What is wrong with the brain in schizophrenia?

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There is a lot of misinformation regarding what is wrong with the brain in schizophrenia. Dr. Thomas Szasz has claimed that nothing is wrong and that schizophrenia is merely a "myth."[1] Dr. Peter Breggin has argued that people with schizophrenia bring the symptoms on themselves because of "cowardice" or "failure of nerve."[2] Dr. Daniel Fisher says schizophrenia is merely "severe emotional distress and loss of social role" brought on by "trauma."[3] Scientologists even claim that the symptoms of schizophrenia are caused by the drugs that are used to treat it.

All such statements indicate a profound ignorance about schizophrenia. Research has now clearly demonstrated that schizophrenia is caused by changes in the brain and that these can be measured by changes in both brain structure and brain function. Over 1,000 such research studies have been published. Schizophrenia is thus a disease of the brain in exactly the same sense that Parkinson's disease, multiple sclerosis, epilepsy, and Alzheimer's disease are diseases of the brain.

The same thing can be said about some other severe psychiatric disorders, specifically bipolar disorder (manic-depressive illness), schizoaffective disorder, severe depression, autism, and severe obsessive-compulsive disorder. Research studies indicate that all of these are also diseases of the brain, although the number of studies on these disorders is far fewer than on schizophrenia.

The following sections will briefly review the evidence for schizophrenia as a brain disease. **The only studies included will be studies carried out on individuals with schizophrenia who, at the time of the study, had never received any antipsychotic medication.** This is often referred to by researchers as being neuroleptic-naïve. Thus, these studies prove that the changes in brain structure and function seen in schizophrenia are clearly caused by the disease process, not by the medications used to treat the disease.

Since 1975, there have been at least 107 such studies. They can be divided into research on structural abnormalities, neurological abnormalities, neuropsychological abnormalities, neurophysiological abnormalities, and cerebral metabolic abnormalities.

1. Structural Abnormalities

The modern era in schizophrenia research can be dated to 1976 with the publication of the first research using the newly developed computerized axial tomography (CT) brain scans, which showed that the brains of individuals with schizophrenia have significantly larger fluid-filled spaces

[1] T.S. Szasz, SCHIZOPHRENIA: THE SACRED SYMBOL OF PSYCHIATRY (1976).
[2] P.R. Breggin, THE PSYCHOLOGY OF FREEDOM (1980).
[3] G. Condon, quoting Daniel Fisher on WTIC-TV, Hartford, Connecticut, April 6, 2005.

(cerebral ventricles) compared to normal controls. The CT scan was the first technology allowing for visualization of brain structures in living patients that could be used to statistically distinguish those with schizophrenia from normal controls.[4] Following the introduction of CT scans, magnetic resonance imaging (MRI) scans have also become widely available for studying brain structures.

Since 1976, a total of thirty-five studies of brain structure have been done on individuals with schizophrenia who had never been medicated.[5] All six studies that measured the size of the brain

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[4] Eve C. Johnstone et al., *Cerebral Ventricular Size and Cognitive Impairment in Chronic Schizophrenia,* 2 LANCET 924, (1976). This research was carried out at Northwick Park Clinical Research Center in London. Although group differences are statistically significant, there is some overlap in ventricular size between individual patients with schizophrenia and normal controls, and so ventricular size cannot be used as a diagnostic marker.

