Thomas Jefferson University and Hospital

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Report on FDG PET brain scan on Robert Bowers (DOB 09/04/1972)

SCAN DATE: 11/19/2021

REPORT DATE: 06/09/2022

History:

A PET scan was performed at UPMC Magee Womens Hospital in Pittsburgh, Pennsylvania on November 19, 2021. At the time of the scan, Mr. Bowers was 49 years old. He is a white male with a current clinical diagnosis of schizophrenia and epilepsy and no known history of head injuries. I was asked to read the PET scan, to interpret the results, and to assess the relevance of the findings to Mr. Bowers' diagnosis of schizophrenia.

Technique:

A brain PET scan was provided which was performed with the injection of 10.16 mCi of FDG using a standard imaging protocol. A qualitative assessment was performed and quantitative analysis of individual brain structures were determined to assess metabolic activity (which is primarily associated with neuronal activity in the gray matter) in approximately 70 regions (with left and right evaluated for structures in both hemispheres). The quantitative analysis was performed using the MIMneuro software program, an FDA approved quantitative analysis software program that compares the patient's scan to a normative database of PET scans from a group of age matched healthy controls.

Findings:

The PET scan is of excellent quality. Visual and quantitative analysis reveals abnormal areas of significantly decreased metabolism in parts of the cerebellum, the hypothalamus, brain stem and pons, as well as the right caudate, right parahippocampus and right medial temporal lobe, and the left amygdala. As detailed in the chart below, significant metabolic abnormalities are indicated where metabolism is 1.65 standard deviations above or below the population mean (as per the MIMneuro software program manual). There is also significant abnormally increased metabolism in several frontal regions including the medial frontal gyrus, middle frontal gyrus, and rectal gyrus. There is also abnormally increased metabolism in the left superior temporal gyrus and right subcallosal region. It should be noted that for all homologous regions, 11 have right more than left metabolism while 52 have left more than right metabolism suggesting a marked hemispheric asymmetry.

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Impression:

Overall, the findings show brain areas of both abnormally increased and decreased metabolism. Typically, areas of abnormally increased metabolism reflect inflammation or a persistent excitatory state in the brain. Areas of abnormally decreased metabolism reflect neuronal injury and dysfunction.

There is abnormally decreased metabolism in the right caudate nucleus which is involved in several brain processes, including regulation of motor/movement function and various cognitive processes, including memory, learning, and emotional response regulation. Since the caudate is part of the dopamine system, it is part of the reward system of the brain that helps a person to feel motivation, desire, and craving. Given the abnormal metabolism in the right caudate, there would be expected dysfunction in these processes.

Abnormally decreased metabolism in the hypothalamus, brain stem, and pons are associated with poor regulation of the autonomic nervous system and the natural fight or flight response. Abnormalities in these structures can be associated with inappropriate stress response, excessive reactions and misperceived threats.

Abnormally decreased metabolism in the amygdala and parahippocampus are associated with unusual emotional responses and emotional dysregulation. Impaired assessment of the environment and misperception of threats, and initiating responses to perceived threats are also associated with dysfunction in these regions

Abnormally decreased metabolism in the cerebellum is linked to impaired motor coordination, but also error processing and learning. In addition, cerebellar abnormalities are increasingly linked to traumatic memories and dysregulated emotions.

Abnormally increased metabolism in the frontal regions is associated with problems with concentration or attention, information processing speed, organizing and planning, impaired abstraction, impaired initiation or generation of thoughts and concepts, impaired theory of mind, social cognition dysregulation, and are also associated with emotional dysregulation. Given the increased metabolism in the frontal lobes, frontotemporal dementia is not likely.

Abnormally increased metabolism in the left medial temporal lobe can be associated with impaired memory, abstract reasoning, and a variety of delusions including religious delusions.

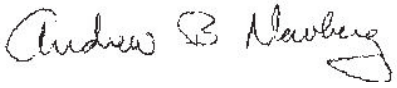
Overall Impression

There are a number of metabolic abnormalities on this PET scan. When there are a large number of brain areas that have abnormal metabolism and asymmetries, the findings are consistent with extensive clinical abnormalities including emotional regulation impairment, cognitive and motor processing problems, and psychotic symptoms. This patient carries the clinical diagnosis of

schizophrenia, a complex disease that has both positive and negative symptoms that are associated with multiple brain abnormalities. For example, schizophrenia has been associated with significantly abnormal asymmetries in the brain, often with the right sided structures less active than the left, as is observed with this patient. In addition, there is recognition of dysfunction in the limbic system, frontal lobes, and striatum in patients with schizophrenia, all of which are abnormal in this patient.

