IMAGING THE BRAIN AS

SCHIZOPHRENIA DEVELOPS:

DYNAMIC & GENETIC BRAIN MAPS

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Abstract

Schizophrenia is a chronic, debilitating psychiatric disorder that affects 0.2-2% of the population worldwide. Often striking without warning in the late teens or early twenties, its symptoms include auditory and visual hallucinations, psychotic outbreaks, bizarre or disordered thinking, depression and social withdrawal. To combat the disease, new antipsychotic drugs are emerging; these atypical neuroleptics target dopamine and serotonin pathways in the brain, offering increased therapeutic efficacy with fewer side effects. Despite their moderate success in controlling some patients' symptoms, little is known about the causes of schizophrenia, and what triggers the disease. Its peculiar age of onset raises key questions: What physical changes occur in the brain as a patient develops schizophrenia? Do these deficits spread in the brain, and can they be opposed? How do they relate to psychotic symptoms? As risk for the disease is genetically transmitted, do a patient's relatives exhibit similar brain changes? Recent advances in brain imaging and genetics provide exciting insight on these questions. Neuroimaging can now chart the emergence and progression of deficits in the brain, providing an exceptionally sharp scalpel to dissect the effects of genetic risk, environmental triggers, and susceptibility genes. Visualizing the dynamics of the disease, these techniques also offer new strategies to evaluate drugs that combat the unrelenting symptoms of schizophrenia.

Introduction

Schizophrenia is a chronic, disabling mental illness. It devastates the lives of patients and their caregivers, and affects 0.2-2% of the worldwide population. Newer medications, such as the atypical neuroleptics (e.g., clozapine, olanzapine, risperidone, and quetiapine) offer patients improved symptom control with fewer neurologic side effects. Even so, many patients remain refractory to treatment and symptoms persist for their entire lifetime.

What triggers schizophrenia still remains an enigma. It typically strikes in young adulthood, with an average age of onset of 25-30 in women and 20-25 in men. Psychotic disturbances include delusions, hallucinations, and bizarre thoughts (so-called 'positive symptoms'). Negative symptoms include chronic depression, flat affect, loss of motivation and social decline. If untreated, the active phase of florid psychotic symptoms may last forever, or it may be controlled to a degree by neuroleptics. Even when medications are effective, psychotic outbreaks are often replaced by a residual phase of poverty of thought or blunted affect. Around 20% of patients have a single psychotic outbreak, and 35% have multiple episodes without severe functional or personality impairments.[1] The remainder of patients have relatively static (10%) or progressive (35%) functional impairments, between psychotic episodes.

The discovery of chlorpromazine in the 1950s revolutionized the treatment of schizophrenia. It, and other classical neuroleptics like it (e.g. haloperidol), alleviate positive symptoms by blocking dopamine D2 receptors in the limbic and prefrontal cortices of the brain. These systems regulate emotional behavior and executive function. Unfortunately, at effective doses, these drugs also block dopamine receptors in the caudate/putamen, often leading to neurologic side effects associated with dopamine depletion, and resembling Parkinson's disease. Newer atypical drugs, including clozapine and olanzapine, have reduced motor side effects, in part due to their weaker affinity for the D2 receptor. They powerfully block the 5-HT2 serotonin and D4 dopamine receptors, and tend to outperform haloperidol in reducing negative symptoms.[2] In the 20% of patients who respond poorly to conventional drugs, a third to two-thirds respond well to clozapine; however, the risk of neutropenia in 3.6% and agranulocytosis in 0.75% of patients on clozapine requires constant monitoring, and underscores the need for safer drugs.

The last ten years have also seen a search for biological markers of schizophrenia in the brain. Advances in brain imaging and genetics, in particular, are clarifying how schizophrenia emerges, its progression, its genetic transmission, and its impact on relatives who are at genetic risk. Its peculiar age of onset raises key questions: What physical changes occur in the brain as a patient develops schizophrenia? Do these deficits spread in the brain, and can they be opposed? How do they relate to psychotic symptoms? Do a patient's relatives exhibit similar brain changes? New brain imaging approaches can now create dynamic maps of the disease spreading in the brain, along with genetic maps that uncover deficit patterns in relatives. We review these techniques and their current uses, next.

