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Here's the article for you. It's in the format requested. It should also fit the style of *Psychiatric Times*. The first paragraph can serve as an abstract, and it's under 250 words. Keywords are also included below. I also mailed the disclosures and other forms you requested to Jason King. Please just email me if you need anything else (lynnt@ucla.edu or thompson@loni.ucla.edu). Thanks so much again for the invitation, it was a pleasure to write this for you. I'm also very happy to contribute again in the future, if you ever need an article.

Best wishes! – Paul

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Keywords for indexing (*up to 20 words*): schizophrenia, MRI, brain scan, gray matter, imaging, psychosis, genetics, brain mapping, drug effects, childhood onset, development, adolescence, teenage, neuroanatomy, dopamine

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Brain Mapping in Adolescents with Very Early Onset Schizophrenia

by Paul Thompson, Ph.D.

Psychiatric Times - March 2003

Schizophrenia is a devastating psychiatric disorder that affects 1% of the population worldwide. Patients often suffer their first psychotic outbreak in their late teens or early twenties. Despite advances in neuroleptic drugs, many patients' symptoms remain refractory to treatment, with recurrent episodes of auditory and visual hallucinations, bizarre delusions, depression and social withdrawal that can last an entire lifetime. Neuroimaging studies now suggest that schizophrenia is a disorder of brain development, with anatomic abnormalities present at disease onset. Teenagers with a severe, early onset form of schizophrenia also exhibit a dynamically spreading wave of cortical gray matter loss, detectable in sequential MRI scans. The tissue loss begins in a small region of the parietal cortex and moves forward to engulf frontal and temporal systems. These deficits correlate with psychotic symptom severity, and may link with cortical dopamine or serotonin dysfunction. The shifting pattern of deficits is distinct from the neurodegeneration observed in the dementias, and may be an exaggeration or derailment of the neuronal

remodeling that normally occurs in late teenage brain development. Computerized tracking of these cortical deficits will help understand how neuroleptic drugs decelerate or block the disease process. Cortical deficits are also detectable in patients' first degree relatives, who are at greatly increased genetic risk for schizophrenia (10% lifetime risk). In future, these dynamic and genetic brain maps may predict imminent onset of the disease, identifying pre-symptomatic brain changes in family members who are candidates for early interventions.

Introduction

One of the greatest enigmas in contemporary psychiatry is why schizophrenia strikes in the late teenage years or young adulthood, often without warning. With an average age of onset around 20-25 in men and 25-30 in women, psychotic outbreaks in schizophrenia may include delusions, hallucinations, and bizarre thoughts (so-called 'positive symptoms'). Negative symptoms include chronic depression, flattened affect, poverty of speech, loss of motivation and social decline. 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 (Green, 1999). The remainder of patients have relatively static (10%) or progressive (35%) functional impairments, between psychotic episodes.

Unlike Alzheimer's disease, where amyloid plaques, neurofibrillary tangles, and neuronal loss are pervasive in the brain at autopsy, there are no widely accepted pathologic hallmarks of schizophrenia. This is frustrating, as a biochemical marker could provide the basis for a diagnostic test, and a target for drug action or disease prevention. Nonetheless, multiple lines of evidence suggest that cortical neurotransmitter function is disturbed in schizophrenia. Abnormalities in cortical dopamine, serotonin, glutamate, GABA (gamma-aminobutyric acid), and norepinephrine, have been intensively investigated. Classical neuroleptics (e.g., haloperidol) alleviate positive symptoms by blocking dopamine (D2-type) receptors in the limbic and prefrontal cortices of the brain, systems that regulate emotion and executive function. Newer atypical drugs, including clozapine and olanzapine, powerfully block the 5-HT2 serotonin and D4 dopamine receptors, and tend to outperform haloperidol in reducing negative symptoms (Bilder et al., 2002). Intriguingly, genetic studies suggest that 2% of schizophrenic patients exhibit a chromosomal deletion in region 22q11, which harbors the gene encoding COMT (catechol-*O*-methyltransferase), a powerful inactivator of dopamine. Mice with targeted deletion of this gene have excess dopamine in the prefrontal cortex. This is consistent with the notion that patients with this deletion (which confers a 25-30% lifetime risk of schizophrenia) may suffer from a functional excess of cortical dopamine, and this may be responsible for their positive symptoms.

