 31) and the yellow area is the retrosplenial region (Brodmann areas 26, 29 & 30).

As the cingulate cortex has received neuropathological attention in schizophrenia it is unsurprising that there has been considerable heterogeneity of results. Whilst some studies have suggested there is no change in ACC pyramidal or interneuron density in schizophrenia (Benes, McSparren et al. 1991),(Cotter, Mackay et al. 2001), 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 report decreased neurons in schizophrenia (Benes, Davidson et al. 1986), and broader study of the ACC cortical thickness reported decreased neuron density across layer II-VI (Chana, Landau et al. 2003). Layer II of the ACC has shown specific changes in schizophrenia, with decreased neurons reported from direct stereological examination and confirmed by meta-analysis (Benes and Bird 1987, Todtenkopf, Vincent et al. 2005), and a possible 25% drop in GABA-neurons in the ACC layer II in schizophrenia (Cotter, Landau et al. 2002). 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 cell type (Benes and Bird 1987), (Benes, McSparren et al. 1991, Ongür, Drevets et al. 1998). Similarly, examination in neuron size has revealed contradictory findings with both no neuron size change (Benes, Davidson et al. 1986, Cotter, Mackay et al. 2001) and decreased neuron size in pyramidal Layers III & V in schizophrenia (Chana, Landau et al. 2003). TH-immunoractive neurons are not changed in number or density in schizophrenia (Benes, Todtenkopf et al. 1997).

Examination of parvalbumin-immuno-reactive neuronal soma showed an increase in density in layer V of the ACC, consistent with the reported shrinkage of this region in schizophrenia (Kalus, Senitz et al. 1997, Williams, Chaudhry et al. 2013). 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 decreased density decreased by 73% in layer II and 52% in layer V density in schizophrenia. (Woo, Walsh et al. 2004). Whilst the density of von Economo neurons (VEN), large bipolar projection neurons, in layer V of the ACC was not changed in schizo-phrenia the VEN density in the right ACC correlated with the age of 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 (Brune, Schobel et al. 2010, Krause, Theiss et al. 2017).

In situ hybridization studies have shown GAP43 and GAD67 mRNA-containing neurons that co-expressed GluR5 mRNA was 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 (Woo, Shrestha et al. 2007, Eastwood and Harrison 1998).

Several studies have reported no overall changes in glial cells in the ACC in schizophrenia (Ongur, Drevets et al. 1998, Hoistad, Heinsen et al. 2013), although examination of the ACC cortical grey matter using Cavalieri's method did find a 33% decrease in total glia in schizophrenia (Stark, Uylings et al. 2004). 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 (Cotter, Mackay et al. 2001). 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 (Cotter, Mackay et al. 2001, Chana, Landau et al. 2003). Also higher glial densities in layers V-VI than in layers II-III in both controls and patients with schizophrenia have been shown (Hoistad, Heinsen et al. 2013). 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 (Drevets, Price et al. 1997, Ongür, Drevets et al. 1998).

Studies examining specific glial cell types rather than total glia have produced more revealing findings. Reduced ADAM12-reactive oligodendrocytes in ACC white matter in schizophrenia (Steiner, Bernstein et al. 2008, Farkas, Lendeckel et al. 2010). No change in cingulate grey or white matter oligodendrocyte number, density or clustering as identified using histology staining (Williams, Hampton et al. 2013, Williams, Pearce et al. 2014, Segal, Schmitz et al. 2009, Mosebach, Keilhoff et al. 2013). 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 (Radewicz, Garey et al. 2000, Steiner, Mawrin et al. 2006).

GFAP-labeled 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 clustering in schizophrenia (Hercher, Chopra et al. 2014, Williams, Pearce et al. 2014), with further experiments suggesting the astrocyte decrease is made up primarily due to a loss of fibrillary astrocytes, similar to observations made in the nucleus basalis (Williams, Hampton et al. 2013, Williams, Pearce et al. 2014). 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 (Williams, Hampton et al. 2013, Williams, Pearce et al. 2014). 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 hybridization showed decreased GFAP mRNA in the white matter and Layer I in schizophrenia (Webster, O'Grady et al. 2005). 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 (Takizawa, Gudla et al. 2008), (Romão, Sousa Vde et al. 2008), 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 (Neame, Safory et al. 2019), 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 (Rosenberg, Artoul et al. 2013, Robin, Oliveira da Cruz et al. 2018). 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 (Katsel, Davis et al. 2005, Felsky, Voineskos et al. 2012, Mosebach, Keilhoff et al. 2013, Voineskos, Felsky et al. 2013, Windrem, Osipovitch et al. 2017, Raabe, Galinski et al. 2018, Raabe, Slapakova et al. 2019, Falkai, Raabe et al. 2020). 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.

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 (Newell, Zavitsanou et al. 2007, Gibbons, Scarr et al. 2013).

Parahippocampal and entorhinal cortex

The first clear demonstration of neuropathological change in the entorhinal cortex were 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 & 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 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 (Jakob and Beckmann 1986, Jakob and Beckmann 1994).

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 (Akil and Lewis 1997), (Bernstein, Krell et al. 1998). 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 (Arnold, Ruscheinsky et al. 1997). 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 (Arnold, Lee et al. 1991), which is in contrast to similar investigation showing a shooting of the primary cingulate cortex in schizophrenia, and also in contrast to the overall reports of more global cortical smoothing. 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 (Schultz, Koch et al. 2010, Schultz, Koch et al. 2010). In discussion of the heterogeneity of these findings several authors have suggested 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 (Heinsen, Gössmann et al. 1996), with the repeated studies showing examining neuronal organisation suggested to be effected by small n sizes (Akil and Lewis 1997, Krimer, Herman et al. 1997, Krimer, Hyde et al. 1997).

A subsequent post-mortem study has reported a decrease in tyrosine-hydroxylase-expressing neurons in the entorhinal cortex in schizophrenia. (Akil, Edgar et al. 2000). 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 (Kaushik, Gorin et al. 2007, Daubner, Le et al. 2011, Howes, Williams et al. 2013, Williams, Galvin et al. 2014), suggesting a neuropathological marker of decreased connectivity in this structure. In a possibly functionally-similar findings, GABAB-receptor protein has been found to be decreased in the pyramidal cells of the entorhinal cortex and layer 5 pyramidal cells in the inferior temporal cortex of postmortem brains in schizophrenia (Mizukami, Ishikawa et al. 2002).

DTI examination of the parahippocamapal 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 (Powell, Guye et al. 2004). 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 regards to age at onset and degree of parahippocampal asymmetry, with increased with age at onset in men but not in women, adding substance to the view that the sex-related dimension of symmetry/asymmetry (McDonald, Highley et al. 2000).

Reductions in volume and cortical thickness of the parahippocampal gyrus have been shown in post-mortem studies (Bogerts, Meertz et al. 1985, Brown, Colter et al. 1986, Colter, Battal et al. 1987, Falkai, Bogerts et al. 1988, Jeste and Lohr 1989, Altshuler, Casanova et al. 1990) although there have also been more negative reports (McDonald, Highley et al. 2000).

A particularly large post-mortem study conducted in the 1980's examined the brains of 232 patients with diagnosed of schizophrenia or affective disorder from a period of 22 years were assessed in a coronal section at the level of the interventricular foramin, showing significantly thinner parahippocampal cortices in schizophrenia but not affective disorders (Brown, Colter et al. 1986).

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.