Brain Development and Schizophrenia

Many studies point to developmental abnormalities that confer a later risk for schizophrenia. Risk factors include obstetric complications such as fetal malnutrition, extreme prematurity, hypoxia, and ischemia[3,4]. People born in winter months[5], or exposed to the influenza virus during the second trimester, have an increased incidence of schizophrenia. According to the 'neurodevelopmental hypothesis', disrupted brain development at this key phase could play a causative role in schizophrenia. A key puzzle is why there is a long gap between an early cerebral insult and the emergence of symptoms twenty or more years later. To explain this, some favor a two-hit (or 'diathesis-stress') model, in which an early developmental or genetic anomaly must be compounded by psychological trauma, viral infection, or some currently unknown trigger later in life for the disease to be expressed. Renewed interest in this hypothesis comes from a recent wave of brain imaging studies identifying features of brain maturation that occur well into adolescence and beyond. These brain imaging studies visualize a sequence of growth spurts in myelination through childhood[6,7], and dramatic waves of gray matter loss believed to reflect synapse production and pruning in the teen years[8,9,10]. Schizophrenia typically strikes at a time when these developmental changes are still occurring. In particular, a natural teenage process of synapse elimination, or pruning, may be accelerated or otherwise derailed in schizophrenia[11].

Mapping Brain Development

Since 1992, Judith Rapoport, M.D. and her colleagues at the National Institute of Mental Health in Bethesda have scanned over 1,000 children and adolescents with high-resolution brain MRIs. What makes this study unique is the fact that these

children return to the clinic to be re-scanned every 2 years. Many children are now receiving their 5th scan, and have grown up in the meantime, leaving a time-lapse movie to record how their brain has developed. The resulting treasure-chest of brain scans charts brain growth in unprecedented detail. Growth spurts and losses can be mapped in individual children, and the resulting patterns can be compared in health and disease[7].

Dynamic Brain Maps. Our recent studies of these scans, in collaboration with the NIMH group, have developed computerized methods to map subtle changes in the developing brain. The goal is to visualize where the brain is growing fastest, measure local growth rates and their statistics, and reveal where gray matter or other types of tissue are lost. Combining and comparing data from multiple subjects, detailed color-coded maps show where, and how fast, these changes occur. They also pinpoint where brain changes are most prominent in disease (see Figure 1). One surprise has been that many brain systems *lose* tissue as a child develops. Parts of the basal ganglia, which control learned motor functions, lose up to 50% of their tissue in a 4-year period leading up to puberty[7].

Early-Onset Schizophrenia

Among those patients scanned at NIMH were 50 adolescents with early-onset schizophrenia (EOS), scanned every 2 years as their disorder developed. A review of 1,000 charts and follow-up screening of 300 families from the U.S. and Canada led to a sample of 50 subjects with EOS (30 boys, 20 girls). These patients had detailed cognitive and clinical evaluations; they satisfied DSM-III-R/DSM-IV criteria for diagnosis of schizophrenia before the age of 13.[12] Rigorous study revealed that their symptoms are continuous with the adult disorder; many patients resemble poor-outcome adult cases. Their brain scans and repeated neuropsychiatric tests therefore hold key information on how schizophrenia develops in the teenage years.

Dynamic Wave of Gray Matter Loss

[insert Figure 1 here]

In studying the schizophrenic patients, we were surprised to see a spreading wave of tissue loss that began in a small region of the brain, the parietal cortices (*see Figure 1, top row, red colors*).[10] This deficit pattern, reported recently in the *Proceedings of the National Academy of Sciences*, moved across the brain like a forest fire. It destroyed more tissue as the disease progressed (*red colors, bottom row*). It eventually engulfed the rest of the cortex after a period of 5 years. Video sequences were also computed from the brain images, to show the dynamics of this process (see website in Figure 1's legend). These maps are color-coded to show different degrees of change, revealing where gray matter is significantly reduced in disease, relative to healthy controls.

At each scan, 12 schizophrenic patients were compared with 12 healthy controls matched for age, gender, and demographics. In each scan, a measure of the local quantity of gray matter was made at each point on the cerebral cortex, and the average pattern of changes was mapped in both patients and controls. At their first scan (an average of 1.5 years after initial diagnosis), patients showed a 10% gray matter deficit in a small region of the cortex. This deficit, observed at the age of 13, was initially confined to parietal brain regions involved in spatial association. Over the 5 succeeding years, this brain tissue loss swept forward into sensory and motor regions. By the age of 18, it had moved into dorsolateral prefrontal and temporal cortices, which were not initially affected. This pattern was replicated in independent groups of male and female patients. Each showed a similar pattern of spreading deficits, reaching a 20%-25% average loss in some regions. Overall, the loss corresponded with impairments in neuromotor, auditory, visual search, and frontal executive functions that characterize schizophrenia. The frontal eye fields lost tissue fastest, at about 5 percent per year, perhaps consistent with the eye-tracking and smooth eye pursuit deficits often reported in patients. The mapping technique also agreed with more conventional methods, in which the total volume of gray matter in each lobe of the brain was measured, and compared over time[13]. An earlier study[14] found that the healthy controls lost cortical gray matter in the frontal (2.6%) and parietal lobes (4.1%);