[5] S.C. Schulz et al., *Treatment Response and Ventricular Brain Enlargement in Young Schizophrenic Patients,* 19 PSYCHOPHARMACOL. BULL. 510–12, (1983); G. Degreef et al. *Increased Prevalence of the Cavum Septum Pellucidum in Magnetic Resonance Scans and Post-Mortem Brains of Schizophrenic Patients,* 45 PSYCHIATRY RES.: NEUROIMAGING 1–13, (1992); J. Lieberman et al., *Qualitative Assessment of Brain Morphology in Acute and Chronic Schizophrenia,* 149 AM. J. PSYCHIATRY 784–94, (1992); M.H. Chakos et al., *Increase in Caudate Nuclei Volumes of First-Episode Schizophrenic Patients Taking Antipsychotic Drugs,* 151 AM. J. PSYCHIATRY 1430–36, (1994); R.E. Gur et al., *Subcortical MRI Volumes in Neuroleptic-Naïve and Treated Patients with Schizophrenia,* 155 AM. J. PSYCHIATRY 1711–17 (1998); M.S. Keshavan et al., *Decreased Caudate Volume in Neuroleptic-Naïve Psychotic Patients,* 155 AM. J. PSYCHIATRY 774–78, (1998); L. Shihabuddin et al., *Dorsal Striatal Size, Shape, and Metabolic Rate in Never-Medicated and Previously Medicated Schizophrenics Performing a Verbal Learning Task,* 55 ARCH. GEN. PSYCHIATRY 235–43, (1998); P.W. Corson et al., *Caudate Size in First-Episode Neuroleptic-Naïve Schizophrenic Patients Measured Using an Artificial Neural Network,* 46 BIOL. PSYCHIATRY 712–20, (1999); R.E. Gur et al., *Reduced Gray Matter Volume in Schizophrenia,* 56 ARCH. GEN. PSYCHIATRY 905–11, (1999); R.E. Gur et al., *Reduced Dorsal and Orbital Prefrontal Gray Matter Volumes in Schizophrenia,* 57 ARCH. GEN. PSYCHIATRY 761–68, (2000); R.E. Gur et al., *Temporolimbic Volume Reductions in Schizophrenia,* 57 ARCH. GEN. PSYCHIATRY 769–75, (2000); U. Ettinger et al., *Magnetic Resonance Imaging of the Thalamus in First-Episode Psychosis,* 158 AM. J. PSYCHIATRY 116–18, (2001); A.R. Gilbert et al., *Thalamic Volumes in Patients with First-Episode Schizophrenia,* 158 AM. J. PSYCHIATRY 618–24, (2001); W. Cahn et al., *Brain Morphology in Antipsychotic-Naïve Schizophrenia: A Study of Multiple Brain Structures,* 181 (suppl 43) BR. J. PSYCHIATRY S66–72, (2002); W. Cahn et al., *Brain Volume Changes in First-Episode Schizophrenia: A 1-Year Follow-up Study,* 59 ARCH. GEN. PSYCHIATRY 1002–10, (2002); H. Gunduz et al., *Basal Ganglia Volumes in First-Episode Schizophrenia and Healthy Comparison Subjects,* 51 BIOL. PSYCHIATRY 801–808, (2002); C.C. Joyal et al., *A Volumetric MRI Study of the Entorhinal Cortex in First Episode Neuroleptic-Naïve Schizophrenia,* 51 BIOL. PSYCHIATRY 1005–1007, (2002); P. Karlsson et al., *PET Study of D_1 Dopamine Receptor Binding in Neuroleptic-Naïve Patients with Schizophrenia,* 159 AM. J. PSYCHIATRY 761–67, (2002); M.S. Keshavan et al., Abnormalities of the Corpus Callosum in First Episode, Treatment Naïve Schizophrenia 72 J. NEUROL. NEUROSURG. PSYCHIATRY 757–60, (2002); M.S. Keshavan et al., *Cavum Septi Pellucidi in First-Episode Patients and Young Relatives at Risk for Schizophrenia,* 7 CNS SPECTRUMS 155–58, (2002); R.G. McCreadie et al., *Structural Brain Differences between Never-Treated Patients with Schizophrenia, with and without Dyskinesia, and Normal Control Subjects: A Magnetic Imaging Study,* 59 ARCH. GEN. PSYCHIATRY 332–36, (2002); S. Tauscher-Wisniewski et al., *Caudate Volume Changes in First Episode Psychosis Parallel the Effects of Normal Aging: A 5-Year Follow-Up Study,* 58 SCHIZOPHR. RES. 185–88, (2002); G. Cherascu et al., *Changes in Morphology of the Thalamus over Time in Subjects with Neuroleptic Naïve Schizophrenia: Effects of Neuroleptic Treatment* (abstract), 60 SCHIZOPHR. RES. 191, (2003); M. M. Haznedar et al., *Cingulate Gyrus Gray and White Matter Volumes in Drug Naïve Schizophrenia Patients* (poster presentation), annual meeting of the American Psychiatric Association (May 2003); M. M. Haznedar et al., *Hippocampus Volume and 3-D Metabolic Mapping in Drug-Naïve Schizophrenia Patients* (poster presentation), annual meeting of the American Psychiatric Association (May 2003); J. Hietala et al., *Regional Brain Morphology and Duration of Illness in Never-Medicated First-Episode Patients with Schizophrenia (letter),* 64 SCHIZOPHR. RES. 79–81, (2003); C.C. Joyal et al., *The Amygdala and Schizophrenia: A Volumetric Magnetic Resonance Imaging Study in First-Episode Neuroleptic-Naïve Patients,* 54 BIOL. PSYCHIATRY 1302–1304, (2003); J.-J. Kim et al., *Morphology of the Lateral Superior Temporal Gyrus in Neuroleptic Naïve Patients with Schizophrenia: Relationship to Symptoms,* 60 SCHIZOPHR. RES. 173–81, (2003); A.L.T. Lacerda et al., *Orbitofrontal Cortex in First-Episode Schizophrenia: An MRI Study* (abstract), 53 BIOL. PSYCHIATRY 116S, (2003); P.R. Szeszko et al., *Smaller Anterior Hippocampal Formation Volume in Antipsychotic-Naïve Patients with First-Episode Schizophrenia,* 160 AM. J. PSYCHIATRY 2190–97, (2003); G. Venkatasubramanian et al., *Corticocerebellar Alterations in Never-Treated Young Age at Onset Schizophrenia* (abstract), 60 SCHIZOPHR. RES. 211, (2003); M. Konasale et al., *Cerebellum Morphometry in First-Episode Psychotic Disorders: Regional Specificity for Psychotic Symptoms and Cognition* (abstract), 55 BIOL. PSYCHIATRY 169S, (2004); G. Venkatasubramanian et al., *Longitudinal Study of MRI Gray Matter Volume in Treatment-Naïve Schizophrenia:*

