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Limbic Structures and Networks in Children and Adolescents With Schizophrenia

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Studies of adults with schizophrenia provide converging evidence for abnormalities in the limbic system. Limbic structures that show consistent patient/control differences in both postmortem and neuroimaging studies include the anterior cingulate and hippocampus, although differences in the amygdala, parahippocampal gyrus, and fornix have also been observed. Studies of white matter in children and adolescents with schizophrenia tend to show findings that are more focal than those seen in adults. Interestingly, these focal abnormalities in early-onset schizophrenia tend to be more localized to limbic regions. While it is unclear if these early limbic abnormalities are primary in the etiology of schizophrenia, there is evidence that supports a developmental progression with early limbic abnormalities evolving over time to match the neuroimaging profiles seen in adults with schizophrenia. Alternatively, the aberrations in limbic structures may be secondary to a more widespread or global pathological processes occurring with the brain that disrupt neural transmission. The goal of this article is to provide a review of the limbic system and limbic network abnormalities reported in children and adolescents with schizophrenia. These findings are compared with the adult literature and placed within a developmental context. These observations from neuroimaging studies enrich our current understanding of the neurodevelopmental model of schizophrenia and raise further questions about primary vs secondary processes. Additional research within a developmental framework is necessary to determine the putative etiologic roles for limbic and other brain abnormalities in early-onset schizophrenia.

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Introduction

The limbic system has long been implicated in the pathogenesis of schizophrenia.[1] More recent studies utilizing magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), or electrophysiological methods have added support for limbic abnormalities in schizophrenia. However, brain abnormalities have not been limited to the limbic lobe, and other brain regions (ie, the prefrontal cortex, cerebellum, and striatum) have also been shown to be aberrant in schizophrenia.[2–6] In light of the multiple brain regions affected and the diversity of symptoms found in individuals with schizophrenia, one intriguing etiologic hypothesis involves aberrant neural connectivity between brain regions.[7–9]

Connectivity between brain regions occurs through microscopic processes because signals travel along neurons and propagate through excitatory or inhibitory synapses. Because the brain encompasses billions of neurons, connectivity is traditionally defined by the path of groups or tracts of neurons. Structural connectivity is defined by the actual neuronal pathways connecting 2 brain regions, often determined by postmortem dye tracing techniques. Structural connectivity can also be measured using DTI, which provides a measure of the coherence of neurons traveling together. However, challenges related to low resolution and artifacts limit the ability of DTI to accurately measure structural connectivity. Finally, functional connectivity is a term used to describe the temporal correlations in the hemodynamic response function between 2 distant brain regions, with the implication that "regions that wire together, fire together."[10] This is typically measured using functional MRI (fMRI). Abnormalities in both structural[11] and functional[12–16] connectivity have been described in adults with schizophrenia, lending support for a "dysconnection syndrome."[8]

Whether this dysconnection occurs as a global process, such as a result of the downregulation of myelin-related genes,[17] or as a downstream effect of an earlier and localized insult[18,19] is unclear. It is possible that a genetically at-risk individual who experiences environmental insults,

whether they be early (prenatal),[20,21] later (ie, marijuana abuse),[22] or a combination of the 2, has an unmasking of the effects of these insults during late adolescence and early adulthood.

In children with schizophrenia, studies have shown striking gray matter reductions on a global level, which shift over time from parietal regions toward prefrontal and limbic regions.[23,24] However, because these gray matter changes occur several years after illness onset, they may reflect a downstream neurodevelopmental effect of an earlier insult. It is much easier to identify the terrible devastation caused by a tsunami than the actual earthquake that was its genesis. Unfortunately we have no ''Richter scale'' to measure the potential upstream processes associated with the etiology of schizophrenia. In addition, it is unclear if the upstream processes are global in their onset or localized to a specific region (ie, prefrontal cortex or hippocampus). Hopefully, the ongoing prodromal or high-risk studies will address this important question. In addition, understanding normative neurodevelopmental trajectories can assist with determining the nature of age-dependent changes or differences between those who develop schizophrenia and those who do not.[25]

The lifespan development of brain connectivity is a dynamic process, with age-related changes associated with neuronal growth and apoptosis, synaptic and dendritic proliferation and pruning, and myelination.[26–32] During the first 2 decades of life, neural growth and pruning occur first in the primary sensorimotor cortex, orbitofrontal cortex, and posterior regions (occipital cortex), progressing later to anterior brain regions (ie, prefrontal cortex).[27,29,33] The cortical association regions, such as those linking the temporal lobe with the parietal and frontal lobes, tend to have protracted developmental trajectories that extend to the second and third decades of life.[34] These developmental trajectories are very interesting when compared with the peak age of onset of schizophrenia, occurring also during this window of development.