patients had faster losses in frontal (10.9%) and parietal (8.5%) regions, and they also suffered a decrease in temporal gray volume (7%), which remained stable in the controls.

Total frontal loss rates correlated with negative symptoms (total SANS scores) at final scan ($p<0.038$). This is consistent with the physiological hypothesis that negative symptoms of schizophrenia may partly derive from reduced dopaminergic activity in frontal cortices. Future studies in larger samples will assess how these loss profiles correlate with specific symptoms, such as auditory or visual hallucinations. Visual hallucinations, for example, may originate from multiple brain regions, perhaps in parietal or occipital rather than temporal cortices, or, if within the temporal lobe, possibly from the small inferior/posterior visual association regions, such as Brodmann area 37. We are currently developing digital mapping methods to isolate which specific regional deficits (e.g., dorsolateral prefrontal, temporal) link most tightly with symptoms and cognitive impairment.

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Medication Effects

We also wanted to address the possibility that drug treatment may have induced these patterns of gray matter loss in the schizophrenic patients. So we also mapped 10 IQ-matched, serially imaged non-schizophrenic subjects, who received identical medication to the patients (primarily for control of chronic mood disorders and aggressive outbursts). While the non-schizophrenic group did show some subtle but significant tissue loss, this was much less marked than for the schizophrenics, and was restricted to superior frontal cortices. No temporal lobe or pervasive frontal deficits were observed in the medication controls, suggesting that the wave of disease progression may be specific to schizophrenia, regardless of medication, and also regardless of gender or IQ.

Normal Gray Matter Pruning

A shifting pattern of deficits in these patients with schizophrenia raises interesting questions. First, tight correlations between the pattern of loss and specific symptoms could point to underlying mechanisms. If the pathogenesis of schizophrenia is a dynamic, gradual process, a five-year window may be available for drugs to oppose the wave of loss. Imaging strategies will be key tools in evaluating their efficacy.

Second, just what causes this progressive wave of tissue loss? Healthy adolescents also lose gray matter in parietal regions, at a more modest rate of approximately 1% per year[10]. The cognitive effects of this process are unclear. Future brain imaging studies will reveal whether the process of normal gray matter maturation, sometimes called 'pruning',[8] obeys a similar shifting pattern. If so, this will clarify whether the schizophrenic wave of loss is an alteration or acceleration of a normal developmental process. An alternative view is that it is a separate process entirely that begins in the teenage years.

Genetic Risk for Schizophrenia

Genetic studies are greatly accelerating our understanding of schizophrenia (see ref. [15] for a recent review). Relatives who are genetically closer to a schizophrenic patient are more likely to develop the disorder themselves, so there is great interest in determining individual relatives' risk for the disease, as well as understanding its genetic transmission. Two key themes are dominant in this work: (1) twin or family studies of disease transmission, and (2) the search for susceptibility genes. Twin and family studies reveal that there is a genetically transmitted risk for schizophrenia: adoption studies confirm this, and also control for differences in family environment that could conceivably promote the disease. Siblings of patients have a 14% lifetime risk of developing schizophrenia, and monozygotic (MZ) twins of patients, who have identical genes, have a 48% risk. Risk therefore increases, the higher the proportion of genetic material in common with a patient. Intriguingly, an identical twin’s risk is not 100%. This shows that genes are not all-important in producing the disease. Discordance studies, where just one of two identical twins has the disease, are designed to study non-genetic triggers, which promote disease expression in some relatives but not others.