Hippocampus

Post-mortem examination of the hippocampal formation size in schizophrenia was first focused on in 1986, where the volume of the whole hippocampal formation, the whole

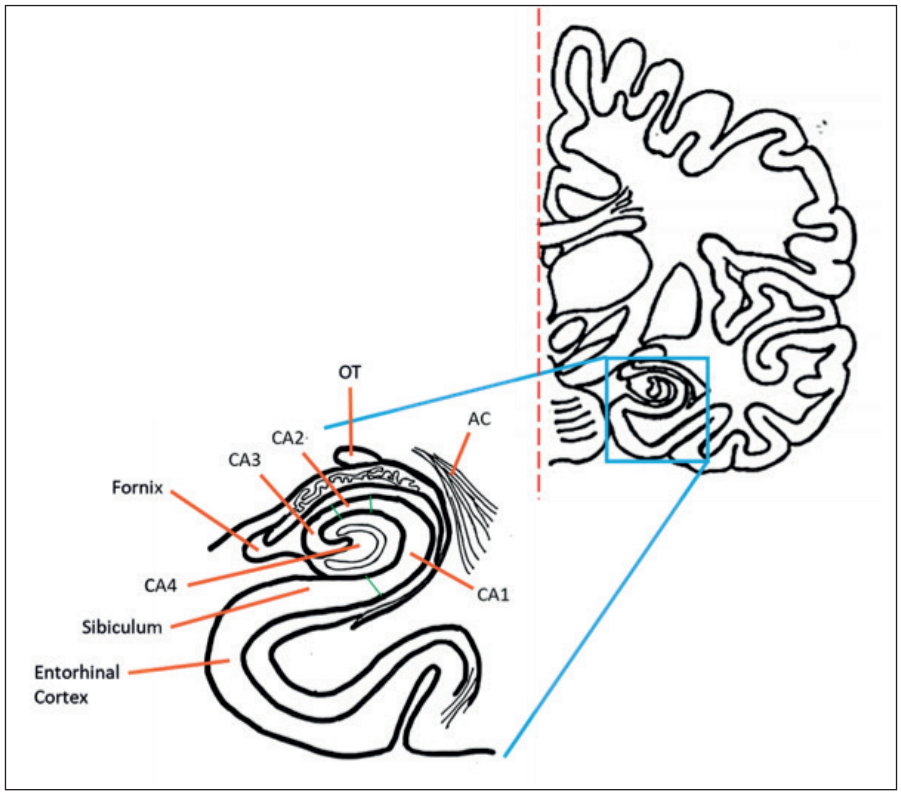

Figure 3. Coronal cut at the level of the hippocampus with expanded diagram showing the hippocampal internal structure outlined in blue. Whilst some hippocampal efferents arise from pyramidal neurons within the hippocampus itself, the majority arise from the sibiculum. CA – Cornus Ammonis, AC - Anterior Commissure, OT - Optic Tract. Dotted red line indicates midline of brain.

pyramidal band, the hippocampal segments CA1-CA2, CA3 and CA4 were reported decreased, with no significant volume reduction of the alveus and fimbria hippocampi and subiculum in schizophrenia (Falkai and Bogerts 1986, Bogerts, Falkai et al. 1990).

Quantitative imaging of the hippocampus in schizophrenia resulted in multiple 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 (Bogerts, Lieberman et al. 1992, Bogerts, Lieberman et al. 1993, Flaum, O'Leary et al. 1995, Becker, Elmer et al. 1996, Altshuler, Bartzokis et al. 2000, Rajarethinam, DeQuardo et al. 2001).

Two subsequent 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 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% (Nelson, Saykin et al. 1998). An overall decrease in hippocampal volume has been reported in schizophrenia using high-resolution structural MRI (Whitworth, Honeder et al. 1998), 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 (Altshuler, Casanova et al. 1990). 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 (Briend, Nelson et al. 2020), 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 (Kovelman and Scheibel 1984), 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 (Jakob and Beckmann 1986, Benes and Bird 1987). Whilst neuropathological examination into the hippocampus has been quite detailed 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 (Bogerts 1997, Dwork 1997), as well as reporting no change in the number of pyramidal neurons or organizational disarray across CA2-4 for the controls and schizophrenic cases has 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 & Bogerts that pyramidal cell loss in CA1-4 was more distinct in the paranoid than in catatonic patients (Benes, Sorensen et al. 1991, Jeste and Lohr 1989, Kovelman and Scheibel 1984, Konradi, Yang et al. 2011, Arnold, Franz et al. 1995, Conrad, Abebe et al. 1991). Examination of both types of hippocampal neurons show no size change in pyramidal cells, while non-pyramidal neurons were found to be selectively reduced by approximately 40% in CA2 of the schizophrenia group (Benes, Kwok et al. 1998), with smaller neurons reported in schizophrenia in other studies (Benes, Sorensen et al. 1991, Arnold, Franz et al. 1995, Zaidel, Esiri et al. 1997). 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 (Zaidel, Esiri et al. 1997). 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. (Zaidel, Esiri et al. 1997).

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 organization, with decreased total number and binding potential of GLU receptors, 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 (Kolomeets, Orlovskaya et al. 2005, Li, Ghose et al. 2015). 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. (Rosoklija, Toomayan et al. 2000). 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 (Popovic, Schmitt et al. 2019), 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 (Schmitt, Steyskal et al. 2009, Falkai, Malchow et al. 2016). 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 10 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 (Falkai, Raabe et al. 2020). 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 (Hertz and Rothman 2016). 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 (Tzingounis and Wadiche 2007). Astrocyte numbers have not been reported changed in the hippocampus in schizophrenia in the same manner as oligodendrocytes (Falkai, Honer et al. 1999, Schmitt, Steyskal et al. 2009). The use of S100β, a calcium-binding protein expressed by oligodendrcoytes and astrocytes, as a marker in post-mortem studies has also showed no change in S100β-immunopositive glia in the hippocampus in paranoid schizophrenia (Steiner, Bernstein et al. 2008).

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 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 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 (Perrone-Bizzozero, Sower et al. 1996).

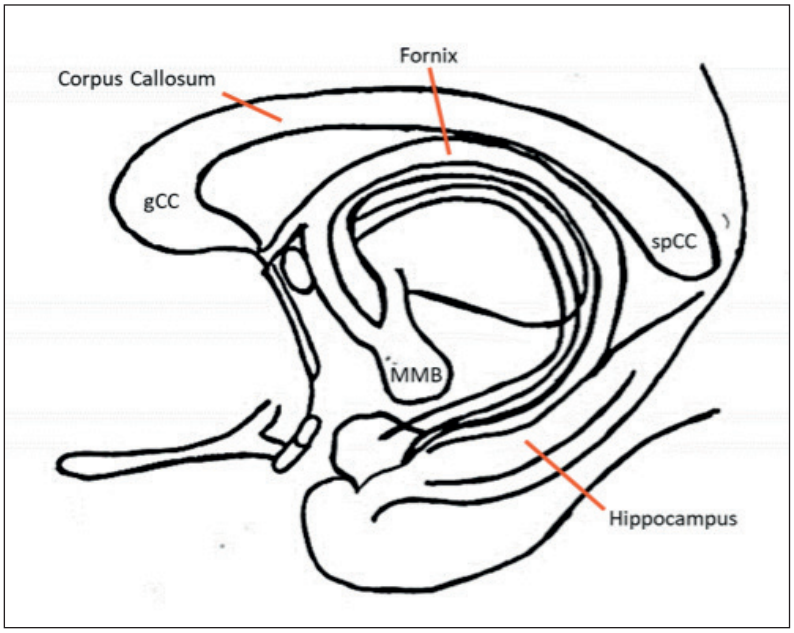

Figure 4. Sagittal view of the fornix projecting from the posterior part of the hippocampus to the underside of the corpus callosum, running beneath the callosum along the midline then descending into the pre-optic region of the brain at its most anterior point. gCC – genu of the Corpus Callosum, spCC – splenium of the Corpus Callosum, MMB – Mamillary Body.

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 (Tamminga, Southcott et al. 2012)

Fornix

The fornix is a bundle of mostly efferent fibres projecting form 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. The majority of the columnar fibres continue ventrally to the hypothalamus via the post-commissural fornix here 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 suggested to have a key role in spatial and verbal memory and memory retrieval which are processes involved in schizophrenia (Fitzsimmons, Kubicki et al. 2009, Thomas, Koumellis et al. 2011), 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 (Fletcher, Raman et al. 2013).