The goal of this article is to review the limbic system anatomy, development, and abnormalities reported in limbic networks in children and adolescents with schizophrenia. Understanding that brain function involves distributed networks and that other brain regions (ie, prefrontal cortex, thalamus, parietal lobe, cerebellum, and striatum) have also been implicated in schizophrenia, it is unclear whether limbic structures are involved within the context of a global or a primary or secondary process. We have restricted the scope of the manuscript to structural MRI and DTI studies due to the lack of published work using fMRI in this population. Children and adolescents with schizophrenia tend to have greater genetic loading,[35] a more severe form of the illness,[36] and are likely closer to the upstream brain abnormalities. In addition, the neurodevelopment in children and adolescents with schizophrenia will be contrasted with typical neurodevelopment because differences in the developmental trajectories may provide clues to the upstream abnormalities.

The Limbic System

Information on the neuronal substrates underlying emotional experience and memory has evolved over the past few centuries. The term ''limbic'' (border, *latin*) was used as far back as the 17th century by Willis, then subsequently by the physician and neuroscientist Pierre Paul Broca (1824–1880), who described ''le grand lobe limbique.''[37] Broca's description of the limbic lobe refers to the cortical structures that form a border around the inner structures of the diencephalon and midbrain on the medial surface of the cerebral hemispheres. In 1937, Papez[38] proposed that the limbic lobe is a neural circuit underlying emotional experience and behavior. Later, MacLean[39] proposed a ''limbic system'' that included subcortical structures such as the hypothalamus, the septal area, the amygdala, and the nucleus accumbens, as well cortical areas such as the orbitofrontal cortex. Shortly afterward, Nauta[40] stressed the connectivity of the other components of this system with the hypothalamus. Since then, there have been continued efforts to define the scope of limbic structures with challenges in deciding which components to include and how the limbic networks function to form emotions.[41]

The advent of neuroimaging has brought greater understanding of the neural substrates of emotion and behavior. In the current understanding, the limbic system or the ''emotional brain'' serves a number of functions vital to maintaining survival, quality of life, and sense of self. This network integrates external and internal information and mediates physiological, behavioral, and psychological responses. In this way, limbic function enables self-awareness and creates an understanding of how we relate to the outside world. The elements of this system work together to interpret information from the outside world in relation to primitive drives (eg, hunger, thirst, sex, parenting) and direct behavior to maintain homeostasis in a changing environment.[42] Through its role in the formation of memories and in the integration of memories with physiological sensations and affective states, limbic function leads to emotion-based decisions that allow for adaptation to the environment on the basis of previous experience. Finally, the limbic system encompasses the neural substrates for pleasure and reward, leading to the motivation that ultimately guides our behavior. The different components that make up the limbic system have rich connections, both with other limbic nodes and with distant brain regions, and thus, the functions described above work only in concert with other brain regions.

Many of these functions attributed to the limbic system are key elements affected in individuals with schizophrenia,

and thus, the limbic system may contribute to the symptoms present in these individuals. These elements include positive symptoms, which involve a disruption in both the intrinsic (ie, hallucinations) and extrinsic (ie, delusions) interpretation of sensory stimuli. Negative symptoms, which involve an interference with the rewards of social communication, flattening of affect, and emotional experiences, and, in many respects, a change in the sense of self (ie, "I feel numb" or "I feel like I've lost a part of me"), can also be attributed at least partially to functions supported by limbic system or networks.

Key Components of the Limbic System

The limbic system can be divided into cortical and subcortical limbic regions. The cortical portion of the limbic system ("limbic lobe") includes the hippocampus, parahippocampal gyrus, and the cingulate gyrus. These regions are made up of phylogenetically older cortical tissue, with fewer than 6 layers (allocortex). The extended cortical nodes of the limbic system include the orbital and medial prefrontal cortex. Finally, the subcortical limbic regions include the amygdala, septal nuclei, nucleus accumbens, mammillary bodies, hypothalamus, the anterior nucleus of the thalamus, and the limbic midbrain.