Risk Genes. Several candidate genes have recently been discovered that affect individual risk for schizophrenia (e.g., [16]). These DNA variations, passed on from parents to their offspring, modify behavioral traits, disease susceptibility and even treatment response. If two randomly selected individuals' genomes were aligned, between 0.1 and 0.2 percent of the nucleotides would not match. About 85% of these sequence variations are *single nucleotide polymorphisms* (SNPs). These are sites where at least 1% of the entire human population has a different base, and they occur roughly every 350 to 1000 base pairs along the genome. About 200,000 of these SNPs, or about half of the total, occur in protein coding regions or upstream regulatory sites. By altering a protein's amino-acid sequence or expression pattern, these functional SNPs are likely to account for almost all human heritable variation, and contribute to common diseases such as Alzheimer's disease, arthritis and diabetes, as well as genetic risk for schizophrenia. To find susceptibility genes and quantitative trait loci, association studies can now identify genetic variation by genotyping individuals at thousands of these loci, using high-throughput SNP detection chips.

Genetic loci that appear to confer susceptibility to schizophrenia have been mapped to regions on chromosomes 1,6,8,10,13, and 18. No single genetic variation is found in all schizophrenia patients. 2% of diagnosed patients, however, exhibit a deletion of chromosomal region 22q11. This 22q11 deletion confers a 25-30% risk of schizophrenia, and results in velocardiofacial syndrome, a disorder characterized by learning disabilities, cardiac defects, and hypernasal speech due to abnormalities of the palate. Remarkably, the gene encoding COMT (catechol-*O*-methyltransferase), which inactivates dopamine in the brain, is also localized to 22q11; and mice with targeted deletion of this gene have excess dopamine in the prefrontal cortex. The action of this candidate gene, which is altered in some patients, is consistent with the dopamine hypothesis. Genetic variations may impair neurotransmitter metabolism, and this feature is consistent with schizophrenia symptoms and how antipsychotic drugs work.

Mapping Genetic Risk

[insert Figure 2 here]

Brain imaging can identify deficit patterns associated with these genetic risks. Genetic brain maps, in particular (Figure 2) show which aspects of brain structure are under strongest genetic control[17]. In disease studies[18], they reveal brain regions at genetic risk for deficits. Recently, we developed a technique to visualize genetic influences on brain structure[17,19]. This technique determines which aspects of brain structure we inherit from our parents: some features, such as the quantity of frontal gray matter, prove to be under tight genetic control, while others are not. Not every part of a brain's structure is strongly predetermined by our genetic blueprint: temporal and hippocampal regions, involved in learning and memory, and some cortical and cerebellar regions, appear to be under greater environmental influence[20,19]. These genetic brain maps can be used to find structural features that are similar among family members, as we shall describe next.

To see how this approach works, consider the color brain maps in Figure 2(a),(b). These are computed from MRI scans of normal twins. Fig. 2(a) shows the correlation the amount of gray matter in identical (MZ) twins, who have exactly the same genes. Red colors denote regions where twins are extremely similar in their quantity of gray matter. The map of correlation coefficients effectively shows how far off you would be, if you used the amount of gray matter in one twin to predict the gray matter in the other. Fig. 2(b) shows the gray matter correlations for fraternal (DZ) twins, who share on average half their genes with each other. These correlations are substantially less. If only the environment is important, it shouldn't matter whether the twins are identical or fraternal. However, the heritability map (Fig. 2(c)) shows that gray matter volume in certain parts of the brain is statistically more closely matched in the identical twins than in twins who were less similar genetically. The high genetic control of frontal brain structure is intriguing, as these are regions where individual differences correlate with cognitive function (specifically IQ),[17,21,22] and where family members have extremely similar brain structure.

To examine the genetic transmission of deficits in schizophrenia, we recently measured differences in cortical gray matter distribution between monozygotic (MZ) twins discordant for schizophrenia[18]. In the identical twins we examined, the schizophrenic member of each pair showed statistically significant deficits (between 5-8%) in superior parietal and dorsolateral prefrontal cortices, and in the left superior temporal gyrus (*disease-specific map*; Fig. 2(d)). No significant differences were found between discordant co-twins in primary somatosensory or primary motor areas. Since the MZ twins were identical genetically, the early loss of parietal cortex in the EOS patients suggests an environmental rather than a genetic origin for the disease. In the frontal and temporal regions, however, where loss occurred relatively late in the EOS patients, deficits were found to be highly heritable (*liability map*; Fig. 2(d)). The liability map shows regions where deficits were found in healthy relatives of patients. These deficits were statistically linked with the degree of genetic affinity to a patient (i.e., worse deficits in MZ than DZ relatives). This shows that these particular deficits are mediated by genetic differences.

Brain imaging provides a biological marker for brain regions at risk in schizophrenia. Genetic brain maps can also be used to search for schizophrenia susceptibility loci, and may in the future map effects of candidate genes on brain structure. A first step in this quest will be extending 'allele sharing' methods, used widely in statistical genetics, to create statistical brain maps of gene effects. Continued hybridization of methods from genetics and brain imaging will accelerate our knowledge of the mechanism of the disease, its genetic transmission, and ultimately a means to block it in individual families.