ventricles found them to be significantly enlarged. For example, Gur et al. reported a 16% increase in ventricular volume in thirty-three never-treated patients compared to sixty-five normal controls. Similarly, McCreadie et al. reported a 20% increase in ventricular volume in forty-two patients compared to thirty-one normal controls. In addition to ventricular size, abnormalities in brain structure in never-treated individuals with schizophrenia have been reported for the frontal cortex, temporal cortex, hippocampus, amygdala, cingulate, thalamus, cerebellum, corpus callosum, and septum pellucidum. The only brain area that has been extensively studied and for which the results of different studies have been contradictory is the basal ganglia, especially its caudate subdivision.

2. Neurological Abnormalities

Since 1976, at least thirty-three studies have reported significantly more neurological abnormalities in individuals with schizophrenia who had never been treated with antipsychotic medications compared to unaffected controls. The neurological abnormalities include abnormal spontaneous movements called dyskinesias, parkinsonian signs, neurological soft signs, and cerebellar signs.

Dyskinesias are spontaneous movements, usually involving the tongue, facial muscles, or arms. Eleven studies have demonstrated that such movements occur more often among never-treated individuals with schizophrenia than among normal controls.[6] For example, Fenton et al. found that 23% of never-treated patients exhibited some form of spontaneous dyskinesia. Eight recent studies have also reported that never-treated patients with schizophrenia have neurological abnormalities resembling those seen in Parkinson's disease, including rigidity, tremor, and slowing of movements.[7] Combining the studies, 91 out of 394 (23%) never-treated patients showed parkinsonian signs.