To simplify the discussion of limbic networks, we will limit the scope of this review to the hippocampus, cingulate cortex, amygdala, and the fornix. These limbic structures have all been studied using both structural and DTI in children and adolescents with schizophrenia.

Cortical Limbic Network

The hippocampus is involved with integrating multimodal information and is responsible for the initial formation of declarative memories before information is transferred to other brain regions for storage. The formation of memories is informed by emotional experience, especially via the connections to the amygdala, which leads to an emotional bias in the selection of memories processed into long-term storage.[43–45] The hippocampus is notably sensitive to stress and also constrains responses to biological stress through the hypothalamic-pituitary-adrenal system. In addition, the hippocampus is known for its unusual capability for postnatal neurogenesis.

The parahippocampus receives widespread input from the cortex and is involved in integrating and filtering multimodal information. It is a primary afferent of the hippocampus and has been shown to play a role in formation of spatial memories.

The cingulate gyrus lies directly superior to the corpus collosum and is anatomically part of the limbic lobe, with widespread connections to the frontal lobes. The cingulate cortex regulates both emotional (ventral portion) and cognitive (dorsal portion) processing.[46] The anterior cingulate is involved in error checking, attention, and conflict monitoring (eg, Durston et al[47]). The cingulate cortex is also involved in mood regulation. For example, specific brain regions have been shown to be abnormally active in clinical depression but revert to normal functioning with treatment.[48,49] A functional relationship between the cingulate and amygdala has been proposed in emotional conflict processing,[50] with amygdala function reflecting the level of emotional conflict and the anterior cingulate activity reflecting conflict resolution.

Subcortical Limbic Networks

The amygdala, nucleus accumbens, hypothalamus, and mamillary bodies are considered as subcortical limbic structures. The amygdala is involved in the regulation of emotional reactions. By means of its connections with the hypothalamus, the amygdala modulates autonomic and endocrine activity. Adjacent and highly connected to the hippocampus, the amygdala is very important in the formation of memories.[51] It receives input from the olfactory system, which explains the close association between smells and feelings as well as the ability of certain scents to elicit vivid memories. The amygdala is thought to be involved in aggression, jealousy, and fear. Animal studies have shown that when stimulated, this area produces a rage reaction, while lesioning induces docility. Human functional imaging studies have consistently shown amygdala activation in response to fear and anger.[52,53]

The Limbic Midbrain

The limbic midbrain refers to the reticular formation, which receives input from the hypothalamus and septal nuclei. This area includes nuclei that are the source of the key neurotransmitters implicated in many emotional and cognitive processes. The raphe nuclei, which produce serotonin, project to widespread areas of the central nervous system. The frontolimbic projections are thought to be particularly important in mood regulation and memory processing.[54–56] The ventral tegmental area, which produces dopamine, projects to frontolimbic areas and is thought to be crucial for emotional and cognitive processing. The locus coeruleus produces norepinephrine, projects to similar areas, and is thought to modulate attention and arousal. The descending pathways of the locus coeruleus connect with nuclei in the pons and medulla (ie, to cranial nerves controlling affective expression). These descending pathways also connect with parasympathetic nuclei controlling autonomic functions influenced by emotion.

Neurocircuitry of the Limbic System

Major white matter tracts interconnecting the limbic structures include the fornix, the mammillothalamic

tract, the cingulum bundle, the medial forebrain bundle, and the stria terminalis. The fornix connects the hippocampus with the septal region and the mammillary nucleus of the hypothalamus. Portions of the fornix link up with the mammillothalamic tract, which connect the mammillary bodies to various thalamic nuclei. The cingulum bundle connects cingulate gyrus with parahippocampus. The medial forebrain bundle interconnects the septal region, the hypothalamus, and the limbic midbrain. This pathway contains many serotonergic, dopaminergic, and noradrenergic fibers from the basal nuclei to the forebrain. The stria terminalis provide the dorsal connection between the amygdala, the hypothalamus, and the septal region. These structures are also interconnected by the ventral amygdalofugal pathway.