Advances in neuroimaging, and structural MRI in particular, have empowered the search for biological markers of schizophrenia. Reduced cortical and hippocampal volume are found consistently in schizophrenia patients, and the ventricular and sulcal CSF spaces are often enlarged. Diffuse gray matter deficits are observed on MRI even in first-episode patients, where the confounding effects of medication on brain structure are ruled out. There is great interest in identifying when these anatomical deficits first appear. If their origins were identified, it may be possible to pinpoint precisely where, and when, an active pathological process begins. This could allow earlier disease detection and targeted interventions.

Abnormal Brain Development

Over twenty years of studies suggest that the origins of schizophrenia, as well as multiple risk factors, may lie in childhood or embryonic brain development. Obstetric risk factors, which confer a later risk for schizophrenia, include fetal malnutrition, extreme prematurity, hypoxia, and ischemia (Cannon et al., 2002). People born in winter months (Kirch, 1993), or exposed to the influenza virus in the second trimester

(Mednick et al., 1988), may also have an increased incidence of schizophrenia. Some studies have contested this association, but others suggest that early viral exposure may increase risk for other psychiatric disorders as well (Akil and Weinberger, 2000). Given the array of proposed risk factors, disrupted brain development may play a causative role in schizophrenia. If this is the case, 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 the developmental hypothesis comes from recent brain imaging studies. These identify a drastic remodeling of brain structure in the teenage years and beyond. Well into adolescence, there are growth spurts in myelination (Thompson et al., 2000), and dramatic waves of gray matter loss (Giedd et al., 1999; Sowell et al., 1999). In a landmark paper, based on MRIs of 145 healthy subjects, Giedd et al. (1999) built quadratic 'growth curves' for gray matter volumes in each lobe of the brain, between the ages of 4 and 21. Perhaps surprisingly, the overall volume of gray matter declined sharply after the age of 12, especially in frontal and parietal cortices. This process continued through adolescence and beyond, with the latest decrements occurring in the frontal cortex (Sowell et al., 1999). Since schizophrenia typically strikes at a time when these developmental changes are still occurring, an intriguing hypothesis is that a normal teenage process of dendritic remodeling and synapse elimination (sometimes called 'pruning') may be accelerated or otherwise derailed in schizophrenia (Feinberg, 1982). This excessive pruning may reach a threshold level where cortical information processing is disrupted. It may also account for the increased neuronal packing density, seen in some cortical layers, in *post mortem* studies of schizophrenia patients (Selemon et al., 1995).

Early Onset Schizophrenia

In a large-scale effort to map the trajectory of brain changes during development, Judith Rapoport, M.D. and her colleagues at the National Institute of Mental Health in Bethesda have scanned over 1,000 children and teenagers with high resolution MRIs. Most of these children have been scanned every 2 years since 1992, leaving a remarkable time-lapse movie showing how their brain developed. Among those patients scanned at NIMH were 50 adolescents with early onset schizophrenia (EOS; 30 boys, 20 girls). These patients satisfied DSM-III-R/DSM-IV criteria for diagnosis of schizophrenia before age 13. Rigorous clinical and cognitive evaluations revealed their symptoms were continuous with the adult disorder; many patients resemble poor-outcome adult cases (Rapoport and Inoff-Germain, 2000).

Brain Mapping

Recently, we studied these brain scans in collaboration with the NIMH group. We developed computerized methods to pinpoint rates of brain growth and gray matter loss in individual children and teenagers, and visualize these patterns as color-coded 3D maps. Combining data from multiple subjects, we compared the amount of gray matter, in multiple cortical regions, across subjects and across sequential scans. This analysis produced color-coded 3D maps of the cortex (see Fig. 1(a)-(b)) showing loss rates, group differences, and highlighting regions where these changes link with outcome measures or symptom severity. The brain maps for EOS patients, reported recently in the *Proceedings of the National Academy of Sciences* (Thompson et al., 2001), revealed a surprisingly dynamic pattern of disease progression. At their first scan, an average of 1.5 years after initial diagnosis, patients showed a 10% gray matter deficit confined to a small region of the parietal cortex involved in spatial association (see Fig. 1(a); *red colors denote greatest loss*). Over the 5 succeeding years, this brain tissue loss swept forward, like a forest fire, into frontal and temporal brain regions (Fig. 1(b)).