Evidence for Cognitive Dysmetria (abstract), 67 SCHIZOPHR. RES. 25, (2004); R. Spinks et al., *Globus Pallidus Volume Is Related to Symptom Severity in Neuroleptic Naïve Patients with Schizophrenia*, 73 SCHIZOPHR. RES. 229–33, (2005); K.L. Narr et al., *Cortical Thinning in Cingulate and Occipital Cortices in First Episode Schizophrenia*, 58 BIOL. PSYCHIATRY 32–40, (2005).

[6] D.G.C. Owens, *Spontaneous Involuntary Disorders of Movement*, 39 ARCH. GEN. PSYCHIATRY 452–61, (1982); D. Rogers, *The Motor Disorders of Severe Psychiatric Illness: A Conflict of Paradigms*, 147 BR. J. PSYCHIATRY 221–32, (1985); R.G. McCreadie et al., *The Scottish First Episode Schizophrenia Study: I. Patient Identification and Categorisation*, 150 BR. J. PSYCHIATRY 331–33, (1987); J.L. Waddington & H.A. Youssef, *The Lifetime Outcome and Involuntary Movements of Schizophrenia Never Treated with Neuroleptic Drugs: Four Rare Cases in Ireland*, 156 BR. J. PSYCHIATRY 106–108, (1990); W. Fenton et al., *Risk Factors for Spontaneous Dyskinesia in Schizophrenia*, 51 ARCH. GEN. PSYCHIATRY 643–50, (1994); A. Chatterjee et al., *Prevalence and Clinical Correlates of Extrapyramidal Signs and Spontaneous Dyskinesia in Never-Medicated Schizophrenic Patients*, 152 AM. J. PSYCHIATRY 1724–29, (1995) (hereinafter CHATTERJEE ET AL., PREVALENCE AND CLINICAL CORRELATES); D.S. Fenn et al., *Movements in Never-Medicated Schizophrenics: A Preliminary Study*, 123 PSYCHOPHARMACOLOGY 206–10, (1996); R.G. McCreadie et al., *Abnormal Movements in Never-Medicated Indian Patients with Schizophrenia*, 168 BR. J. PSYCHIATRY 221–26, (1996) (hereinafter MCCREADIE ET AL., ABNORMAL MOVEMENTS); M. Gervin et al., *Spontaneous Abnormal Involuntary Movements in First-Episode Schizophrenia and Schizophreniform Disorder: Baseline Rate in a Group of Patients from an Irish Catchment Area*, 155 AM. J. PSYCHIATRY 1202–1206, (1998); B.K. Puri et al., *Spontaneous Dyskinesia in First Episode Schizophrenia*, 66 J. NEUROL. NEUROSURG. PSYCHIATRY 76–78, (1999) (hereinafter PURI ET AL., SPONTANEOUS DYSKINESIA); W. Honer et al., *Are Movement Disorders a Part of the Syndrome or Consequences of Treatment?* (abstract), 53 SCHIZOPHR. RES. 11, (2002); L. Cortese et al., *Relationship of Neuromotor Disturbances to Psychosis Symptoms in First-Episode Neuroleptic-Naïve Schizophrenia Patients*, 75 SCHIZOPHR. RES. 65–75, (2005) (herinafter CORTESE ET AL., RELATIONSHIP OF NEUROMOTOR DISTURBANCES).