Cortical areas thought of as extended nodes of the limbic system include the orbitofrontal cortex and the medial prefrontal cortex, which are referred to as the "limbic forebrain."[51] The orbitofrontal cortex is important for integrating sensory information and making emotion-based decisions. The prefrontal cortex has reciprocal connections that regulate the lower limbic structures, which is an important neural relationship in behavioral inhibition. For example, descending projections to the nucleus accumbens exert regulatory control over reward-seeking behavior.[51] Finally, the memory performance has been shown to be either enhanced or worsened based on emotional experiences attributed to the function of the amygdala.[57,58] These findings highlight the connectivity between limbic and prefrontal brain regions.

Development of the Limbic System

The vast majority of limbic system development occurs before birth. At approximately 6 weeks of gestational life, the hippocampal formation appears along the mediadorsal region of the telencephalon and is the first cortical region to differentiate.[59] The anterior portion of the hippocampus and the hippocampal fissure precede development of the posterior region,[60] and by 10 weeks gestational age, much of the temporal lobe consists of the hippocampus. The parahippocampal gyrus and the uncus undergo considerable expansion starting at 16 weeks, such that by 18 weeks their volume exceeds that of the hippocampus.[59] There is little information regarding postnatal development of the limbic system.

The gross morphology of the hippocampus attains adult characteristics by 30 weeks gestational age.[61] The hippocampus has been shown to change little in volume during late childhood and adolescence,[62,63] although specific morphologic changes do take place. Between the ages of 4 and the mid-20s, the hippocampus has been shown to undergo enlargement of the posterior aspect with a reduction of anterior region.[64] In addition, specific white matter pathways in the hippocampus continue to myelinate during adolescence.[65]

While developing later than the hippocampal formation, the amygdala largely completes its structural development by birth.[66] However, the volume of the amygdala continues to increase well into adolescence.[67] While the majority of myelination is completed during the first 4 years of life,[34] continued myelination has been shown in tracts connecting limbic structures with other brain structures.[65,68]

Neuroimaging of Limbic Structures

Structural Imaging of the Limbic System in Early-Onset Schizophrenia

The majority of neuroimaging studies that examined nodes within the limbic system in children and adolescents with schizophrenia utilized structural MRI (see table 1). Methodological approaches have varied between the different research groups, such as differences in MRI sequences, image resolution, and postprocessing of the images. Postprocessing algorithms tend to take one of 3 forms: region of interest,[62,69,71] voxel-based,[23] or surface-based approaches.[24,75] The region of interest approach, although time consuming for nonautomated algorithms, takes into account intersubject variability and thus traditionally has been the gold standard for volume measurements. Voxel-based approaches warp brains into a standard stereotactic space, apply spatial filters to account for structural variability, and perform groupwise statistics on a voxel-by-voxel basis while correcting for multiple tests. Finally, surface-based approaches derive measures of cortical thickness or gray matter volume by utilizing sulcal or gyral patterns to constrain the measurement.[79] Rather than yielding volume measures, surface-based approaches yield measures of cortical thickness, surface area, and measures of sulcal and gyral curvatures.

One of the earliest studies of the limbic system in children and adolescents with schizophrenia appeared as a part of a longitudinal study of childhood-onset schizophrenia (COS) at the intramural program of the National Institute of Mental Health (NIMH).[80] A cross-sectional study in their group of patients with COS revealed no patient/control differences in the volume of the amygdala or hippocampus but an increased volume of the total and posterior superior temporal gyrus.[69] A subsequent cross-sectional study of the same cohort found no temporal lobe volume differences between patients, controls, and a group with psychotic disorder not otherwise specified.[73]

In a 2-year follow-up study of the same group, the COS patients had a significantly greater reduction in temporal lobe structures compared with controls.[71] When not controlling for intracranial volume (ICV), gray matter volume reductions were found in the right temporal lobe, bilateral superior temporal gyrus, posterior superior temporal gyrus, right anterior temporal gyrus, left hippocampus, and the amygdala. Because patients with schizophrenia

Table 1. Studies of Temporal Lobe Structures, Neurochemicals, or Microstructure in Children and Adolescents With Schizophrenia