A Window of Opportunity

In summary, we reviewed several schizophrenia studies in which brain imaging visualizes the disease process and its genetic transmission. With brain mapping approaches, differences in a diseased population, or one with known genetic risk, can be visualized by reference to a normative standard. We also described the recent detection of a dynamic wave of gray matter loss in early-onset schizophrenia. This process began in a brain region where deficits are not highly heritable, and subsequently invaded the frontal cortex, which is at significant genetic risk for developing deficits. Intriguingly, deficits moved in a shifting pattern, enveloping increasing amounts of cortex throughout adolescence. These deficits are severe and correlate strongly with symptom severity, but their progression does not appear to be complete until at least seven years after symptom onset. This provides a window of opportunity for drug treatment to oppose the spread of the disease.

New imaging methods, including those linking brain deficits with specific risk genes, are likely to be at the forefront in discovering triggers and underlying risks for schizophrenia. Schizophrenia may be promoted or triggered by a non-genetic factor, including possibly psychological trauma, an infectious agent or virus, or an abnormal process that is currently unknown during pre- or post-natal development. Even so, the disease process has a strongly heritable component, and brain regions are subtly impaired in unaffected relatives. Imaging methods also show promise for early detection of the disease, especially in relatives who are at genetic risk; dynamic brain maps can also monitor disease progression, which may be advantageous in charting the effects of drugs in clinical trials.

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Figures and Legends

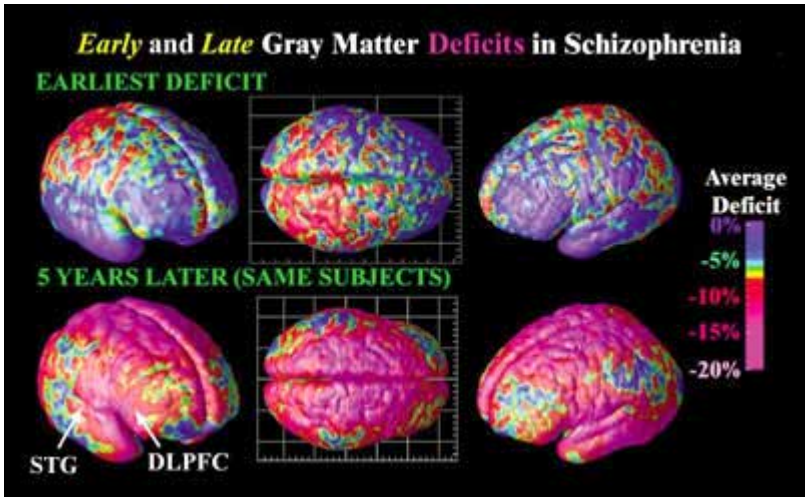

Fig. 1. Dynamic Brain Maps: Mapping Brain Changes in Schizophrenia. Derived from high-resolution magnetic resonance images (MRI scans), the above images were created after repeatedly scanning 12 schizophrenia subjects over five years, and comparing them with matched 12 healthy controls, scanned at the same ages and intervals. Severe loss of gray matter is indicated by red and pink colors, while stable regions are in blue. STG denotes the superior temporal gyrus, and DLPFC denotes the dorsolateral prefrontal cortex. Video sequences showing these dynamic changes can be viewed on the Internet at: http://www.loni.ucla.edu/~thompson/MOVIES/SZ/sz.html (Reprinted with permission from Thompson PM et al., *Proceedings of the National Academy of Sciences of the USA*, 98[20]:11650-11655[10]).