[7] M.P. Caligiuri et al., *Parkinsonism in Neuroleptic-Naïve Schizophrenic Patients*, 150 AM. J. PSYCHIATRY 1343–48, (1993); CHATTERJEE ET AL., PREVALENCE AND CLINICAL CORRELATES; MCCREADIE ET AL., ABNORMAL MOVEMENTS; L.C. Kopala et al., *Risperidone in First-Episode Schizophrenia: Improvement in Symptoms and Pre-Existing Extrapyramidal Signs*, 2 INTERNATIONAL JOURNAL OF PSYCHIATRY IN CLINICAL PRACTICE S19–S25, (1998); PURI ET AL., SPONTANEOUS DYSKINESIA; W.G. Honer et al., *Extrapyramidal Symptoms and Signs in First-Episode, Antipsychotic Exposed and Non-Exposed Patients with Schizophrenia or Related Psychotic Illness*, 19 J.

Neurological abnormalities called soft signs have also been extensively investigated in individuals with schizophrenia. Soft signs include such things as being unable to identify the type of coin placed in the hand without looking at it. Since 1992, fourteen research groups have assessed the presence of neurological soft signs in never-medicated patients with schizophrenia.[8] Finally, a recent study compared neurological signs of cerebellar dysfunction in 155 never-treated individuals with schizophrenia to 155 matched normal controls. Among the patients, 21% had signs of cerebellar dysfunction, such as having an abnormal gait, whereas only 5% of the normal controls had such abnormalities.[9]

3. Neuropsychological Abnormalities

For almost two centuries, it has been observed that individuals with schizophrenia have deficits in some neuropsychological functions, especially memory, attention, and planning (also called executive function). Since 1994, ten studies have been carried out on patients who had never received antipsychotic medications confirming these observations. For example, Brickman et al. compared twenty-nine never-medicated adolescents with schizophrenia to seventeen matched normal controls and reported that the patient group performed significantly worse than the normal controls, especially on memory, attention, and executive functioning.[10] In addition to these ten

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PSYCHOPHARMACOL. 277–85, (2005); CORTESE ET AL., RELATIONSHIP OF NEUROMOTOR DISTURBANCES; and S.A. Chong et al., *Spontaneous Parkinsonism in Antipsychotic-Naïve Patients with First-Episode Psychosis*, 50 CAN. J. PSYCHIATRY 429–31, (2005).