All opinions expressed herein are held to a reasonable degree of medical certainty.

Sincerely,



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Quantitative Results from MIMneuro Software Analysis: The scores represent the patient's metabolic value compared to a database of normal controls (provided by the software program). The Z-score refers to standard deviations above or below the mean of the normal controls for each region and where appropriate, left and right hemispheres (as well as the difference between the hemispheres). The MIMneuro software uses 1.65 standard deviations above or below the mean as being considered abnormal. The MIMneuro software manual states that brain region abnormalities are statistically significant when they are 1.65 standard deviations or further from the mean of the normals (corresponding to a 95% statistical significance level).

Structure	Z-Score	L Z-Score	R Z-Score
Hypothalamus	-2.67	N/A	N/A
Inferior Occipital Gyrus	-2.22	-1.69	-1.93
Inferior Cerebellar Peduncle	-2.12	-1.65	-2.33
Brain Stem	-1.90	N/A	N/A
Middle Cerebellar Peduncle	-1.85	-1.57	-1.98
Pons	-1.73	N/A	N/A
Amygdala	-1.70	-2.30	-1.07
Medulla	-1.67	N/A	N/A
Caudate	-1.44	-1.18	-1.73
Midbrain	-1.44	N/A	N/A
Temporal Operculum	-1.41	-1.11	-1.37
Superior Cerebellar Peduncle	-1.33	-1.20	-1.35
Parahippocampal Gyrus	-1.21	-0.55	-1.70
Medial Temporal Lobe	-1.17	-0.51	-1.67
Hippocampus	-1.03	-0.39	-1.47
Postcentral Gyrus	-0.99	-1.23	-0.58
Superior Occipital Gyrus	-0.96	-0.80	-0.98
Globus Pallidus	-0.86	-0.65	-1.05
Occipital Lobe	-0.79	-0.54	-1.02
Fusiform Gyrus	-0.77	-0.58	-0.82
Cerebellar Vermis	-0.63	N/A	N/A
Cerebellum	-0.62	N/A	N/A
Cerebellar Hemisphere	-0.60	-0.46	-0.73
Putamen	-0.57	-0.27	-0.82
Cuneus	-0.53	-0.31	-0.72
Pontine Tegmentum	-0.51	N/A	N/A
Supramarginal Gyrus	-0.44	0.12	-1.04
Middle Occipital Gyrus	-0.38	-0.20	-0.48
Paracentral Lobule	-0.37	-0.59	-0.08
Primary Visual Cortex	-0.35	-0.14	-0.57

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Thalamus	-0.30	-0.45	-0.11
Nucleus Accumbens	-0.23	0.03	-0.56
Lingual Gyrus	-0.20	0.05	-0.36
Superior Parietal Lobule	-0.20	-0.27	-0.10
Inferior Temporal Gyrus	-0.18	0.28	-0.61
Anterior Orbital Gyrus	-0.16	0.18	-0.51
Insula	-0.14	-0.30	0.09
Parietal Lobe	-0.01	0.00	-0.03
Angular Gyrus	0.00	-0.16	0.19
Middle Temporal Gyrus	0.09	0.49	-0.22
Precentral Gyrus	0.29	0.88	-0.31
Temporal Lobe	0.35	0.86	-0.28
Inferior Frontal Gyrus, Pars Triangularis	0.44	0.67	0.24
Inferior Frontal Gyrus, Pars Opercularis	0.45	0.52	0.31
Anterior Cingulate Gyrus	0.51	0.50	0.51
Heschl Gyrus	0.59	0.28	0.81
Posterior Cingulate Gyrus	0.62	0.95	0.30
Retrosplenial Area	0.63	0.97	0.22
Inferior Frontal Gyrus	0.63	0.83	0.43
Lateral Temporal Lobe	0.64	1.06	0.05
Cingulate Gyrus	0.67	0.81	0.47
Middle Orbital Gyrus	0.70	1.08	0.21
Precuneus	0.85	1.19	0.26
Medial Orbital Gyrus	0.87	0.89	0.78
Lateral Orbital Gyrus	0.90	1.27	0.17
Orbitofrontal Region	1.00	1.34	0.54
Superior Temporal Gyrus	1.29	1.58	0.63
Inferior Frontal Gyrus, Pars Orbitalis	1.33	1.69	0.91
Temporal Pole	1.33	1.22	1.16
Rolandic Operculum	1.39	1.00	1.29
Posterior Orbital Gyrus	1.45	1.93	0.83
Subcallosal Area	1.57	1.40	1.67
Gyrus Rectus	1.87	2.14	1.62
Superior Frontal Gyrus	1.88	2.04	1.46
Middle Frontal Gyrus	1.90	2.20	1.36
Supplementary Motor Area	2.22	2.46	1.69
Inferior Medial Frontal Gyrus	2.32	2.86	1.63
Frontal Lobe	2.33	2.70	1.79
Olfactory Cortex	2.76	3.50	1.68
Superior Medial Frontal Gyrus	3.21	3.09	3.05