Structural MRI consistently shows decreased fractional anisotropy in the fornix in chronic schizophrenia (Kuroki, Kubicki et al. 2006, Takei, Yamasue et al. 2008, Zhou, Shu et al. 2008, Fitzsimmons, Kubicki et al. 2009, Qiu, Tuan et al. 2010, Abdul-Rahman, Qiu et al. 2011). 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 (Hori 1995, Kim, Tien et al. 1995, Oikawa, Sasaki et al. 2001, Kuroki, Kubicki et al. 2006, Lee, Fletcher et al. 2012, Fletcher, Raman et al. 2013, Koenig, Sakaie et al. 2014). Whilst neuropathological studies of the fornix in schizophrenia report no differences in fibre number or axonal myelin thickness examined under high-resolution oil-immersion microscopy, but have shown increased fibre density compared with controls (Chance, Highley et al. 1999, Williams, Sharma et al. 2015, Williams, Sharma et al. 2019), possibly illustrating how anatomically-unchanged axonal fibres are packed more densely in the fornix, explaining both the imaging and neuropathological findings.

Mamillary Bodies

It has been suggested that all neurons within the mammillary bodies are thought to project to the anterior thalamic nuclei. In rodents the lack of mammillary interneurons is seen as proof of its role as a relay nucleus, although primate and human studies demonstrate interneuron presence (Guillery 1955, Veazey, Amaral et al. 1982, Veazey, Amaral et al. 1982, Dixon, Garrick et al. 2004, Bernstein, Krause et al. 2007, Vann, Saunders et al. 2007). The mamillary bodies have not been examined in great detail, but a neuropathological study utilising the optical dissector methods of cell quantification on Nissl-stained sections has suggested that neurons within them are significantly larger and less dense in schizophrenia than in control cases (Briess, Cotter et al. 1998). In a more recent study of 15 post-mortem brains of schizophrenics and 15 matched control brains the volumes of mamillary bodies did not differ between schizophrenia cases and controls. However, consistent with Briess *et al's* 1998 paper the number of neurons as well as the resulting neuronal densities was bilaterally reduced in schizophrenia (on left side by 38.9%, on right side by 22%). Although no changes were reported in the number of GAD-expressing or calretinin-containing neurons, the number of parvalbumin-immunoreactive mamillary body neurons was less than half in schizophrenia than in controls, a cell population of glutamate- and aspartate-containing neurons projecting mainly to the anterior thalamus (Bernstein, Krause et al. 2007).

Anterior Thalamic Nucleus

The anterior thalamic nucelus is the most prominent nucleus of the thalamic anterior nuclear group. Damage to either the medial temporal lobe or the medial diencephalon often results in anterograde amnesia, and extensive hippocampal-Anterior Nuclear Group (ANG) interconnections support the idea that these structures constitute a brain network crucial for memory and cognition (Wright, Sharma et al. 1999, Wright, Erichsen et al. 2010, Jankowski, Ronnqvist et al. 2013). As such, the ANG is the main relay for the limbic system, receiving the MTT and hippocampal afferents and projecting to the cingulate gyrus, the anterior part of which has been strongly implicated in the symptomatology of schizophrenia.

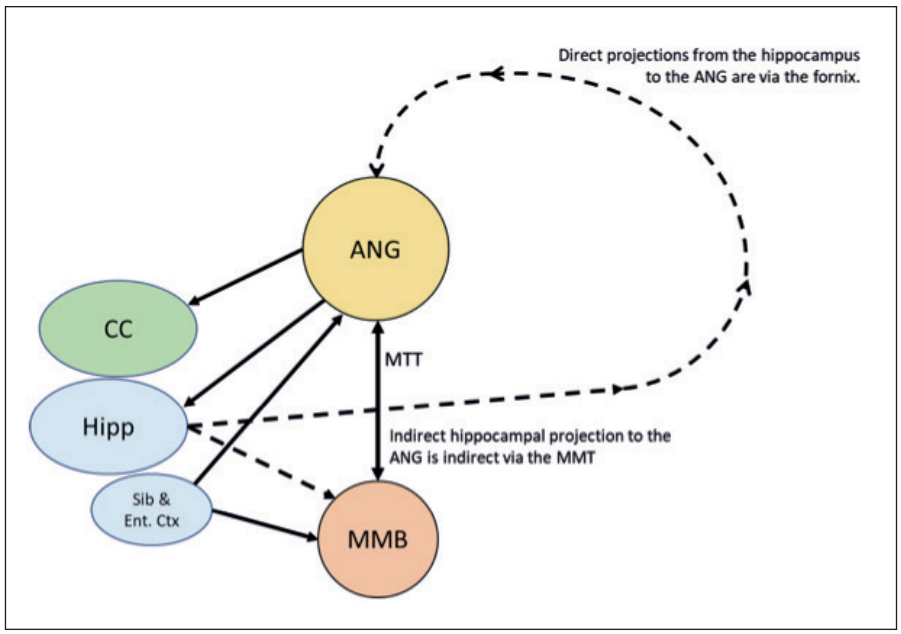

Figure 5. The connections of the Anterior Nuclear Group within the Papez circuit. Even though the Papez circuit has a defined pathway, interconnections between the neuroanatomical regions are present also. ANG – Anterior Nuclear Group, CC – Cingulate Cortex, Hipp – Hippocampus, Sib. – Sibiculum, Ent. Ctx. _ Entorhinal Cortex, MMB – Mamillary Body, MTT – Mammilothalamic Tract (Amaral and Cowan 1980, Naber and Witter 1998, Aggleton and Brown 1999, Wright, Sharma et al. 1999, Van Groen and Wyss 2003, Saunders, Mishkin et al. 2005, Shibata and Naito 2005, Wright, Erichsen et al. 2010, Yeo and Jang 2011, Jankowski, Ronnqvist et al. 2013)

Examination of the left thalami of 8 male schizophrenia brains and 8 male matched controls has suggested that the ANG has decreased total neuron number (-16%) (Young, Manaye et al. 2000). 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 mediodorsal thalamus and pulvinar (Danivas, Kalmady et al. 2013).

The ANG is a key 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 (Wright, Sharma et al. 1999, Wright, Erichsen et al. 2010, Jankowski, Ronnqvist et al. 2013). As such, the ANG is the main relay for the limbic system, receiving the MTT and hippocampal afferents and projecting to the cingulate gyrus, the anterior part of which has been strongly implicated in the symptomatology of schizophrenia.

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Overall

Given the region-specific neuropathological changes and the inevitability of heterogenous findings it is remarkable how consistently that the structures of the Papez circuit show changes in schizophrenia. Every part of the Papez loop has been revealed to be altered in some manner in schizophrenia, and given the importance of these structures in limbic and memory regulation there is a clear potential link between these reported changes, the circuit as whole and the altered functionality in schizophrenia, which will be discussed in the next paper.

References

Abdul-Rahman, M. F., A. Qiu and K. Sim (2011). "Regionally specific white matter disruptions of fornix and cingulum in schizophrenia." *PLoS One* **6**(4): e18652.

Aggleton, J. P. and M. W. Brown (1999). "Episodic memory, amnesia, and the hippocampal-anterior thalamic axis." *Behav Brain Sci* **22**(3): 425-444; discussion 444-489.

Akil, M., C. L. Edgar, J. N. Pierri, S. Casali and D. A. Lewis (2000). "Decreased density of tyrosine hydroxylase-immunoreactive axons in the entorhinal cortex of schizophrenic subjects." *Biol Psychiatry* **47**(5): 361-370.

Akil, M. and D. A. Lewis (1997). "Cytoarchitecture of the entorhinal cortex in schizophrenia." *Am J Psychiatry* **154**(7): 1010-1012.

Altshuler, L. L., G. Bartzokis, T. Grieder, J. Curran, T. Jimenez, K. Leight, J. Wilkins, R. Gerner and J. Mintz (2000). "An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia." *Biol Psychiatry* **48**(2): 147-162.

Altshuler, L. L., M. F. Casanova, T. E. Goldberg and J. E. Kleinman (1990). "The hippocampus and parahippocampus in schizophrenia, suicide, and control brains." *Arch Gen Psychiatry* **47**(11): 1029-1034.