[8] J. Schröder, J. et al., *Neurological Soft Signs in Schizophrenia* 6 SCHIZOPHR. RES. 25–30, (1992); P. Rubin, P. et al., *Neurological Abnormalities in Patients with Schizophrenia or Schizophreniform Disorder at First Admission to Hospital: Correlations with Computerized Tomography and Regional Cerebral Blood Flow Findings* 90 ACTA PSYCHIATR. SCAND. 385–90, (1994); R.D. Sanders et al. *Neurological Examination Abnormalities in Neuroleptic-Naïve Patients with First-Break Schizophrenia: Preliminary Results* 151 AM. J. PSYCHIATRY 1231–33, (1994); S. Gupta et al., *Neurological Soft Signs in Neuroleptic-Naïve and Neuroleptic-Treated Schizophrenic Patients and in Normal Comparison Subjects* 152 AM. J. PSYCHIATRY 191–96, (1995); L. Flyct et al., *Neurological Signs and Psychomotor Performance in Patients with Schizophrenia, Their Relatives and Healthy Controls*, 86 PSYCHIATRY RES. 113–29, (1999); S. Browne et al., *Determinants of Neurological Dysfunction in First Episode Schizophrenia* 30 PSYCHOL. MED. 1433–41, (2000); M.-O. Krebs et al., *Validation and Factorial Structure of a Standardized Neurological Examination Assessing Neurological Soft Signs in Schizophrenia* 45 SCHIZOPHR. RES. 245–60, (2000); M.-O. Krebs et al., *Disorganisation Syndrome Is Correlated to Sensory Neurological Soft Signs in Medicated and Neuroleptic Naïve Schizophrenic Patients* (abstract) 53 SCHIZOPHR. RES. 232, (2002); T. Shibre et al., *Neurological Soft Signs (NSS) in 200 Treatment-Naïve Cases with Schizophrenia: A Community-Based Study in a Rural Setting* 56 NORD. J. PSYCHIATRY 425–31, (2002); G. Venkatasubramanian et al., *Neurological Soft Signs in Never-Treated Schizophrenia* 108 ACTA PSYCHIATR. SCAND. 144–46, (2003); M.S. Keshavan et al., *Diagnostic Specificity and Neuroanatomical Validity of Neurological Abnormalities in First-Episode Psychoses* 160 AM. J. PSYCHIATRY 1298–1304, (2003); E.Y. Chen et al., *Motor Soft Neurological Signs in First Episode Schizophrenia: A Two-Year Longitudinal Study* (abstract) 60 SCHIZOPHR. RES. 129, (2003); P. Whitty et al., *Prospective Evaluation of Neurological Soft Signs in First-Episode Schizophrenia in Relation to Psychopathology: State* versus *Trait Phenomena*, 33 PSYCHOL. MED. 1479–84, (2003); and R.E. Scheffer, *Abnormal Neurological Signs at the Onset of Psychosis* 70 SCHIZOPHR. RES. 19–26, (2004). Studies of neurological soft signs are especially useful in understanding the role of antipsychotic medications in schizophrenia. Studies done on patients with schizophrenia who were on and off medications at the time of testing suggest that the medications either have no effect on the presence of neurological soft signs or decrease such neurological findings. *See* T.C. Manschreck et al., *Disturbed Voluntary Motor Activity in Schizophrenic Disorder* 12 PSYCHOL. MED. 73–84, (1982); T. Kolakowska et al., *Schizophrenia with Good and Poor Outcome. III: Neurological 'Soft' Signs, Cognitive Impairment and Their Clinical Significance* 146 BR. J. PSYCHIATRY 348–57, (1985); and G. Goldstein & R.D. Sanders, *The Effects of Antipsychotic Medication on Neurological Examination Abnormalities in Schizophrenia* (abstract) 60 SCHIZOPHR. RES. 4, (2003).

[9] B.-C. Ho, *Cerebellar Dysfunction in Neuroleptic Naïve Schizophrenia Patients: Clinical, Cognitive, and Neuroanatomic Correlates of Cerebellar Neurologic Signs*, 55 BIOL. PSYCHIATRY 1146–53, (2004).

[10] *See* A.M. Brickman et al., *Neuropsychological Functioning in First-Break, Never-Medicated Adolescents with Psychosis*, 192 J. NERV. MENT. 615–22, (2004). *See also* A.J. Saykin et al., *Neuropsychological Deficits in Neuroleptic Naïve Patients with First-Episode Schizophrenia*, 51 ARCH. GEN. PSYCHIATRY 124–31, (1994); R.G. McCreadie et al., *Poor Memory, Negative Symptoms and Abnormal Movements in Never-Treated Indian Patients with Schizophrenia*, 171 BR. J. PSYCHIATRY 360–63, (1997); I. Lussier & E. Stip, *Memory and Attention Deficits in Drug Naïve Patients with*

studies, three other research groups studied individuals with first-episode schizophrenia, some of whom had never been medicated and some of whom had been briefly medicated, and reported that the never medicated patients had significant neuropsychological deficits.[11]

4. Neurophysiological Abnormalities

Electrical impulses are one method used to communicate between brain cells. As noted previously, electroencephalograms (EEGs) have been used for many years to assess brain function in schizophrenia. Consistent with past studies, two recent studies used EEGs to examine sleep patterns in never-medicated individuals with schizophrenia, and both reported more abnormalities in the patients compared to the normal controls.[12]