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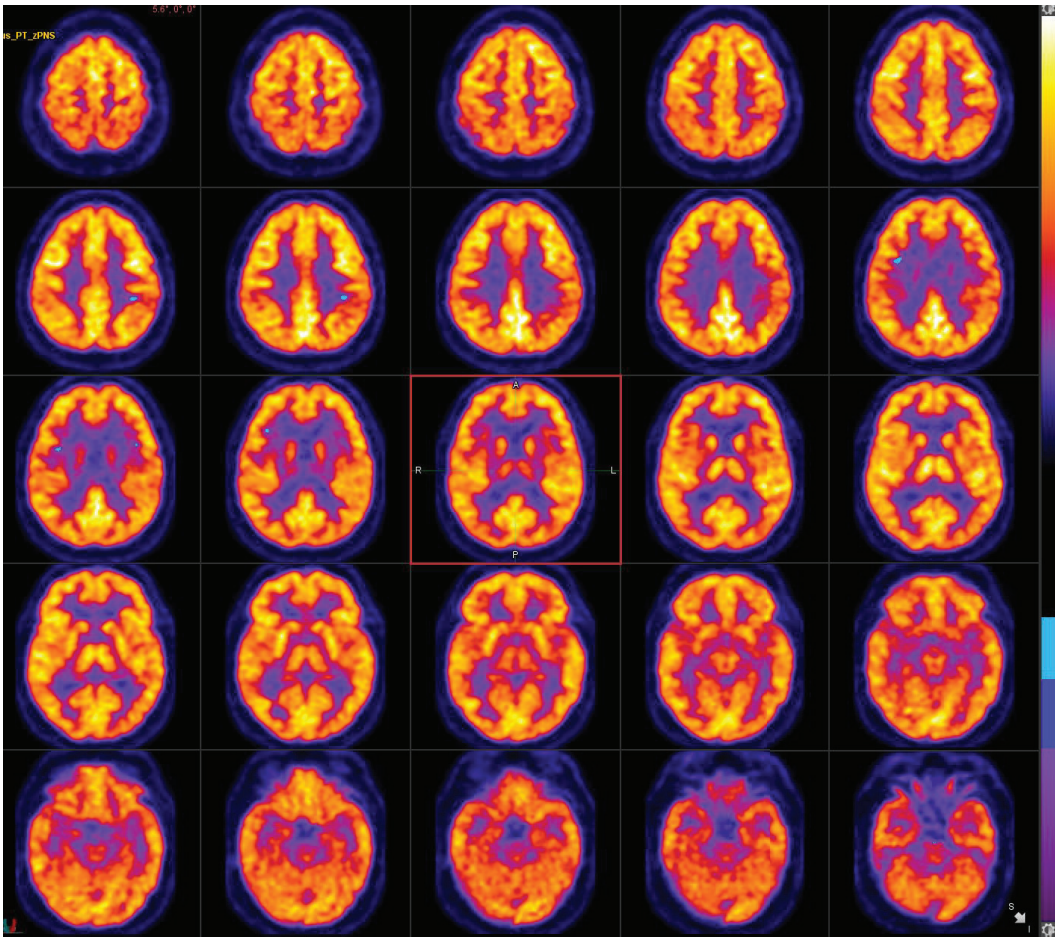
The figure below is a screen capture of the images as displayed in the MIMneuro software.