Male and female patients showed a similar, dynamically spreading pattern of deficits. The frontal eye fields lost tissue fastest (5% per year); frontal and temporal regions were spared initially, but were subsequently

engulfed. By age 18, gray matter was reduced by up to 20-25% in some brain regions. Consistent with earlier reports, the healthy controls lost gray matter in frontal (2.6%) and parietal (4.1%) areas. By contrast, patients lost gray matter significantly faster (10.9% and 8.5% in frontal and parietal lobes). They even sustained progressive losses (7%) in temporal regions, which remained stable in healthy controls.

Symptoms and Medication

The spreading deficits correlated, in some respects, with functional decline as well. Total frontal loss rates correlated with negative symptoms (total SANS scores) at final scan ($p<0.038$). This makes sense, as negative symptoms are thought to derive in part from reduced dopaminergic activity in frontal cortices. At an individual level, rates of temporal loss correlated strongly with SAPS total scores at final scan ($p<0.015$, *left hemisphere*; $p<0.004$, *right hemisphere*). Faster losses in both the superior temporal gyri and the entire temporal cortices were significantly associated with a more severe clinical profile of positive symptoms (e.g., hallucinations or delusions). While tissue loss rates were not significantly linked with the rate of change in SAPS scores from baseline ($p>0.05$), and SAPS scores were not linked with the amount of tissue at baseline ($p>0.05$), loss rates were a good predictor of positive symptoms at follow-up, i.e. the remaining symptoms that were refractory to medication.

To rule out confounding medication effects, a second medication- and IQ-matched control group was also studied, consisting of patients diagnosed with psychosis not otherwise specified (PNOS). These patients exhibited only mild tissue loss, essentially confined to superior frontal cortices, in a highly circumscribed pattern. Importantly, the pervasive, unrelenting spread of tissue loss was specific to schizophrenia, and was not medication induced (although its rate could well be modulated by medication).

An exciting open question is how strongly different neuroleptic drugs combat this wave of loss. Clinical studies in adult patients, using MRI to assess cortical integrity, suggest that atypical drugs decelerate overall gray matter loss, while gray matter progressively declines in patients taking haloperidol alone (J. Lieberman, *pers. commun.*). In both teenage and adult onset patients, these progressive losses appear to continue for a long period after diagnosis (here 7 years), offering a window of opportunity for interventions. Dynamic brain maps, such as the ones shown here, may help evaluate the spatial selectivity of these medication responses, when comparing different neuroleptics. Computational brain maps also make it easy to stratify cohorts into subgroups with different symptom profiles. Patterns of brain change in responders may, in the future, be compared with groups who remain refractory to treatment.

Pathologic Mechanism and Specificity

A shifting pattern of deficits raises perplexing questions. Is the wave of gray matter loss an exaggeration of a ‘normal wave’ of gray matter pruning? Or is it a separate process entirely that begins in the teenage years? Could it be a neurodegenerative process, similar to the progressive wave of gray matter loss seen in Alzheimer’s disease (see Fig. 1(c)-(e); Thompson et al., 2003)?

The strongest evidence against extensive neuronal loss in schizophrenia is the lack of reactive gliosis. Glial cell swelling and proliferation is the brain’s natural response to neuronal cell death, and is strikingly absent in *post mortem* studies. Nonetheless, *in vivo* proton MR spectroscopy studies show that frontal *N*-acetylaspartate is reduced, and this is a good marker of neuronal integrity. Positron emission tomography also shows reduced frontal lobe glucose metabolism, in both early- and adult-onset patients. Impaired cortical activation is also seen in functional MRI studies of working memory and executive function. These deficits are clearest in tasks (e.g. Wisconsin Card Sorting) that place heavy demands on frontal systems.

