Studies of Individuals with Schizophrenia Never Treated with Antipsychotic Medications: A Review

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Summary

A review of 65 studies of individuals with schizophrenia who had never been treated with antipsychotic medications indicates significant abnormalities in brain structure and function. Neurological and neuropsychological measures show the most consistent and largest group differences between those affected and normal controls. Measures of structural differences and cerebral metabolic function are significant but less impressive. Electrophysiological differences also are found, but most such studies are older and have methodological problems. The brain abnormalities implicate a variety of interrelated brain regions, primarily the medial temporal, prefrontal, thalamic, and basal ganglia areas. It is concluded that schizophrenia is a brain disease in the same sense that Parkinson's disease and multiple sclerosis are, and that the brain abnormalities in schizophrenia are inherent in the disease process and not medication-related. The challenge for the future is to use the new molecular techniques to study these brain areas and elevate our understanding of schizophrenia's etiology to the next level.

> Insanity in its various forms is now universally admitted to be a disease—differing, indeed, from ordinary disease as to its nature and phenomena—but a disease notwithstanding, and therefore to be viewed in the same light and treated on the same principles as those which regulate medical practice in other branches. The haze of mystery with which ignorance and superstition had invested it in former ages, and which by repelling investigation prevented proper efforts being made for its removal, has been set aside, and the more rational idea prevails that it is merely an accident of our fallen humanity, involving nothing supernatural in its occurrence so as to remove it from the range of scientific investigation and of ordinary treatment.
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> James F. Duncan, 1875
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> President's Address, *Journal of Mental Science* 21, 316

Introduction

One of the defining characteristics of 20th-century psychiatry was an ongoing controversy regarding the nature of schizophrenia. Sociologists, psychologists, psychoanalysts, family interaction theorists, geneticists, and a variety of neuroscientists all

weighed in, often generating more heat than light. Szasz (1976) even claimed that schizophrenia does not exist but is merely "the sacred symbol of psychiatry."

In recent years, as evidence has accumulated that there are abnormalities in brain structure and function in individuals with schizophrenia, the controversy has shifted. Critics of psychiatry have argued that, insofar as brain abnormalities do exist, they are caused by the use of antipsychotic medications. Breggin (1991), for example, claimed: "Dozens of studies have since come out indicating that neuroleptic-treated patients have such severe brain damage that it can be detected as shrinkage of the brain on the newer radiology techniques, such as the CT scan…."

Such views have been widely cited by Scientologists and other antipsychiatry advocates and continue to be repeated in the media. For example, science journalist Robert Whitaker, in his 2002 book *Mad in America,* described schizophrenia as "a term being loosely applied to people with widely disparate emotional problems" and asserted that most of the symptoms of schizophrenia are induced by antipsychotic medications:

> The image we have today of schizophrenia is not that of madness—whatever that might be—in its natural state. All of the traits that we have come to associate with schizophrenia—the awkward gait, the jerking arm movements, the vacant facial expression, the sleepiness, the lack of initiative—are symptoms due, at least in large part, to a drug-induced deficiency in dopamine transmission. (Whitaker, 2002)

The best way to ascertain the validity of such claims is to examine studies of schizophrenia carried out on individuals who have never been treated with antipsychotic medications. A total of 65 such studies were identified, which can be grouped into those examining structural, neurological, neuropsychological, electrophysiological, and cerebral metabolic abnormalities of the brain. In addition to these, a small number of studies exist on other aspects of brain function (e.g., evoked potentials, eye movements, vestibular reactivity), but these were not included in this review. Also not included were studies carried out on individuals who were experiencing their first episode of schizophrenia but who had been treated briefly with antipsychotic medications.

Structural Abnormalities

Structural abnormalities of the brains of individuals with schizophrenia have been observed for two centuries. Haslam, who examined the brains of individuals with insanity after their deaths, reported in 1809 that in many cases "the lateral ventricles were very much enlarged" (Haslam, 1809). Hecker (1871) in Germany and Southard (1915) in the United States made similar observations; the latter reported moderate or marked hydrocephalus in 8 of 25 consecutive cases of schizophrenia autopsied.

Following the development of pneumoencephalography in the 1920s, Jacobi and Winkler (1927) used this technique on 19 patients with schizophrenia and reported that 18

of them had enlarged cerebral ventricles. Table 1 summarizes other pneumoencephalographic studies carried out on individuals with schizophrenia prior to the introduction of antipsychotic medications. Some of the patients had been previously treated with electro-convulsive therapy (ECT), but Huber (1957) specifically compared those who had had ECT and those who had not and reported no difference in the ventricular size.