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References:

Shinto, et al. "Hyperfrontality" as seen on FDG PET in unmedicated schizophrenia patients with positive symptoms. Clin Nucl Med. 2014;39(8):694-7. doi: 10.1097/RLU.0000000000000502.

Abstract

Introduction: Decreased frontal activity has been reported widely in unmedicated schizophrenic patients with predominantly negative symptoms. Not many studies have assessed the frontal lobe status in unmedicated patients with positive symptoms.

Patients and methods: Fifty-one patients with schizophrenia (all unmedicated, 38 never medicated) and 12 healthy age-matched controls were evaluated with FDG PET CT. The patients met ICD-10 and DSM-IV criteria for schizophrenia, and all reported psychotic, "positive" symptoms when tested.

Results: Schizophrenic patients with positive symptoms had a hypermetabolic frontal metabolic pattern on quantification by region to occipital ratio comparison. Associated statistically significant differences were also found when comparing ratios of occipital to thalamic, striatal and temporal cortex in schizophrenic patients.

Conclusion: The finding of a hyperfrontality in unmedicated and never medicated psychotic schizophrenic patients is observed when there is a predominance of positive symptoms. There could be a possible disruption of cortico-striato-thalamic feedback loops causing hyperfrontality as seen in experimentally induced models of psychosis.

Soyka, et al. Hypermetabolic pattern in frontal cortex and other brain regions in unmedicated schizophrenia patients. Results from a FDG-PET study. Comparative Study Eur Arch Psychiatry Clin Neurosci. 2005;255(5):308-12. doi: 10.1007/s00406-005-0563-0.

Abstract

We report results of a FDG-PET study in 10 patients with schizophrenia (6 unmedicated, 4 never medicated) and 12 healthy age-matched controls. The patients met ICD-10 and DSM-IV criteria for schizophrenia and all reported psychotic, "positive" symptoms when tested. Schizophrenic patients had higher absolute CMRGlu values in almost all quantified regions compared to normal subjects. Using the occipital cortex as the reference region patients showed a hyperfrontal metabolic pattern. Other significant regional differences were found with respect to thalamus, striatum and temporal cortex. The finding of a hyperfrontality in un- and never medicated

psychotic schizophrenic patients must be discussed in the light of the psychopathological symptoms of patients when tested, a possible disruption of cortico-striato-thalamic feedback loops and recent findings of a hyperfrontality in experimentally induced psychosis (ketamine- and psilocybin-model of schizophrenia).

Seethalakshmi, et al. Regional brain metabolism in schizophrenia: An FDG-PET study. Indian J Psychiatry. 2006;48(3):149-53. doi: 10.4103/0019-5545.31577.

Abstract

Background: Recent technological advances have established beyond any doubt the biological nature of schizophrenia. Functional neuroimaging using FDG-PET forms an important technique in understanding the biological underpinnings of psychopathology of schizophrenia.

Methods: Eighteen male patients diagnosed as having schizophrenia and having active psychosis as determined by PANSS were subjected to FDG-PET scanning under resting conditions. The glucose uptake in selected regions of interest was studied across the spectrum of schizophrenia.

Results: Chronicity and severity of illness did not influence cerebral glucose metabolism. Participants with negative schizophrenia had significantly decreased metabolism in all regions of the brain as compared to the positive type. The positive syndrome of schizophrenia was associated with significantly increased glucose metabolism in the medial temporal regions, basal ganglia and left thalamic regions. Hypometabolism was also noted in the cerebellum.

Conclusion: While a number of brain areas can be identified as potential causative regions and hypotheses regarding putative mechanisms can be formed, the considerable heterogeneity of schizophrenia poses a great challenge in the precise delineation of the disease process.

Gur and Chin. Laterality in functional brain imaging studies of schizophrenia. Schizophr Bull. 1999;25(1):141-56. doi: 10.1093/oxfordjournals.schbul.a033361.