Studies	*n* Scz/Ctrls	Mean Age (Range)	Imaging Modality	Approach	Findings
Jacobsen et al[69]	21/41	14.6 y	Structural	ROI	Patients lacked the typical right greater than left asymmetry of the hippocampus. No volume difference in hippocampal or amygdala volume between patients and controls.
Bertolino et al[70]	14/14	16.4 y	Structural	H-MRSA	Patients had decreased NAA/creatine ratios in the hippocampal regions bilaterally.
Jacobsen et al[71]	10/17	15.2–17.4	Structural	ROI	Patients demonstrated decreases greater than controls in the superior temporal gyrus and in the left hippocampus.
Giedd et al[62]	42/74	14.4 y	Structural	ROI	Patients had a nonlinear decline in hippocampal volume compared with controls. The decline reached a plateau as the children reached early adulthood.
Friedman et al[72]	20/16		Structural	ROI	Patients demonstrated increased CSF in the sulci of the temporal lobes, implicating smaller temporal lobe volume and gray matter loss.
Kumra et al[73]	44/64	14.4 y	Structural	ROI	No difference in temporal lobe volumes between patients and controls with schizophrenia
Levitt et al[74]	13/20	14.2 y (8.6–20)	Structural	ROI	Patients had significantly larger amygdala volumes compared with controls. No difference in hippocampal volumes.
Thompson et al[23]	12/12	13.9 y	Structural	Voxel based	Patients had like a longitudinal loss of gray matter loss that started in the parietal lobes and moved into the medial temporal lobes with age.
White et al[75]	42/24	17.7 y (12–19)	Structural	Surface based	Patients had a decrease in cortical thickness in both the gyral and sulcal regions of the temporal lobe.
Marquardt et al[76]	13/18	12.0 y (6–17)	Structural	ROI	Patients had an age-related decrease in the volume of the anterior cingulate. The patients also had differences in lateralization.
Kumra et al[77]	26/34	15.2 y	DTI	Voxel based	Patients had a decrease in FA of the left anterior cingulate.
Vidal et al[24]	12/12	14.1 y	Structural	Surface based	Patients had a decrease in gray matter in the cingulate cortex, with relative sparing of the limbic system.
White et al[78]	15/15	15.2 y (9–19)	DTI	Voxel based	Patients had a decrease in FA in the left posterior hippocampus.
Nugent et al[63]	29/31	14.6–24.4	Structural	ROI	Patients had an approximate 9% decrease in hippocampal volume and also underwent different morphological changes over time.
Kendi et al (submitted)	15/15	15.2 y (9–19)	Structural and DTI	ROI	Patients had a smaller fornix volume without differences in FA or AD.

Note: Scz/Ctrls, schizophrenic patient/control; ROI, region of interest; H-MRSA, hydrogen magnetic resonance spectroscopic imaging; NAA, N-acetylaspartate; CSF, cerebral spinal fluid; DTI, diffusion tensor imaging; FA, fractional anisotropy; AD, average or mean diffusivity.

have smaller ICV, these findings may represent more global brain volume changes.

The longitudinal findings in the NIMH cohort were extended by an NIMH/University of California Los Angeles (UCLA) collaboration that applied novel, voxel-based approaches to the NIMH longitudinal COS subjects.[23] These voxel-based approaches demonstrated a wave of gray matter loss in the COS group that progressed from parietal regions into the posterior temporal lobes and anterior cingulate.

Further support for a decrease in temporal lobe volume in adolescents with schizophrenia comes from a finding of increased sulcal fluid in the temporal lobe of adolescents with schizophrenia.[72] Finally, cortical thickness of temporal lobe gray matter was shown to be reduced in an independent sample of children and adolescents with schizophrenia compared with an age-matched control group.[75]

Findings from studies of hippocampal volumes in children and adolescents are mixed. Two cross-sectional studies of hippocampal volumes in COS subjects yielded no patient/control differences.[69,74] Two of the 3 longitudinal studies of hippocampal volume from the same NIMH cohort demonstrated no patient/control volume differences at time 1 in the study. However, there was an average of 14% reduction in hippocampal volume in patients over a 2-year period.[62,71] A recent study from the National Institutes of Health/UCLA collaboration on the COS cohort assessed morphologic changes along the length of the hippocampus and found smaller hippocampi in patients both at time 1 (mean age 14 years) and at time 2 (mean age 24.4 years).[63] Nugent et al[63] reported changes along the length of the hippocampus, without an age by volume interaction. Overall, the adult studies of schizophrenia show an average hippocampal volume loss of approximately 5%.[81,82]

Summarizing the structural imaging studies in children and adolescents with schizophrenia, there is a question whether the limbic system is spared from volume loss early in the course of the illness. However, since individuals at high-risk showed early reduced volumes of the hippocampus[79], additional longitudinal studies of individuals at risk will help tease apart the role of the hippocampus and other limbic structures in those who convert to schizophrenia.[83] One limitation of these studies is that there are only a small number of groups performing this work and several of the sites have overlapping participants, some who are quite ill. This may limit the generalizability of the studies, and replication of these findings at different sites will strengthen the findings.