Rather than widespread cell loss (as in the dementias), it is more likely that neuronal shrinkage, reductions in dendritic complexity and synaptic loss, as well as vascular changes, may underlie the gray matter

changes observed here in schizophrenia. An intriguing hypothesis is that schizophrenia patients may suffer an abnormal intensification of whatever regional gray matter loss occurs in healthy subjects at their specific age of onset. This idea may reconcile why deficits in EOS and adult onset cases differ, somewhat, in their scope and severity. Predominantly frontal and temporal gray matter losses tend to be reported in adult onset patients, while more pervasive losses are seen in early onset studies. Frontal and temporal lobes are the last to show gray matter loss in healthy controls. These systems may be especially vulnerable if the disease begins in young adulthood, while they are being actively remodeled. Additional cortical systems may be vulnerable if the disease hits earlier, in the early teenage years.

Genetics, the Prodrome, and the Future

Two final studies illustrate the usefulness of neuroimaging as a biomarker in schizophrenia. In a recent twin study (Cannon et al., 2002), we detected frontal and temporal cortical deficits (around 5-8%) in healthy relatives of patients, who are at increased genetic risk for developing the disease. These deficits were correlated with the degree of genetic affinity to a patient (i.e., worse deficits in identical twins of patients than fraternal twins, for example, as the latter share fewer genes with a patient). Patients' siblings and children have a 10% lifetime risk of developing schizophrenia, much greater than the 1% risk in the general population.

Isolation of a brain deficit that is an index of liability for schizophrenia is important for two reasons. First, a heritable biomarker, found in at-risk relatives, can be used in genetic association and linkage studies. MRI differences between relatives can be covaried with the number of alleles they share with a patient at a candidate marker locus, to see if particular genetic loci play a role in increasing liability. The notion of genetic linkage (which links trait variation with allelic variation at a marker locus), can be generalized to the notion of a brain map of linkage, showing brain deficits that are linked with allelic variations (see Thompson et al., 2003, for examples). As neuroimaging and genetic databases increase in size and content, the merger of genetics and neuroimaging will empower the search for (and characterization of) susceptibility genes. This is likely to clarify their effects on brain phenotype and disease progression in human populations.

Secondly, analysis of brain changes in those at genetic risk may help identify relatives who are in the prodromal (i.e. pre-symptomatic) phase of the disease. In high-risk relatives, differing MRI patterns can already quantify the statistical risk that the onset of the disease is imminent (Pantelis et al., 2002). Since individual outcomes depend heavily on how early the disease process is detected, relatives with both genetic and neuroimaging risk markers may be able to use this information proactively. Armed with this knowledge, they may in the future opt for early interventions and drug treatment, before the ravages of the disease have set in.

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Dr. Thompson has developed several neuroimaging approaches for investigating brain changes in schizophrenia, childhood development, and Alzheimer's disease. He is assistant professor of neurology at the UCLA School of Medicine, in Los Angeles.