Another technique commonly used in psychiatric research to measure neurophysiological function is a type of electrical impulse called an evoked potential, elicited by auditory, visual, or sensory input. For example, a startle reflex, measured electrically, may be evoked by a loud sound. Three recent studies of evoked potentials have been carried out on never-medicated individuals with schizophrenia; all three showed significantly more abnormalities in the patients than in normal controls.[13] Another measure of neurophysiological brain function is the recently developed transcranial magnetic stimulation (TMS), in which the brain is stimulated using magnets. A study of twenty-one neuroleptic-naïve individuals with schizophrenia reported them to be significantly different from twenty-one normal controls on some TMS measures.[14] These studies suggest

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Schizophrenia, 48 SCHIZOPHR. RES. 45–55, (2001); D. Schuepbach et al., *Selective Attention in Neuroleptic-Naïve First-Episode Schizophrenia: A Two-Year Follow-Up* (abstract), 51 BIOL. PSYCHIATRY 118S, (2002); and J.G. Kerns et al., *Context-Processing Deficits and Decreased Prefrontal Cortex Activity: Specific Associations with Unmedicated, First-Episode Schizophrenia and with Disorganization Symptoms* (abstract), 60 SCHIZOPHR. RES. 225, (2003); S.K. Hill et al. *Impairment of Verbal Memory and Learning in Antipsychotic-Naïve Patients with First-Episode Schizophrenia,* 68 SCHIZOPHR. RES. 127–36, (2004); K.P. Good et al., *The Relationship of Neuropsychological Test Performance with the PANSS in Antipsychotic Naïve, First-Episode Psychosis Patients,* 68 SCHIZOPHR. RES. 11–19, (2004); S. Krieger, *Executive Function and Cognitive Subprocesses in First-Episode, Drug-Naïve Schizophrenia: An Analysis of N-Back Performance,* 162 AM. J. PSYCHIATRY 1206–8, (2005); B.E. Snitz et al., *Lateral and Medial Hypofrontality in First-Episode Schizophrenia: Functional Activity in a Medication-Naïve State and Effects of Short-Term Atypical Antipsychotic Treatment,* 162 AM. J. PSYCHIATRY 2322–29 (2005).

[11] D.M. Censits et al., *Neuropsychological Evidence Supporting a Neurodevelopmental Model of Schizophrenia: A Longitudinal Study,* 24 SCHIZOPHR. RES. 289–98, (1997); S. Mohamed et al., *Generalized Cognitive Deficits in Schizophrenia: A Study of First-Episode Patients,* 56 ARCH. GEN. PSYCHIATRY 749–54, (1999); and E.M. Riley et al., *Neuropsychological Functioning in First-Episode Psychosis—Evidence of Specific Deficits,* 43 SCHIZOPHR. RES. 47–55, (2000). There are recent studies that show that antipsychotic medications improve neuropsychological functioning; see, for example, R.S. Keefe et al., *The Effects of Atypical Antipsychotic Drugs on Neurocognitive Impairment in Schizophrenia: A Review and Meta-Analysis,* 25 SCHIZOPHR. BULL. 201–22, (1999); H.Y. Meltzer & S.R. McGurk, *The Effects of Clozapine, Risperidone, and Olanzapine on Cognitive Function in Schizophrenia,* 25 SCHIZOPHR. BULL. 233–55, (1999); and M.C.G. Merlo et al., *Improvement of Cognitive Functions in Acute First-Episode Psychosis Treated with Risperidone* (abstract), 53 SCHIZOPHR. RES. 27, (2002).

[12] R. Ganguli et al., *Electroencephalographic Sleep in Young, Never-Medicated Schizophrenics,* 44 ARCH. GEN. PSYCHIATRY 36–44, (1987) and Julie Poulin et al., *Sleep Architecture and Its Clinical Correlates in First Episode and Neuroleptic-Naïve Patients with Schizophrenia,* 62 SCHIZOPHR. RES. 147–53, (2003).