Newer methodologies, with higher imaging resolution and more advanced image processing algorithms, may be able to detect more subtle changes earlier in the illness. However, even with the older methodologies, the current literature suggests that once the children and adolescents with schizophrenia progress to adulthood, they display the same neurobiological abnormalities seen in adults.

DTI of the Limbic System in Early-Onset Schizophrenia

DTI has properties that allow for high-resolution in vivo measurements of the coherence of neuronal fibers.[84] While it is often used to study myelinated neuronal fiber bundles, it also is a valid measurement of nonmyelinated fibers that traverse in the same direction. One of the primary outcome measures in DTI studies is fractional anisotropy (FA), which can provide a measure of the integrity of white matter. DTI is prone to susceptibility artifacts that are caused by air/tissue, such as between the air in the sinuses or orbital frontal cortex. These artifacts are similar to those seen in functional MRI and are especially pronounced in the anterior temporal and orbitofrontal regions of the brain, complicating DTI studies of these regions.

There are 4 published studies to date that utilized DTI in samples of children and adolescents with schizophrenia.[73,78,85,86] Whereas the first study utilized an ROI approach that did not measure specific limbic regions,[85] the subsequent 3 studies, which 2 had independent samples,[77,78] utilized voxel-based approaches and demonstrated significant patient-control differences within limbic networks, namely the anterior cingulate[77] and the hippocampus.[78] In addition, by adding 10 subjects to the group studied by Kumra et al,[77] Serene et al[86] found additional regions of lower FA in early-onset schizophrenia, including the parahippocampal gyrus.

A summary of DTI studies in children and adolescents with schizophrenia demonstrates disrupted connectivity in regions of the left anterior cingulate,[77] left hippocampus,[78] and the left hippocampal gyrus.[86] These results are consistent with those of similar studies of DTI in adults with schizophrenia.[87–91] These studies are limited by relative small sample sizes and potential artifacts related to structural heterogeneity between the patient and control groups.

Because the finding of decreased FA in the posterior hippocampus raised questions as to the integrity of connecting pathways with this region,[78] an ROI study was conducted on the same subjects who demonstrated hippocampal abnormalities to measure the volume and white matter integrity of the fornix, the major efferent pathway from the hippocampus (Mustafa Kendi, Ayse Tuba Karagulle Kendi, Stephane Lehericy, et al, submitted). Interestingly, there was a reduction in the volume of the fornix without a significant decrease in FA between patients and controls, suggesting the possibility that an early disruption in the hippocampus may alter the number of white matter fibers emanating from the hippocampus and connecting to the mammillary bodies and thalamus. Alternatively, 15 subjects may lack the power necessary to show significant differences, especially

because the voxel resolution used in the DTI analyses (2 × 2 × 2 mm) is considerably lower than that obtained using our high-resolution structural imaging sequence (0.625 × 0.625 × 1.5 mm).

Studies in adults with schizophrenia have shown decreases in both the FA and cross-sectional area of the fornix.[88,90] Thus, longitudinal assessments of the integrity of the fornix will be important to evaluate the developmental trajectory of these limbic networks. Because a number of studies of adults with schizophrenia demonstrate global changes in white matter microstructure,[92,93] one possibility is that white matter changes are more focal in children and adolescents and that abnormalities increase with a longer duration of illness. Whether these white matter differences are a primary disruption in schizophrenia or a downstream process will require further exploration.

Postmortem Studies of Limbic Structures in Schizophrenia

Postmortem studies are the gold standard for evaluating the histology of anatomic connectivity between brain regions. These studies are challenging and time consuming. They also have the obvious limitation of the inability to examine dynamic changes in the living brain. Nevertheless, they provide important data on cell count, size, and the neural pathways between regions. Postmortem studies in schizophrenia rely on older, chronic patients with multiple confounding variables (eg, medication duration or chronic medical conditions). Considerable work has been done to define an exhaustive database of the neural pathways in the macaque[94]; however, no similar database exists for humans. There are no postmortem studies of children and adolescents with schizophrenia.