Amaral, D. G. and W. M. Cowan (1980). "Subcortical afferents to the hippocampal formation in the monkey." *J Comp Neurol* **189**(4): 573-591.

Arnold, S. E., B. R. Franz, R. C. Gur, R. E. Gur, R. M. Shapiro, P. J. Moberg and J. Q. Trojanowski (1995). "Smaller neuron size in schizophrenia in hippocampal subfields that mediate cortical-hippocampal interactions." *Am J Psychiatry* **152**(5): 738-748.

Arnold, S. E., V. M. Lee, R. E. Gur and J. Q. Trojanowski (1991). "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* **88**(23): 10850-10854.

Arnold, S. E., D. D. Ruscheinsky and L. Y. Han (1997). "Further evidence of abnormal cytoarchitecture of the entorhinal cortex in schizophrenia using spatial point pattern analyses." *Biol Psychiatry* **42**(8): 639-647.

Baumann, P. S., A. Griffa, M. Fournier, P. Golay, C. Ferrari, L. Alameda, M. Cuenod, J. P. Thiran, P. Hagmann, K. Q.

Do and P. Conus (2016). "Impaired fornix-hippocampus integrity is linked to peripheral glutathione peroxidase in early psychosis." *Transl Psychiatry* **6**(7): e859.

Becker, T., K. Elmer, F. Schneider, M. Schneider, W. Grodd, M. Bartels, S. Heckers and H. Beckmann (1996). "Confirmation of reduced temporal limbic structure volume on magnetic resonance imaging in male patients with schizophrenia." *Psychiatry Res* **67**(2): 135-143.

Benes, F. M. and E. D. Bird (1987). "An analysis of the arrangement of neurons in the cingulate cortex of schizo-phrenic patients." *Arch Gen Psychiatry* **44**(7): 608-616.

Benes, F. M., J. Davidson and E. D. Bird (1986). "Quantitative cytoarchitectural studies of the cerebral cortex of schizo-phrenics." *Arch Gen Psychiatry* **43**(1): 31-35.

Benes, F. M., E. W. Kwok, S. L. Vincent and M. S. Todtenkopf (1998). "A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives." *Biol Psychiatry* **44**(2): 88-97.

Benes, F. M., J. McSparren, E. D. Bird, J. P. SanGiovanni and S. L. Vincent (1991). "Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients." *Arch Gen Psychiatry* **48**(11): 996-1001.

Benes, F. M., I. Sorensen and E. D. Bird (1991). "Reduced neuronal size in posterior hippocampus of schizophrenic patients." *Schizophr Bull* **17**(4): 597-608.

Benes, F. M., M. S. Todtenkopf and J. B. Taylor (1997). "Differential distribution of tyrosine hydroxylase fibers on small and large neurons in layer II of anterior cingulate cortex of schizophrenic brain." *Synapse* **25**(1): 80-92.

Bernstein, H. G., S. Krause, D. Krell, H. Dobrowolny, M. Wolter, R. Stauch, K. Ranft, P. Danos, G. F. Jirikowski and B. Bogerts (2007). "Strongly reduced number of parvalbu-min-immunoreactive projection neurons in the mammillary bodies in schizophrenia: further evidence for limbic neuropat-hology." *Ann N Y Acad Sci* **1096**: 120-127.

Bernstein, H. G., D. Krell, B. Baumann, P. Danos, P. Falkai, S. Diekmann, H. Henning and B. Bogerts (1998). "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* **33**(3): 125-132.

Bhattacharyya, K. B. (2017). "James Wenceslaus Papez, His Circuit, and Emotion." *Ann Indian Acad Neurol* **20**(3): 207-210.

Bogerts, B. (1988). "The brains of the Vogt collection." *Arch Gen Psychiatry* **45**(8): 774.

Bogerts, B. (1997). "The temporolimbic system theory of posi-tive schizophrenic symptoms." *Schizophr Bull* **23**(3): 423-435.

Bogerts, B., P. Falkai, M. Haupts, B. Greve, S. Ernst, U. Tapernon-Franz and U. Heinzmann (1990). "Post-mortem volume measurements of limbic system and basal ganglia structures in chronic schizophrenics. Initial results from a new brain collection." *Schizophr Res* **3**(5-6): 295-301.

Bogerts, B., J. A. Lieberman, M. Ashtari, R. M. Bilder, G. Degreef, G. Lerner, C. Johns and S. Masiar (1993). "Hippocampus-amygdala volumes and psychopathology in chronic schizophrenia." *Biol Psychiatry* **33**(4): 236-246.

Bogerts, B., J. A. Lieberman, R. M. Bilder, M. Ashtari, G. Degreef, G. Lerner, C. Johns and S. Masiar (1992). "A volumetric MRI study of limbic structures in chronic schizophrenia--relationship to psychopathology." *Clin Neuropharmacol* **15 Suppl 1 Pt A**: 112A-113A.

Bogerts, B., E. Meertz and R. Schönfeldt-Bausch (1985). "Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage." *Arch Gen Psychiatry* **42**(8): 784-791.

Briend, F., E. A. Nelson, O. Maximo, W. P. Armstrong, N. V. Kraguljac and A. C. Lahti (2020). "Hippocampal glutamate and hippocampus subfield volumes in antipsychotic-naive first episode psychosis subjects and relationships to duration of untreated psychosis." *Transl Psychiatry* **10**(1): 137.

Briess, D., D. Cotter, R. Doshi and I. Everall (1998). Mamillary body abnormalities in schizophrenia. *Lancet.* England. **352**: 789-790.

Brown, R., N. Colter, J. A. Corsellis, T. J. Crow, C. D. Frith, R. Jagoe, E. C. Johnstone and L. Marsh (1986). "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* **43**(1): 36-42.

Brune, M., A. Schobel, R. Karau, A. Benali, P. M. Faustmann, G. Juckel and E. Petrasch-Parwez (2010). "Von Economo neuron density in the anterior cingulate cortex is reduced in early onset schizophrenia." *Acta Neuropathol* **119**(6): 771-778.

Bzdok, D., A. Heeger, R. Langner, A. R. Laird, P. T. Fox, N. Palomero-Gallagher, B. A. Vogt, K. Zilles and S. B. Eickhoff (2015). "Subspecialization in the human posterior medial cortex." *Neuroimage* **106**: 55-71.

Chana, G., S. Landau, C. Beasley, I. P. Everall and D. Cotter (2003). "Two-dimensional assessment of cytoarchitecture in the anterior cingulate cortex in major depressive disorder, bipolar disorder, and schizophrenia: evidence for decreased neuronal somal size and increased neuronal density." *Biol Psychiatry* **53**(12): 1086-1098.

Chance, S. A., J. R. Highley, M. M. Esiri and T. J. Crow (1999). "Fiber content of the fornix in schizophrenia: lack of evidence for a primary limbic encephalopathy." *Am J Psychiatry* **156**(11): 1720-1724.

Choi, S. H., Y. B. Kim, S. H. Paek and Z. H. Cho (2019). "Papez Circuit Observed by in vivo Human Brain With 7.0T MRI Super-Resolution Track Density Imaging and Track Tracing." *Front Neuroanat* **13**: 17.

Colter, N., S. Battal, T. J. Crow, E. C. Johnstone, R. Brown and C. Bruton (1987). "White matter reduction in the parahippocampal gyrus of patients with schizophrenia." *Arch Gen Psychiatry* **44**(11): 1023.

Conrad, A. J., T. Abebe, R. Austin, S. Forsythe and A. B. Scheibel (1991). "Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon." *Arch Gen Psychiatry* **48**(5): 413-417.

Cotter, D., S. Landau, C. Beasley, R. Stevenson, G. Chana, L. MacMillan and I. Everall (2002). "The density and spatial distribution of GABAergic neurons, labelled using calcium binding proteins, in the anterior cingulate cortex in major depressive disorder, bipolar disorder, and schizophrenia." *Biol Psychiatry* **51**(5): 377-386.