Abstract

Brain laterality in schizophrenia has been examined through the application of functional neuroimaging methods. These methods have included the 133Xenon technique for measuring cerebral blood flow (CBF); positron emission tomography for assessing rates of glucose metabolism, CBF, and neuroreceptor functioning; single photon emission computerized tomography for studying CBF and neuroreceptors; and functional magnetic resonance imaging for measuring changes attributable to CBF. This article highlights the application of this technology in schizophrenia research, emphasizing more recent studies that have evaluated hemispheric differences. There is evidence for lateralized abnormalities in some studies that have

examined this dimension. In general, the results implicate abnormalities in left hemispheric activity. Recent advances in basic and clinical neuroscience provide an opportunity for focused application of functional imaging in neurobiological studies of schizophrenia.

Siegel, et al. Cortical-striatal-thalamic circuits and brain glucose metabolic activity in 70 unmedicated male schizophrenic patients. Am J Psychiatry. 1993;150(9):1325-36. doi: 10.1176/ajp.150.9.1325.

Abstract

Objective: The cortical-striatal-thalamic circuit modulates cognitive processing and thus may be involved in the cognitive dysfunction in schizophrenia. The imaging of metabolic rate in the structures making up this circuit could reveal the correlates of schizophrenia and its main symptoms.

Method: Seventy male schizophrenic patients underwent [18F]-fluorodeoxyglucose positron emission tomography after a period of at least 4 weeks during which they had not received neuroleptic medication and were compared to 30 age-matched male normal comparison subjects.

Results: Analyses revealed decreased metabolism in medial frontal cortex, cingulate gyrus, medial temporal lobe, corpus callosum, and ventral caudate and increased metabolism in the left lateral temporal and occipital cortices in the schizophrenic cohort. Consistent with previous studies, the schizophrenic group had lower hypofrontality scores (ratios of lateral frontal to occipital metabolism) than did comparison subjects. The lateral frontal cortical metabolism of schizophrenic patients did not differ from that of comparison subjects, while occipital cortical metabolism was high, suggesting that lateral hypofrontality is due to abnormalities in occipital rather than lateral frontal activity. Hypofrontality was more prominent in medial than lateral frontal cortex. Brief Psychiatric Rating Scale (BPRS) scores, obtained for each schizophrenic patient on the scan day, were correlated with regional brain glucose metabolic rate. Medial frontal cortical and thalamic activity correlated negatively with total BPRS score and with positive and negative symptom scores. Lateral frontal cortical metabolism and hypofrontality scores did not significantly correlate with negative symptoms. Analyses of variance demonstrated a reduced right greater than left asymmetry in the schizophrenic patients for the lateral cortex as a whole, with simple interactions showing this effect specifically in temporal and frontal cortical regions.

Conclusions: Low metabolic rates were confirmed in medial frontal cortical regions as well as in the basal ganglia, consistent with the importance of the cortical-striatal-thalamic pathways in schizophrenia. Loss of normal lateralization patterns was also observed on an exploratory basis. Correlations with negative symptoms and group differences were more prominent in medial than

lateral frontal cortex, suggesting that medial regions may be more important in schizophrenic pathology.

Gruzelier. Functional neuropsychophysiological asymmetry in schizophrenia: a review and reorientation. Review Schizophr Bull. 1999;25(1):91-120. doi: 10.1093/oxfordjournals.schbul.a033370.

Abstract

In reviewing the neuropsychophysiological evidence of functional asymmetry it is proposed that schizophrenia is characterized by a greater dispersion of leftward and rightward asymmetries. The two extremes are represented by active (left greater than right) and withdrawn (right greater than left) syndromes, as is the case with psychometric schizotypy. Syndrome-asymmetry relations extended beyond fronto-temporal systems to include posterior activity, infracortical motoneuron excitability, and individual differences in interhemispheric connectivity and directional biases. Central to these are lateral imbalances in thalamo-cortical and callosal arousal systems, while centrality to schizophrenia follows evidence of reversals in asymmetry with changes in symptom profile, clinical recovery, and neuroleptic treatment. Affinities are found in intact animals from challenge-induced turning tendencies representing coordinated activity of attentional, motor, and reinforcement systems. In both patients and animals, neuroleptics have reciprocal interhemispheric effects, with a bidirectionality that depends on syndrome or endogenous turning preference. Bidirectionality implicates nonspecific thalamic system (NSTS) and not limbic projections. It is proposed that the asymmetries arise from endogenous influences of genes, hormones, and early experience including stressors on NSTS asymmetry, and these underpin approach/withdrawal behavior that is manifested in temperament, personality, and clinical syndrome, and which precedes language development.