One of the more consistent patient/control differences in adult postmortem studies of schizophrenia is found in the hippocampus.[95–98] Studies have demonstrated a reduction in volume,[96] a decrease in neuronal numbers,[95,98,99] altered neurocircuitry,[100,101] white matter abnormalities,[102] and a decrease in the size of the neurons.[103,104] Not all studies demonstrate a reduction in hippocampal volume [105,106] or a decrease in neuronal number,[102,103] although this does not exclude the possibility of histological changes in cellular structures.[107]

Other limbic structures implicated in postmortem studies of schizophrenia include regions of the cingulate cortex and amygdala. Studies of the cingulate cortex have shown a reduction in neuronal number[108] and a reduction in the number and orientation of interneurons.[108,109] Interestingly, alterations in specific neuronal fiber orientations (ie, interneurons) may allow specific structures to be identified utilizing DTI described below. Finally, postmortem studies in patients with schizophrenia have also shown volume reductions in the parahippocampal gyrus[105,110] and the amygdala.[96]

Discussion

An interesting but difficult question concerns the nature of the relationship between pathology in the limbic system and the clinical presentation of schizophrenia. Based on its function and extensive afferent and efferent projections to multiple brain regions, symptoms ranging from flattened affect, hallucinations, altered emotional responses, apathy, and cognitive changes could all be easily subsumed under the rubric of limbic dysfunction.[18] Although lesions or abnormalities of specific limbic structures or pathways do not explain the full spectrum of clinical symptoms present in schizophrenia, they have been shown to correlate with positive symptoms.[111,112] For example, there are numerous studies linking medial temporal lobe volume or function to the positive symptoms of schizophrenia.[113–116]

Thus, the functions subsumed by the limbic system, coupled with the numerous studies showing aberrations in limbic structures and networks in schizophrenia, make it difficult to exclude a limbic role in the pathophysiology of schizophrenia. However, the majority of studies evaluate the neurobiology of schizophrenia after the onset of clinical symptoms. Thus, it is difficult to determine if limbic pathology plays a primary role in the genesis of schizophrenia or is a secondary, downstream process of the illness. If primary, the etiology may not be specific to limbic networks but encompass global brain processes that involve many brain regions (ie, myelination). Such a global insult would provide a rationale for the myriad of brain regions involved in the illness.

Alternatively, the limbic system could be secondarily affected by an insult that involves focal cortical or subcortical regions. In such a scenario, an aberration or insult occurring early in development could disrupt downstream connectivity. Brain insults that have no apparent initial effects can adversely alter later neurodevelopmental processes.[117] For example, rats with lesions to the hippocampus or amygdala show specific deficits that vary with the age at which the lesion was performed.[118,119] Not only could such a situation also occur in humans, but variations in the timing or nature of the insult, coupled with genetic liability, may contribute to the heterogeneity of the illness. Interactions between genetic and environmental toxins, such as cannabis, may also have differential effects that interact with age-critical neurodevelopmental processes.[22]

One integrating theory of schizophrenia involves a primary insult to the hippocampus.[18,120] This theory posits that an insult to the hippocampus result in downstream effects on limbic circuits. These insults propagate through the anterior cingulate and thalamus to other cortical regions. The primary factors in the illness may be related to NMDA function,[115,121–123] altered dopaminergic activity,[120] abnormal interneuron development,[107,109] an early migration of interneurons from the medial ganglionic