Cotter, D., D. Mackay, S. Landau, R. Kerwin and I. Everall (2001). "Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder." *Arch Gen Psychiatry* **58**(6): 545-553.

Danivas, V., S. V. Kalmady, G. Venkatasubramanian and B. N. Gangadhar (2013). "Thalamic shape abnormalities in antipsychotic naïve schizophrenia." *Indian J Psychol Med* **35**(1): 34-38.

Daubner, S. C., T. Le and S. Wang (2011). "Tyrosine hydroxylase and regulation of dopamine synthesis." *Arch Biochem Biophys* **508**(1): 1-12.

Dixon, G., T. Garrick, I. Whiteman, M. Sarris, S. Sithamparanathan and C. G. Harper (2004). "Characterization of gabaergic neurons within the human medial mamillary nucleus." *Neuroscience* **127**(2): 365-372.

Drevets, W. C., J. L. Price, J. R. Simpson, R. D. Todd, T. Reich, M. Vannier and M. E. Raichle (1997). "Subgenual prefrontal cortex abnormalities in mood disorders." *Nature* **386**(6627): 824-827.

Dwork, A. J. (1997). "Postmortem studies of the hippocampal formation in schizophrenia." *Schizophr Bull* **23**(3): 385-402.

Eastwood, S. L. and P. J. Harrison (1998). "Hippocampal and cortical growth-associated protein-43 messenger RNA in schizophrenia." *Neuroscience* **86**(2): 437-448.

Falkai, P. and B. Bogerts (1986). "Cell loss in the hippocampus of schizophrenics." *Eur Arch Psychiatry Neurol Sci* **236**(3): 154-161.

Falkai, P., B. Bogerts and M. Rozumek (1988). "Limbic pathology in schizophrenia: the entorhinal region--a morphometric study." *Biol Psychiatry* **24**(5): 515-521.

Falkai, P., W. G. Honer, S. David, B. Bogerts, C. Majtenyi and

T. A. Bayer (1999). "No evidence for astrogliosis in brains of schizophrenic patients. A post-mortem study." *Neuropathol Appl Neurobiol* **25**(1): 48-53.

Falkai, P., B. Malchow, K. Wetzestein, V. Nowastowski, H. G. Bernstein, J. Steiner, T. Schneider-Axmann, T. Kraus, A. Hasan, B. Bogerts, C. Schmitz and A. Schmitt (2016). "Decreased Oligodendrocyte and Neuron Number in Anterior Hippocampal Areas and the Entire Hippocampus in Schizophrenia: A Stereological Postmortem Study." *Schizophr Bull* **42 Suppl 1**: S4-S12.

Falkai, P., F. Raabe, B. Bogerts, T. Schneider-Axmann, B. Malchow, L. Tatsch, V. Huber, L. Slapakova, H. Dobrowolny, C. Schmitz, L. Cantuti-Castelvetri, M. Simons, J. Steiner and A. Schmitt (2020). "Association between altered hippocampal oligodendrocyte number and neuronal circuit structures in schizophrenia: a postmortem analysis." *Eur Arch Psychiatry Clin Neurosci* **270**(4): 413-424.

Farkas, N., U. Lendeckel, H. Dobrowolny, S. Funke, J. Steiner, G. Keilhoff, A. Schmitt, B. Bogerts and H. G. Bernstein (2010). "Reduced density of ADAM 12-immunoreactive oligodendrocytes in the anterior cingulate white matter of patients with schizophrenia." *World J Biol Psychiatry* **11**(3): 556-566.

Felsky, D., A. N. Voineskos, J. P. Lerch, A. Nazeri, S. A. Shaikh, T. K. Rajji, B. H. Mulsant and J. L. Kennedy (2012). "Myelin-associated glycoprotein gene and brain morphometry in schizophrenia." *Front Psychiatry* **3**: 40.

Fitzsimmons, J., M. Kubicki, K. Smith, G. Bushell, R. S. Estepar, C. F. Westin, P. G. Nestor, M. A. Niznikiewicz, R. Kikinis, R. W. McCarley and M. E. Shenton (2009). "Diffusion tractography of the fornix in schizophrenia." *Schizophr Res* **107**(1): 39-46.

Flaum, M., D. S. O'Leary, V. W. Swayze, 2nd, D. D. Miller, S. Arndt and N. C. Andreasen (1995). "Symptom dimensions and brain morphology in schizophrenia and related psychotic disorders." *J Psychiatr Res* **29(**4): 261-276.

Fletcher, E., M. Raman, P. Huebner, A. Liu, D. Mungas, O. Carmichael and C. DeCarli (2013). "Loss of fornix white matter volume as a predictor of cognitive impairment in cognitively normal elderly individuals." *JAMA Neurol* **70**(11): 1389-1395.

Gibbons, A. S., E. Scarr, S. Boer, T. Money, W. J. Jeon, C. Felder and B. Dean (2013). "Widespread decreases in cortical muscarinic receptors in a subset of people with schizophrenia." *Int J Neuropsychopharmacol* **16**(1): 37-46.

Guillery, R. W. (1955). "A quantitative study of the mamillary bodies and their connexions." *J Anat* **89**(1): 19-32.

Heinsen, H., E. Gössmann, U. Rüb, W. Eisenmenger, M. Bauer, G. Ulmar, B. Bethke, M. Schüler, H. P. Schmitt, M. Götz, U. Lockemann and K. Püschel (1996). "Variability in the human entorhinal region may confound neuropsychiatric diagnoses." *Acta Anat (Basel)* **157**(3): 226-237.

Hercher, C., V. Chopra and C. L. Beasley (2014). "Evidence for morphological alterations in prefrontal white matter glia in schizophrenia and bipolar disorder." *J Psychiatry Neurosci* **39**(6): 376-385.

Hertz, L. and D. L. Rothman (2016). "Glucose, Lactate, ββHydroxybutyrate, Acetate, GABA, and Succinate as Substrates for Synthesis of Glutamate and GABA in the Glutamine-Glutamate/GABA Cycle." *Adv Neurobiol* **13**: 9-42.

Hoistad, M., H. Heinsen, B. Wicinski, C. Schmitz and P. R. Hof (2013). "Stereological assessment of the dorsal anterior cingulate cortex in schizophrenia: absence of changes in neuronal and glial densities." *Neuropathol Appl Neurobiol* **39**(4): 348-361.

Hori, A. (1995). "Unilateral volume loss of the fornix in patients with seizures caused by ipsilateral hippocampal sclerosis." *AJR Am J Roentgenol* **164**(5): 1304.

Howes, O. D., M. Williams, K. Ibrahim, G. Leung, A. Egerton, P. K. McGuire and F. Turkheimer (2013). "Midbrain dopamine function in schizophrenia and depression: a post-mortem and positron emission tomographic imaging study." *Brain* **136**(Pt 11): 3242-3251.

Jakob, H. and H. Beckmann (1986). "Prenatal developmental disturbances in the limbic allocortex in schizophrenics." *J Neural Transm* **65**(3-4): 303-326.

Jakob, H. and H. Beckmann (1994). "Circumscribed malformation and nerve cell alterations in the entorhinal cortex of

schizophrenics. Pathogenetic and clinical aspects." *J Neural Transm Gen Sect* **98**(2): 83-106.

Jankowski, M. M., K. C. Ronnqvist, M. Tsanov, S. D. Vann, N. F. Wright, J. T. Erichsen, J. P. Aggleton and S. M. O'Mara (2013). "The anterior thalamus provides a subcortical circuit supporting memory and spatial navigation." *Front Syst Neurosci* **7**: 45.

Jeste, D. V. and J. B. Lohr (1989). "Hippocampal pathologic findings in schizophrenia. A morphometric study." *Arch Gen Psychiatry* **46**(11): 1019-1024.

Kalus, P., D. Senitz and H. Beckmann (1997). "Altered distribution of parvalbumin-immunoreactive local circuit neurons in the anterior cingulate cortex of schizophrenic patients." *Psychiatry Res* **75**(1): 49-59.