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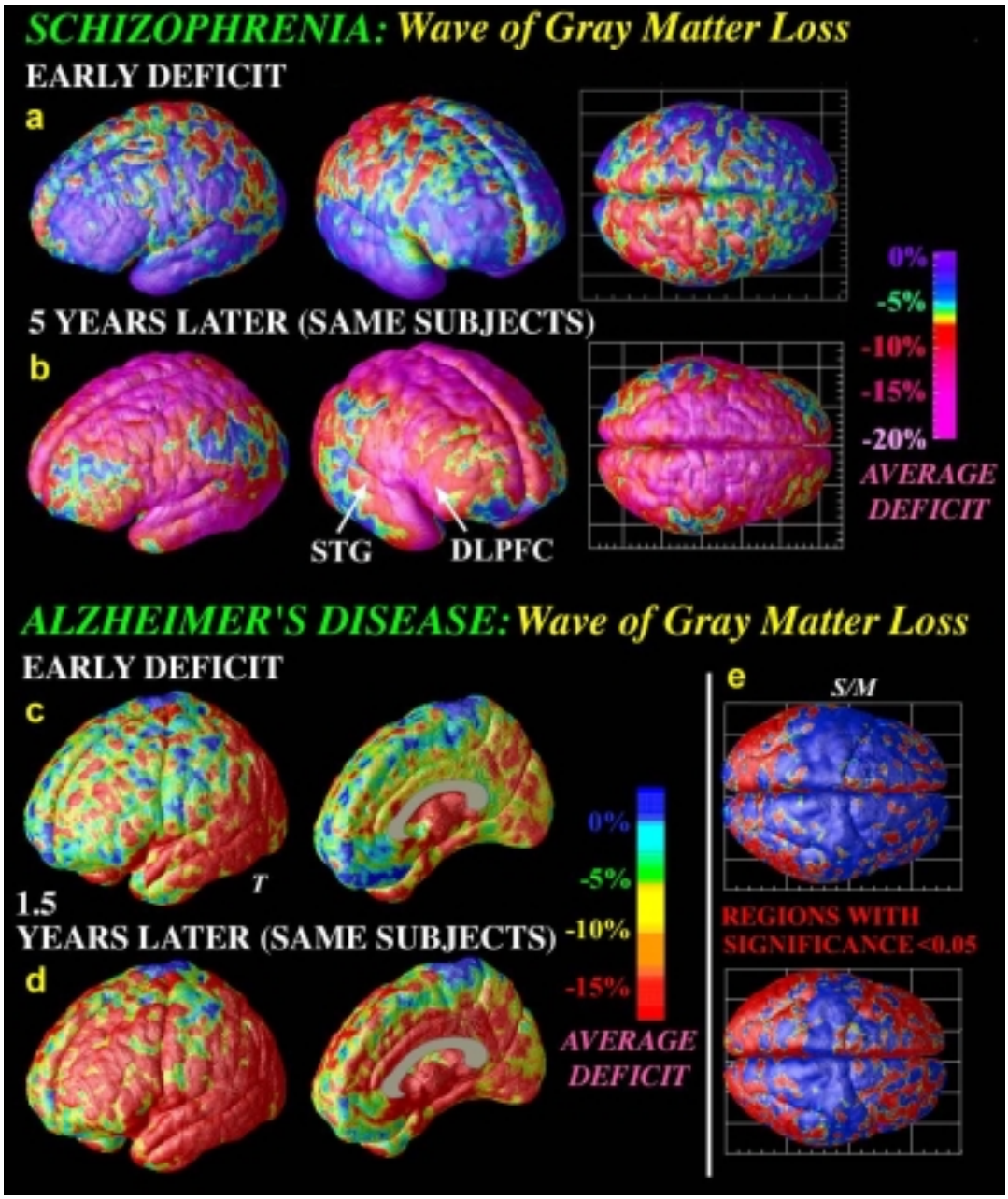

Figure 1. *Dynamic Brain Maps: Mapping Progressive Brain Changes in Schizophrenia and Alzheimer's Disease*. Derived from high-resolution MRI scans, maps (a) and (b) show the average profile of gray matter losses in 12 schizophrenia subjects over five years, relative to 12 matched healthy controls, scanned at the same ages and intervals (Thompson et al., 2001). Severe gray matter loss is indicated by red and pink colors, while stable regions are in blue. Schizophrenic patients show early deficits in parietal regions; deficits then spread anteriorly into frontal regions as the disease progresses. For comparison, (c) and (d) show the average pattern of gray matter deficits in 14 Alzheimer's disease (AD) patients relative to 17 matched healthy elderly controls, also scanned longitudinally (Thompson et al., 2003). As their average MMSE scores declined from 18 to 13 over one and a half years, the AD patients' deficits spread rapidly from temporal and limbic regions (c) into the frontal cortices (d). Primary sensory and motor cortices are comparatively spared (*labeled S/M* in (e); *blue colors denote no detectable loss*). STG denotes the superior temporal gyrus, and DLPFC denotes the dorsolateral prefrontal cortex. Video sequences showing these dynamic changes may be viewed on the Internet at: http://www.loni.ucla.edu/~thompson/MOVIES/SZ/sz.html and http://www.loni.ucla.edu/~thompson/AD_4D/dynamic.html (Reprinted with permission from Thompson PM et al., *Proceedings of the National Academy of Sciences of the USA*, 98[20]:11650-11655).

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