Núñez, et al. Global brain asymmetry is increased in schizophrenia and related to avolition. Acta Psychiatr Scand. 2017;135(5):448-459. doi: 10.1111/acps.12723.

Abstract

Objective: Schizophrenia may be the result of a failure of the normal lateralization process of the brain. However, whole-brain asymmetry has not been assessed up to date. Here, we propose a novel measure of global brain asymmetry based on the Dice coefficient to quantify similarity between brain hemispheres.

Method: Global gray and white matter asymmetry was calculated from high-resolution T1 structural images acquired from 24 patients with schizophrenia and 26 healthy controls, age- and

sex-matched. Some of the analyses were replicated in a much larger sample (n = 759) obtained from open-access online databases.

Results: Patients with schizophrenia had more global gray matter asymmetry than controls. Additionally, increased gray matter asymmetry was associated with avolition, whereas the inverse relationship was found for anxiety at a trend level. These analyses were replicated in a larger sample and confirmed previous results.

Conclusion: Our findings suggest that global gray matter asymmetry is related to the concept of developmental stability and is a useful indicator of perturbations during neurodevelopment.

Devinsky, et al. Spirituality and religion in epilepsy. Epilepsy Behav. 2008;12(4):636-43. doi: 10.1016/j.yebeh.2007.11.011.

Abstract

Revered in some cultures but persecuted by most others, epilepsy patients have, throughout history, been linked with the divine, demonic, and supernatural. Clinical observations during the past 150 years support an association between religious experiences during (ictal), after (postictal), and in between (interictal) seizures. In addition, epileptic seizures may increase, alter, or decrease religious experience especially in a small group of patients with temporal lobe epilepsy (TLE). Literature surveys have revealed that between .4% and 3.1% of partial epilepsy patients had ictal religious experiences; higher frequencies are found in systematic questionnaires versus spontaneous patient reports. Religious premonitory symptoms or auras were reported by 3.9% of epilepsy patients. Among patients with ictal religious experiences, there is a predominance of patients with right TLE. Postictal and interictal religious experiences occur most often in TLE patients with bilateral seizure foci. Postictal religious experiences occurred in 1.3% of all epilepsy patients and 2.2% of TLE patients. Many of the epilepsy-related religious conversion experiences occurred postictally. Interictal religiosity is more controversial with less consensus among studies. Patients with postictal psychosis may also experience interictal hyper-religiosity, supporting a "pathological" increase in interictal religiosity in some patients. Although psychologic and social factors such as stigma may contribute to religious experiences with epilepsy, a neurologic mechanism most likely plays a large role. The limbic system is also often suggested as the critical site of religious experience due to the association with temporal lobe epilepsy and the emotional nature of the experiences. Neocortical areas also may be involved, suggested by the presence of visual and auditory hallucinations, complex ideation during many religious experiences, and the large expanse of temporal neocortex. In contrast to the role of the temporal lobe in evoking religious experiences, alterations in frontal functions may contribute to increased religious interests as a personality trait. The two main forms of religious experience, the ongoing belief pattern and set of convictions (the religion of

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the everyday man) versus the ecstatic religious experience, may be predominantly localized to the frontal and temporal regions, respectively, of the right hemisphere.

Allen, et al. Emerging Temporal Lobe Dysfunction in People at Clinical High Risk for Psychosis. Front Psychiatry. 2019;10:298. doi: 10.3389/fpsyt.2019.00298. eCollection 2019.

Abstract

Clinical high-risk (CHR) individuals have been increasingly utilized to investigate the prodromal phases of psychosis and progression to illness. Research has identified medial and lateral temporal lobe abnormalities in CHR individuals. Dysfunction in the medial temporal lobe, particularly the hippocampus, is linked to dysregulation of glutamate and dopamine via a hippocampal-striatal-midbrain network that may lead to aberrant signaling of salience underpinning the formation of delusions. Similarly, lateral temporal dysfunction may be linked to the disorganized speech and language impairments observed in the CHR stage. Here, we summarize the significance of these neurobiological findings in terms of emergent psychotic symptoms and conversion to psychosis in CHR populations. We propose key questions for future work with the aim to identify the neural mechanisms that underlie the development of psychosis.