Katsel, P., K. L. Davis and V. Haroutunian (2005). "Variations in myelin and oligodendrocyte-related gene expression across multiple brain regions in schizophrenia: a gene ontology study." *Schizophr Res* **79**(2-3): 157-173.

Kaushik, P., F. Gorin and S. Vali (2007). "Dynamics of tyrosine hydroxylase mediated regulation of dopamine synthesis." *J Comput Neurosci* **22**(2): 147-160.

Kim, J. H., R. D. Tien, G. J. Felsberg, A. K. Osumi and N. Lee (1995). "Clinical significance of asymmetry of the fornix and mamillary body on MR in hippocampal sclerosis." *AJNR Am J Neuroradiol* **16**(3): 509-515.

Koenig, K. A., K. E. Sakaie, M. J. Lowe, J. Lin, L. Stone, R. A. Bermel, E. B. Beall, S. M. Rao, B. D. Trapp and M. D. Phillips (2014). "Hippocampal volume is related to cognitive decline and fornicial diffusion measures in multiple sclerosis." *Magn Reson Imaging* **32**(4): 354-358.

Kolomeets, N. S., D. D. Orlovskaya, V. I. Rachmanova and N. A. Uranova (2005). "Ultrastructural alterations in hippocampal mossy fiber synapses in schizophrenia: a postmortem morphometric study." *Synapse* **57**(1): 47-55.

Konradi, C., C. K. Yang, E. I. Zimmerman, K. M. Lohmann, P. Gresch, H. Pantazopoulos, S. Berretta and S. Heckers (2011). "Hippocampal interneurons are abnormal in schizophrenia." *Schizophr Res* **131**(1-3): 165-173.

Kovelman, J. A. and A. B. Scheibel (1984). "A neurohistological correlate of schizophrenia." *Biol Psychiatry* **19**(12): 1601-1621.

Krause, M., C. Theiss and M. Brüne (2017). "Ultrastructural Alterations of Von Economo Neurons in the Anterior Cingulate Cortex in Schizophrenia." *Anat Rec (Hoboken)* **300**(11): 2017-2024.

Krimer, L. S., M. M. Herman, R. C. Saunders, J. C. Boyd, T. M. Hyde, J. M. Carter, J. E. Kleinman and D. R. Weinberger (1997). "A qualitative and quantitative analysis of the entorhinal cortex in schizophrenia." *Cereb Cortex* **7**(8): 732-739.

Krimer, L. S., T. M. Hyde, M. M. Herman and R. C. Saunders (1997). "The entorhinal cortex: an examination of cyto- and myeloarchitectonic organization in humans." *Cereb Cortex* **7**(8): 722-731.

Kuroki, N., M. Kubicki, P. G. Nestor, D. F. Salisbury, H. J. Park, J. J. Levitt, S. Woolston, M. Frumin, M. Niznikiewicz, C. F. Westin, S. E. Maier, R. W. McCarley and M. E. Shenton (2006). "Fornix integrity and hippocampal volume in male schizophrenic patients." *Biol Psychiatry* **60**(1): 22-31.

Lee, D. Y., E. Fletcher, O. T. Carmichael, B. Singh, D. Mungas, B. Reed, O. Martinez, M. H. Buonocore, M. Persianinova and C. Decarli (2012). "Sub-Regional Hippocampal Injury is Associated with Fornix Degeneration in Alzheimer's Disease." *Front Aging Neurosci* **4**: 1.

Li, W., S. Ghose, K. Gleason, A. Begovic, J. Perez, J. Bartko, S. Russo, A. D. Wagner, L. Selemon and C. A. Tamminga (2015). "Synaptic proteins in the hippocampus indicative of increased neuronal activity in CA3 in schizophrenia." *Am J Psychiatry* **172**(4): 373-382.

McDonald, B., J. R. Highley, M. A. Walker, B. M. Herron, S. J. Cooper, M. M. Esiri and T. J. Crow (2000). "Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: A postmortem study." *Am J Psychiatry* **157**(1): 40-47.

Mizukami, K., M. Ishikawa, S. Hidaka, M. Iwakiri, M. Sasaki and S. Iritani (2002). "Immunohistochemical localization of

GABAB receptor in the entorhinal cortex and inferior temporal cortex of schizophrenic brain." *Prog Neuropsychopharmacol Biol Psychiatry* **26**(2): 393-396.

Mosebach, J., G. Keilhoff, T. Gos, K. Schiltz, L. Schoeneck, H. Dobrowolny, C. Mawrin, S. Müller, M. L. Schroeter, H. G. Bernstein, B. Bogerts and J. Steiner (2013). "Increased nuclear Olig1-expression in the pregenual anterior cingulate white matter of patients with major depression: a regenerative attempt to compensate oligodendrocyte loss?" *J Psychiatr Res* **47**(8): 1069-1079.

Naber, P. A. and M. P. Witter (1998). "Subicular efferents are organized mostly as parallel projections: a double-labeling, retrograde-tracing study in the rat." *J Comp Neurol* **393**(3): 284-297.

Neame, S., H. Safory, I. Radzishevsky, A. Touitou, F. Marchesani, M. Marchetti, S. Kellner, S. Berlin, V. N. Foltyn, S. Engelender, J. M. Billard and H. Wolosker (2019). "The NMDA receptor activation by d-serine and glycine is controlled by an astrocytic Phgdh-dependent serine shuttle." *Proc Natl Acad Sci U S A* **116**(41): 20736-20742.

Nelson, M. D., A. J. Saykin, L. A. Flashman and H. J. Riordan (1998). "Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study." *Arch Gen Psychiatry* **55**(5): 433-440.

Newell, K. A., K. Zavitsanou, S. K. Jew and X. F. Huang (2007). "Alterations of muscarinic and GABA receptor binding in the posterior cingulate cortex in schizophrenia." *Prog Neuropsychopharmacol Biol Psychiatry* **31**(1): 225-233.

Nishio, Y., M. Hashimoto, K. Ishii and E. Mori (2011). "Neuroanatomy of a neurobehavioral disturbance in the left anterior thalamic infarction." *J Neurol Neurosurg Psychiatry* **82**(11): 1195-1200.

Oikawa, H., M. Sasaki, Y. Tamakawa and A. Kamei (2001). "The circuit of Papez in mesial temporal sclerosis: MRI." *Neuroradiology* **43**(3): 205-210.

Ongur, D., W. C. Drevets and J. L. Price (1998). "Glial reduction in the subgenual prefrontal cortex in mood disorders." *Proc Natl Acad Sci U S A* **95**(22): 13290-13295.

Ongür, D., W. C. Drevets and J. L. Price (1998). "Glial reduction in the subgenual prefrontal cortex in mood disorders." *Proc Natl Acad Sci U S A* **95**(22): 13290-13295.

Palomero-Gallagher, N., H. Mohlberg, K. Zilles and B. Vogt (2008). "Cytology and receptor architecture of human anterior cingulate cortex." *J Comp Neurol* **508**(6): 906-926.

Palomero-Gallagher, N., K. Zilles, A. Schleicher and B. A. Vogt (2013). "Cyto- and receptor architecture of area 32 in human and macaque brains." *J Comp Neurol* **521**(14): 3272-3286.

Papez, J. (1937). A proposed mechanism of emotion. Arch Neurol Psychiatry. **38**: 725–743.

Papez, J. W. (1995). "A proposed mechanism of emotion. 1937." *J Neuropsychiatry Clin Neurosci* **7**(1): 103-112.

Perrone-Bizzozero, N. I., A. C. Sower, E. D. Bird, L. I. Benowitz, K. J. Ivins and R. L. Neve (1996). "Levels of the growth-associated protein GAP-43 are selectively increased in association cortices in schizophrenia." *Proc Natl Acad Sci U S A* **93**(24): 14182-14187.

Popovic, D., A. Schmitt, L. Kaurani, F. Senner, S. Papiol, B. Malchow, A. Fischer, T. G. Schulze, N. Koutsouleris and P. Falkai (2019). "Childhood Trauma in Schizophrenia: Current Findings and Research Perspectives." *Front Neurosci* **13**: 274.