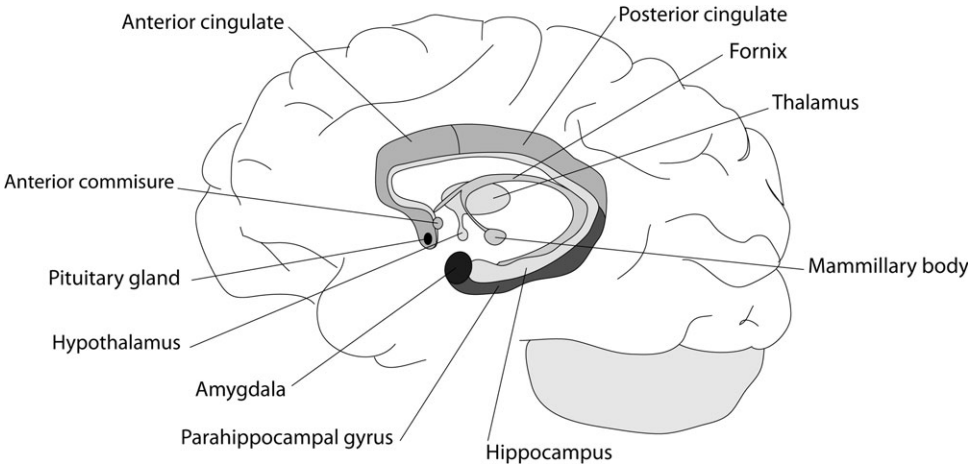

Fig. 1. Main Structures Within the Limbic System.

eminence,[124] or to a disruption in the myelination of critical pathways.[17,65,78]

While a primary insult to the hippocampus is certainly a possibility, an alternate theory is that the primary insult involves either localized regions of the prefrontal cortex or an insult to the pathways connecting prefrontal with distant brain regions.[7,9,125,126] This theory is supported by studies in children and adolescents with schizophrenia that demonstrate prefrontal abnormalities.[23,24,62,127] In addition, prefrontally mediated functions continue to develop into adolescence.[128,129] Finally, association cortices, such as the prefrontal cortex, have an extended period of myelination, through adolescence and into young adulthood.[34,130,131]

One perplexing question is how an early insult to a vulnerable individual might remain dormant, becoming unmasked in the clinical presentation of schizophrenia during late adolescence and early adulthood. Studies evaluating typical brain development during the age of risk for schizophrenia may be helpful in implicating specific networks or regions. Brain regions that show the greatest dynamic change over this period of development are more likely to be involved in the "unmasking." This is in contrast to regions that have an earlier developmental trajectory and thus relatively more static in relation to development. With this in mind, 2 possible "unmasking" processes include regional aberrations in synaptic pruning [27] and myelination.[65]

Synaptic pruning is thought to be one process reflected in gray matter decreases seen in structural MRI studies. Structural imaging techniques have found dramatic decreases in gray matter volume during typical development between childhood and adulthood.[31,32,132–135] These changes include decreases in gray matter within the medial temporal lobe.[135] More pronounced gray matter decreases, including those in nodes of the limbic system, occur in children and adolescents with schizophrenia.[23,24,62,72,127] Cortical thickness has also been shown to be reduced in measures of the temporal lobe in children and adolescents with schizophrenia.[75] While it is not clear if these gray matter changes are primary or secondary processes of the illness, there is support for greater differences in structures that show more dynamic changes during the age of risk of schizophrenia.

Alternatively, while myelination is mostly complete by 4 years of age, it continues into early adulthood.[34,130,135] Not only have specific neural connections within the limbic system been shown to myelinate during adolescence,[65] but schizophrenia has been shown to be associated with downregulation of myelin-related genes.[17] Because females on average have earlier rates of myelination than males,[131] disruption in myelination of key areas would predict an earlier age of onset in females, which is not the case. It is possible that differential rates between boys and girls in age-related changes in the volumes of limbic structures[132] may have a sex-related influence in the onset of schizophrenia.

In conclusion, there is considerable evidence that specific nodes within the limbic system are abnormal in children and adolescents with schizophrenia. What is less clear is the time course for emergence of these deficits and the specificity of these abnormalities in children and adolescents with schizophrenia. Both structural and diffusion imaging studies in children and adolescents with schizophrenia support the presence of abnormalities in limbic structures, although it is unclear if these changes are secondary to an underlying primary insult. Decreases in the volume of limbic structures may become progressively smaller throughout adolescence,[62,71] perhaps as a result of early microstructural abnormalities that are present early in the course of the illness.[78]

Teasing apart primary from secondary processes is a challenge. Studies of high-risk populations, including samples that include genetic high-risk populations (ie, offspring of individuals with schizophrenia or individuals with 22q11.2 deletion syndrome) may be the most

productive approach to address this question. Studies of those who are already exhibiting symptoms (ie, behaviorally at risk) may already be showing downstream effects of the primary process, although they would certainly be closer to the primary process. Future work involving the longitudinal tracking of individuals at increased risk may help tease apart the role of the limbic system as a primary or downstream abnormality in the neurobiology of the schizophrenia.

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