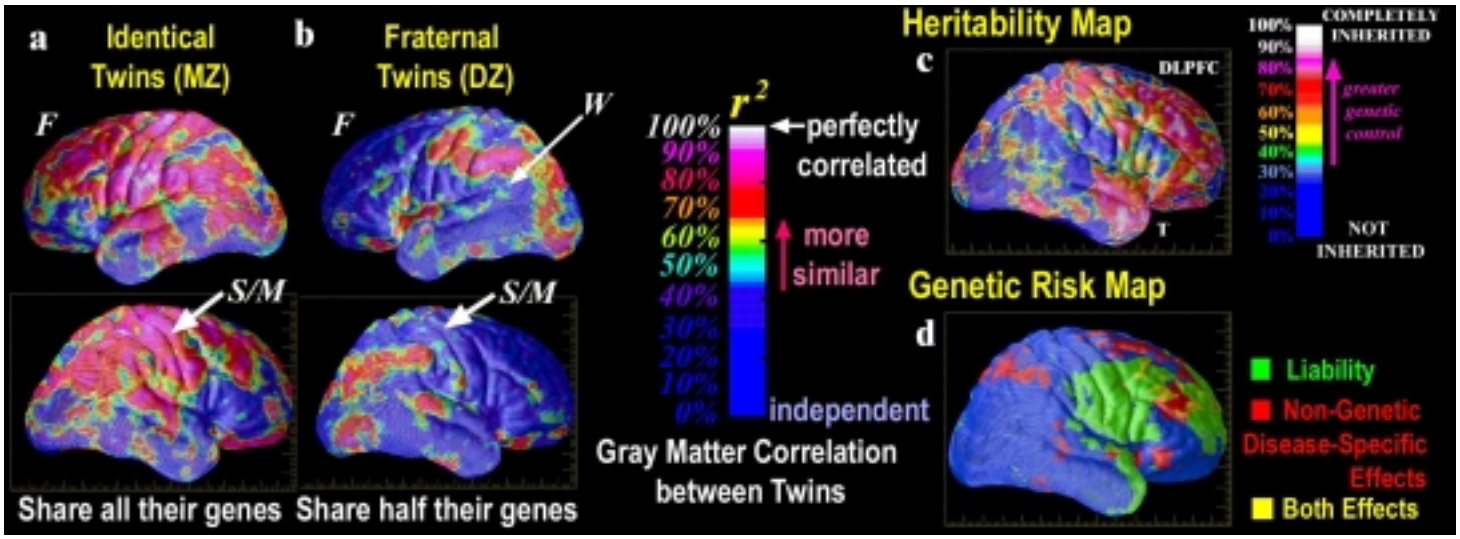

Figure 2. *Genetic Influences on Brain Structure: Mapping Heritability and Liability*. Color-coded maps (a,b) show local gray matter correlations between MZ and DZ twins. (c): A map of heritability statistics (h^2, computed from Falconer's

heritability formula) estimates the proportion of anatomic variation attributable to genetic factors. An anatomical band encompassing frontal, sensorimotor, and parietal cortices (*red colors*) is under strong genetic control. In (d), the liability map (*green colors*) reveals frontal brain regions where gray matter deficits are found in healthy MZ and DZ twins of schizophrenia patients. Greater deficits are found in relatives who are genetically closer to a patient. Red colors show regions with deficits in schizophrenic twins relative to their genetically identical healthy MZ co-twins. These disease-specific differences must be due to non-genetic factors. (Panels a-c reprinted with permission from Thompson PM et al., *Nature Neuroscience* 4(12):1253-1258[17]; panel (d) adapted from Cannon TD et al., *Proceedings of the National Academy of Sciences of the USA* 99(5):3228-3233[18]).

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CME Quiz Questions

Type A Questions

Please select the single best choice:

1. MRI studies show that patients with early-onset schizophrenia (EOS) lose cortical gray matter in a front-to-back wave.

A. True
B. False

2. Which of the following statements, about the genetics of schizophrenia, is *not true*:

A. Siblings of patients have a 14% lifetime risk of developing schizophrenia, and monozygotic (MZ) twins of patients have a 48% lifetime risk
B. The risk for developing schizophrenia is the same in monozygotic and dizygotic twins of patients
C. Deletion of chromosome 22q11 confers a 25-30% risk of schizophrenia
D. The gene encoding COMT (catechol-*O*-methyltransferase), which inactivates dopamine in the brain, is localized to chromosome 22q11

Type K Questions

Use the following key to answer the next two questions:

A if only choices 1,2, and 3 are correct
B if only choices 1 and 3 are correct
C if only choices 2 and 4 are correct
D if only choice 4 is correct
E if all choices are correct

3. Which of the following are risk factors for the development of schizophrenia?

1. fetal malnutrition
2. fetal exposure to the influenza virus during the second trimester
3. being a first-degree relative of a patient
4. extremely premature birth

4. Which of the following statements correctly describe normal childhood or adolescent brain development?

1. normal teenagers lose cortical gray matter in frontal and parietal lobes
2. growth spurts occur in language systems around the age of puberty
3. the basal ganglia may lose brain tissue before puberty
4. the brain has usually reached its adult size by the age of 8

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