Powell, H. W., M. Guye, G. J. Parker, M. R. Symms, P. Boulby, M. J. Koepp, G. J. Barker and J. S. Duncan (2004). "Noninvasive in vivo demonstration of the connections of the human parahippocampal gyrus." *Neuroimage* **22**(2): 740-747.

Qiu, A., T. A. Tuan, P. S. Woon, M. F. Abdul-Rahman, S. Graham and K. Sim (2010). "Hippocampal-cortical structural connectivity disruptions in schizophrenia: an integrated perspective from hippocampal shape, cortical thickness, and integrity of white matter bundles." *Neuroimage* **52**(4): 1181-1189.

Raabe, F. J., S. Galinski, S. Papiol, P. G. Falkai, A. Schmitt and M. J. Rossner (2018). "Studying and modulating

schizophrenia-associated dysfunctions of oligodendrocytes with patient-specific cell systems." *NPJ Schizophr* **4**(1): 23.

Raabe, F. J., L. Slapakova, M. J. Rossner, L. Cantuti-Castelvetri, M. Simons, P. G. Falkai and A. Schmitt (2019). "Oligodendrocytes as A New Therapeutic Target in Schizophrenia: From Histopathological Findings to Neuron-Oligodendrocyte Interaction." *Cells* **8**(12).

Radewicz, K., L. J. Garey, S. M. Gentleman and R. Reynolds (2000). "Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics." *J Neuropathol Exp Neurol* **59**(2): 137-150.

Rajarethinam, R., J. R. DeQuardo, J. Miedler, S. Arndt, R. Kirbat, J. A. Brunberg and R. Tandon (2001). "Hippocampus and amygdala in schizophrenia: assessment of the relationship of neuroanatomy to psychopathology." *Psychiatry Res* **108**(2): 79-87.

Robin, L. M., J. F. Oliveira da Cruz, V. C. Langlais, M. Martin-Fernandez, M. Metna-Laurent, A. Busquets-Garcia, L. Bellocchio, E. Soria-Gomez, T. Papouin, M. Varilh, M. W. Sherwood, I. Belluomo, G. Balcells, I. Matias, B. Bosier, F. Drago, A. Van Eeckhaut, I. Smolders, F. Georges, A. Araque, A. Panatier, S. H. R. Oliet and G. Marsicano (2018). "Astroglial CB(1) Receptors Determine Synaptic D-Serine Availability to Enable Recognition Memory." *Neuron* **98**(5): 935-944.e935.

Romão, L. F., O. Sousa Vde, V. M. Neto and F. C. Gomes (2008). "Glutamate activates GFAP gene promoter from cultured astrocytes through TGF-beta1 pathways." *J Neurochem* **106**(2): 746-756.

Rosenberg, D., S. Artoul, A. C. Segal, G. Kolodney, I. Radzishevsky, E. Dikopoltsev, V. N. Foltyn, R. Inoue, H. Mori, J. M. Billard and H. Wolosker (2013). "Neuronal D-serine and glycine release via the Asc-1 transporter regulates NMDA receptor-dependent synaptic activity." *J Neurosci* **33**(8): 3533-3544.

Rosoklija, G., G. Toomayan, S. P. Ellis, J. Keilp, J. J. Mann, N. Latov, A. P. Hays and A. J. Dwork (2000). "Structural abnormalities of subicular dendrites in subjects with schizophrenia and mood disorders: preliminary findings." *Arch Gen Psychiatry* **57**(4): 349-356.

Saunders, R. C., M. Mishkin and J. P. Aggleton (2005). "Projections from the entorhinal cortex, perirhinal cortex, presubiculum, and parasubiculum to the medial thalamus in macaque monkeys: identifying different pathways using disconnection techniques." *Exp Brain Res* **167**(1): 1-16.

Schmitt, A., C. Steyskal, H. G. Bernstein, T. Schneider-Axmann, E. Parlapani, E. L. Schaeffer, W. F. Gattaz, B. Bogerts, C. Schmitz and P. Falkai (2009). "Stereologic investigation of the posterior part of the hippocampus in schizophrenia." *Acta Neuropathol* **117**(4): 395-407.

Schultz, C. C., K. Koch, G. Wagner, M. Roebel, I. Nenadic, C. Schachtzabel, J. R. Reichenbach, H. Sauer and R. G. Schlösser (2010). "Complex pattern of cortical thinning in schizophrenia: results from an automated surface based analysis of cortical thickness." *Psychiatry Res* **182**(2): 134-140.

Schultz, C. C., K. Koch, G. Wagner, M. Roebel, C. Schachtzabel, I. Nenadic, C. Albrecht, J. R. Reichenbach, H. Sauer and R. G. Schlösser (2010). "Psychopathological correlates of the entorhinal cortical shape in schizophrenia." *Eur Arch Psychiatry Clin Neurosci* **260**(4): 351-358.

Segal, D., C. Schmitz and P. R. Hof (2009). "Spatial distribution and density of oligodendrocytes in the cingulum bundle are unaltered in schizophrenia." *Acta Neuropathol* **117**(4): 385-394.

Shibata, H. (1992). "Topographic organization of subcortical projections to the anterior thalamic nuclei in the rat." *J Comp Neurol* **323**(1): 117-127.

Shibata, H. and J. Naito (2005). "Organization of anterior cingulate and frontal cortical projections to the anterior and laterodorsal thalamic nuclei in the rat." *Brain Res* **1059**(1): 93-103.

Stark, A. K., H. B. Uylings, E. Sanz-Arigita and B. Pakkenberg (2004). "Glial cell loss in the anterior cingulate cortex, a subregion of the prefrontal cortex, in subjects with schizophrenia." *Am J Psychiatry* **161**(5): 882-888.

Steiner, J., H. G. Bernstein, H. Bielau, N. Farkas, J. Winter, H. Dobrowolny, R. Brisch, T. Gos, C. Mawrin, A. M. Myint and B. Bogerts (2008). "S100B-immunopositive glia is elevated in

paranoid as compared to residual schizophrenia: a morphometric study." *J Psychiatr Res* **42**(10): 868-876.

Steiner, J., C. Mawrin, A. Ziegeler, H. Bielau, O. Ullrich, H. G. Bernstein and B. Bogerts (2006). "Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization." *Acta Neuropathol* **112**(3): 305-316.

Takei, K., H. Yamasue, O. Abe, H. Yamada, H. Inoue, M. Suga, K. Sekita, H. Sasaki, M. Rogers, S. Aoki and K. Kasai (2008). "Disrupted integrity of the fornix is associated with impaired memory organization in schizophrenia." *Schizophr Res* **103**(1-3): 52-61.

Takizawa, T., P. R. Gudla, L. Guo, S. Lockett and T. Misteli (2008). "Allele-specific nuclear positioning of the monoallelically expressed astrocyte marker GFAP." *Genes Dev* **22**(4): 489-498.

Tamminga, C. A., S. Southcott, C. Sacco, A. D. Wagner and S. Ghose (2012). "Glutamate dysfunction in hippocampus: relevance of dentate gyrus and CA3 signaling." *Schizophr Bull* **38**(5): 927-935.

Thomas, A. G., P. Koumellis and R. A. Dineen (2011). "The fornix in health and disease: an imaging review." *Radiographics* **31**(4): 1107-1121.

Todtenkopf, M. S., S. L. Vincent and F. M. Benes (2005). "A cross-study meta-analysis and three-dimensional comparison of cell counting in the anterior cingulate cortex of schizophrenic and bipolar brain." *Schizophr Res* **73**(1): 79-89.

Triarhou, L. C. (2008). "Centenary of Christfried Jakob's discovery of the visceral brain: an unheeded precedence in affective neuroscience." *Neurosci Biobehav Rev* **32**(5): 984-1000.

Tzingounis, A. V. and J. I. Wadiche (2007). "Glutamate transporters: confining runaway excitation by shaping synaptic transmission." *Nat Rev Neurosci* **8**(12): 935-947.