[13] Torben Mackeprang et al., *Effects of Antipsychotics on Prepulse Inhibition of the Startle Response in Drug-Naïve Schizophrenic Patients,* 52 BIOL. PSYCHIATRY 863–73, (2002), and Katja Ludewig et al., *Deficits in Prepulse Inhibition and Habituation in Never-Medicated, First-Episode Schizophrenia* 54 BIOL. PSYCHIATRY 121–28, (2003). Another recent study included five patients who had never been medicated and two others who had been off all medication for more than six months. It showed that antipsychotic medication improves neurophysiological function, as measured by the acoustic startle reflex; *see* Almut I. Weike et al., *Effective Neuroleptic Medication Removes Prepulse Inhibition Deficits in Schizophrenia Patients,* 47 BIOL. PSYCHIATRY 61–70, (2000); M. Valkonen-Korhonen, *Altered Auditory Processing in Acutely Psychotic Never-Medicated First-Episode Patients,* 17 BRAIN RES. COGN. BRAIN RES. 747–58, (2003).

[14] P. Eichhammer et al., *Cortical Excitability in Neuroleptic-Naïve First-Episode Schizophrenic Patients,* 67 SCHIZOPHR. RES. 253–59, (2004).

abnormal electrical and magnetic circuits in the brains of individuals with schizophrenia, evidence of neurophysiological dysfunction.

5. Cerebral Metabolic Abnormalities

The measurement of cerebral metabolic activity is comparatively new and technically complex. Three ways of doing this are by positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). Since it is known that antipsychotic medications can affect these tests,[15] it is important to use individuals who have not been treated whenever possible.

Since 1991, twenty-one studies have examined cerebral metabolic abnormalities in individuals with schizophrenia never treated with antipsychotic medications. Representative of these studies is one by Braus et al., in which twelve never-medicated patients with schizophrenia were compared to eleven normal controls by functional MRI. According to the researchers: "In comparison with control subjects, patients showed reduced activation in the right thalamus, the right prefrontal cortex, and the parietal lobe . . . bilaterally."[16] Of the twenty-one studies reported to date, all except one found more cerebral metabolic abnormalities in the individuals with schizophrenia compared to the controls.

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[15] R.T. Loeber et al., *Cerebellar Blood Volume in Bipolar Patients Correlates with Medication*, 51 BIOL. PSYCHIATRY 370–76, (2002).

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6. Summary

In summary, since 1975 at least 107 separate studies have demonstrated that individuals with schizophrenia, who have never been treated with antipsychotic medications, have significant abnormalities in brain structure and function. This listing of studies includes only those related to brain abnormalities; additional studies have been carried out on antipsychotic-naïve patients with schizophrenia that have demonstrated other types of abnormalities such as altered interleukins, nerve growth factor, and red blood cell membrane essential fatty acids.[17] Studies of medication-naïve patients thus demonstrate that abnormalities in schizophrenia are part of the disease process, not a result of medication being taken to treat the disease.

For neurological, neuropsychological, neurophysiological, and metabolic abnormalities of cerebral function, in fact, there is evidence suggesting that antipsychotic medications decrease the abnormalities and return the brain to more normal function.[18] This is consistent with the known effectiveness of antipsychotic medications in reducing the clinical symptoms of schizophrenia.

The 107 studies cited, which were restricted to those in which the patients had not previously taken antipsychotic medication, are part of a much larger cohort of studies of cerebral structure and function in patients who had been medicated. Studies of neurologic soft signs in schizophrenia, for example, number over 50, and studies of neuropsychological abnormalities number well over 200.[19] Altogether, there are now over 1,000 published studies on brain structure and function in individuals with schizophrenia.

It should also be emphasized that none of the cerebral abnormalities cited above are specific to schizophrenia. All of them can be found in some other brain diseases and occasionally in normal individuals, although they occur statistically more frequently in individuals with schizophrenia. Thus, the brain abnormalities found in schizophrenia are similar to the tremor seen in many patients with Parkinson's disease. Tremor may also be found in other brain diseases; it occurs in some normal individuals [benign intention tremor], but it occurs statistically much more frequently in Parkinson's disease.

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