Van Groen, T. and J. M. Wyss (2003). "Connections of the retrosplenial granular b cortex in the rat." *J Comp Neurol* **463**(3): 249-263.

Vann, S. D., R. C. Saunders and J. P. Aggleton (2007). "Distinct, parallel pathways link the medial mammillary bodies to the anterior thalamus in macaque monkeys." *Eur J Neurosci* **26**(6): 1575-1586.

Veazey, R. B., D. G. Amaral and W. M. Cowan (1982). "The morphology and connections of the posterior hypothalamus in the cynomolgus monkey (Macaca fascicularis). I. Cytoarchitectonic organization." *J Comp Neurol* **207**(2): 114-134.

Veazey, R. B., D. G. Amaral and W. M. Cowan (1982). "The morphology and connections of the posterior hypothalamus in the cynomolgus monkey (Macaca fascicularis). II. Efferent connections." *J Comp Neurol* **207**(2): 135-156.

Vertes, R. P., Z. Albo and G. Viana Di Prisco (2001). "Theta-rhythmically firing neurons in the anterior thalamus: implications for mnemonic functions of Papez's circuit." *Neuroscience* **104**(3): 619-625.

Vogt, B., P. Hof and L. Vogt (2004). *Cingulate Gyrus*. New York, Academic.

Vogt, B. A. (2005). "Pain and emotion interactions in subregions of the cingulate gyrus." *Nat Rev Neurosci* **6**(7): 533-544.

Vogt, B. A. (2016). "Midcingulate cortex: Structure, connections, homologies, functions and diseases." *J Chem Neuroanat* **74**: 28-46.

Vogt, B. A., J. R. Absher and G. Bush (2000). Human retrosplenial cortex: where is it and is it involved in emotion? *Trends Neurosci*. England. **23**: 195-197.

Vogt, B. A., G. R. Berger and S. W. Derbyshire (2003). "Structural and functional dichotomy of human midcingulate cortex." *Eur J Neurosci* **18**(11): 3134-3144.

Vogt, B. A., D. N. Pandya and D. L. Rosene (1987). "Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents." *J Comp Neurol* **262**(2): 256-270.

Vogt, B. A., L. Vogt, N. B. Farber and G. Bush (2005). "Architecture and neurocytology of monkey cingulate gyrus." *J Comp Neurol* **485**(3): 218-239.

Vogt, B. A., L. Vogt and S. Laureys (2006). "Cytology and functionally correlated circuits of human posterior cingulate areas." *Neuroimage* **29**(2): 452-466.

Voineskos, A. N., D. Felsky, N. Kovacevic, A. K. Tiwari, C. Zai, M. M. Chakravarty, N. J. Lobaugh, M. E. Shenton, T. K. Rajji, D. Miranda, B. G. Pollock, B. H. Mulsant, A. R. McIntosh and J. L. Kennedy (2013). "Oligodendrocyte genes, white matter tract integrity, and cognition in schizophrenia." *Cereb Cortex* **23**(9): 2044-2057.

Webster, M. J., J. O'Grady, J. E. Kleinman and C. S. Weickert (2005). "Glial fibrillary acidic protein mRNA levels in the cingulate cortex of individuals with depression, bipolar disorder and schizophrenia." *Neuroscience* **133**(2): 453-461.

Whitworth, A. B., M. Honeder, C. Kremser, G. Kemmler, S. Felber, A. Hausmann, C. Wanko, H. Wechdorn, F. Aichner, C. H. Stuppaeck and W. W. Fleischhacker (1998). "Hippocampal volume reduction in male schizophrenic patients." *Schizophr Res* **31**(2-3): 73-81.

Williams, M., R. K. Pearce, S. R. Hirsch, O. Ansorge, M. Thom and M. Maier (2014). "Fibrillary astrocytes are decreased in the subgenual cingulate in schizophrenia." *Eur Arch Psychiatry Clin Neurosci* **264**(4): 357-362.

Williams, M. R., R. Chaudhry, S. Perera, R. K. Pearce, S. R. Hirsch, O. Ansorge, M. Thom and M. Maier (2013). "Changes in cortical thickness in the frontal lobes in schizophrenia are a result of thinning of pyramidal cell layers." *Eur Arch Psychiatry Clin Neurosci* **263**(1): 25-39.

Williams, M. R., K. Galvin, B. O'Sullivan, C. D. MacDonald, E. W. Ching, F. Turkheimer, O. D. Howes, R. K. Pearce, S. R. Hirsch and M. Maier (2014). "Neuropathological changes in the substantia nigra in schizophrenia but not depression." *Eur Arch Psychiatry Clin Neurosci* **264**(4): 285-296.

Williams, M. R., T. Hampton, R. K. Pearce, S. R. Hirsch, O. Ansorge, M. Thom and M. Maier (2013). "Astrocyte decrease in the subgenual cingulate and callosal genu in schizophrenia." *Eur Arch Psychiatry Clin Neurosci* **263**(1): 41-52.

Williams, M. R., P. Sharma, K. L. Fung, R. K. Pearce, S. R. Hirsch and M. Maier (2015). "Axonal myelin increase in the callosal genu in depression but not schizophrenia." *Psychol Med* **45**(10): 2145-2155.

Williams, M. R., P. Sharma, C. Macdonald, R. K. B. Pearce, S. R. Hirsch and M. Maier (2019). "Axonal myelin decrease in the splenium in major depressive disorder." *Eur Arch Psychiatry Clin Neurosci* **269**(4): 387-395.

Windrem, M. S., M. Osipovitch, Z. Liu, J. Bates, D. Chandler-Militello, L. Zou, J. Munir, S. Schanz, K. McCoy, R. H. Miller, S. Wang, M. Nedergaard, R. L. Findling, P. J. Tesar and S. A. Goldman (2017). "Human iPSC Glial Mouse Chimeras Reveal Glial Contributions to Schizophrenia." *Cell Stem Cell* **21**(2): 195-208.e196.

Woo, T. U., K. Shrestha, C. Amstrong, M. M. Minns, J. P. Walsh and F. M. Benes (2007). "Differential alterations of kainate receptor subunits in inhibitory interneurons in the anterior cingulate cortex in schizophrenia and bipolar disorder." *Schizophr Res* **96**(1-3): 46-61.

Woo, T. U., J. P. Walsh and F. M. Benes (2004). "Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder." *Arch Gen Psychiatry* **61**(7): 649-657.

Wright, I. C., T. Sharma, Z. R. Ellison, P. K. McGuire, K. J. Friston, M. J. Brammer, R. M. Murray and E. T. Bullmore (1999). "Supra-regional brain systems and the neuropathology of schizophrenia." *Cereb Cortex* **9**(4): 366-378.

Wright, N. F., J. T. Erichsen, S. D. Vann, S. M. O'Mara and J. P. Aggleton (2010). "Parallel but separate inputs from limbic cortices to the mammillary bodies and anterior thalamic nuclei in the rat." *J Comp Neurol* **518**(12): 2334-2354.

Yeo, S. S. and S. H. Jang (2011). "The effect of thalamic hemorrhage on the fornix." *Int J Neurosci* **121**(7): 379-383.

Young, K. A., K. F. Manaye, C. Liang, P. B. Hicks and D. C. German (2000). "Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia." *Biol Psychiatry* **47**(11): 944-953.

Zaidel, D. W., M. M. Esiri and P. J. Harrison (1997). "Size, shape, and orientation of neurons in the left and right hippocampus: investigation of normal asymmetries and alterations in schizophrenia." *Am J Psychiatry* **154**(6): 812-818.

Zaidel, D. W., M. M. Esiri and P. J. Harrison (1997). "The hippocampus in schizophrenia: lateralized increase in neuronal density and altered cytoarchitectural asymmetry." *Psychol Med* **27**(3): 703-713.

Zhou, Y., N. Shu, Y. Liu, M. Song, Y. Hao, H. Liu, C. Yu, Z. Liu and T. Jiang (2008). "Altered resting-state functional connectivity and anatomical connectivity of hippocampus in schizophrenia." *Schizophr Res* **100**(1-3): 120-132.