Since the introduction of CT and MRI technology, over 200 studies have examined brain structure in individuals with schizophrenia (Shenton et al., 2001). It is now known that such studies require an adequate control group, since some psychiatrically normal individuals also have structural changes in their brains (Buckley et al., 1992). It is also known that antipsychotic medications may increase the size of the basal ganglia and thalamus (Chakos et al., 1994; Gur et al, 1998), so structural studies should be carried out, whenever possible, on individuals who have never been treated with antipsychotic medications. Such studies have examined various brain structures in ten different groups of patients (Schulz et al., 1983; Lieberman et al., 1992, Degreef et al., 1992, Chakos et al., 1994; Shihabuddin et al., 1998; Keshavan et al., 1998, 2002, Gilbert et al., 2001, Venkatasubramanian et al., 2002b; Corson et al., 1999; Gur et al., 1998, 1999, 2000a, 2000b; Ettinger et al., 2001; McCreadie et al., 2002; Joyal et al., 2002; Karlsson et al., 2002).

Ventricular size was assessed for four of these groups. Schulz et al. (1983), using CT, compared 8 never-treated adolescents with schizophrenia and 18 normal controls; 7 of the 8 had enlarged ventricles, defined as “larger than the value of the mean plus two standard deviations of the control group.” Lieberman et al. (1992), using MRI to compare

62 never-treated patients with 42 normal controls, reported enlarged ventricles in 18 percent of the former and 2 percent of the latter ($p<0.05$). Gur et al. (1999 and personal communication 2002), using MRI to compare 33 never-treated patients with 65 normal controls, reported a 16 percent increase in ventricular volume in the patients ($p=0.052$, t test, 2-tailed). McCreadie et al. (2002), using MRI to compare 42 never-treated patients with 31 normal controls, reported a 20 percent increase in total ventricular (right and left) volume ($p=0.098$, t test, 2-tailed). Thus, modern studies, using CT and MRI, have confirmed older studies, using pneumoencephalography, showing increased ventricular size in individuals with schizophrenia who have never been treated.

Studies of other cerebral structures have been less conclusive. Within the basal ganglia, six studies have been done on the size of the caudate; three of these reported it to be significantly smaller in never-treated patients (Keshavan et al., 1998; Shihabbudin et al., 1998; Corson et al., 1999), one reported a trend in this direction for total caudate and a significant decrease for left caudate alone (McCreadie et al., 2002), and three other studies reported no differences between patients and controls (Chakos et al., 1994; Gur et al., 1998 and personal communication 2002; Karlsson et al., 2002). A significant increase in the size of the globus pallidus was reported by Gur et al. (1998 and personal communication 2002) ($p=0.024$, t test, 2-tailed). Gur et al. (1998 and personal communication 2002) also found a trend toward an increase in the size of the putamen ($p=0.064$), whereas Keshavan et al. (1998) reported a trend in the opposite direction, and Karlsson et al. (2002) found no difference.

Three studies measured the size of the thalamus in never-treated patients. Gur et al. (1998 and personal communication 2002), comparing 42 patients to 94 normal controls, reported a 10 percent reduction in the thalamus in the patients ($p=0.042$, t test, 2-tailed). Gilbert et al. (2001), comparing 16 patients to 25 normal controls, found an 18 percent reduction among the patients ($p=0.008$, analysis of covariance). Ettinger et al. (2001), comparing 13 antipsychotic-naïve patients and 25 non-antipsychotic-naïve patients to 29 normal controls, reported a 5 percent reduction among the patients ($p=0.05$, analysis of covariance) and no difference between those who were antipsychotic-naïve and those who were not ($p=0.99$).

Examining other structures, Lieberman et al. (1992), comparing 62 never-treated patients to 42 normal controls, found that 24 percent of the patients and 7 percent of the controls had "questionable" or "abnormal" frontal/parietal cortex ($p<0.05$), and that 44 percent of the patients and 21 percent of the controls had "questionable" or "abnormal" medial temporal structures ($p<0.01$). Gur et al. (1999, 2000a, 2000b, personal communication 2002), comparing up to 36 never-treated patients to up to 62 normal controls, assessed gray and white matter volume on a variety of frontal and temporal lobe regions. Although the gray matter was reduced in most regions in the patient group compared to the controls, the differences achieved statistical significance only for the lateral dorsal prefrontal area ($p=0.02$, t test, 2-tailed). Joyal et al. (2002), comparing the entorhinal cortex in 18 antipsychotic-naïve patients to 22 normal controls, reported that this area was significantly smaller in the patients ($p=0.009$, Pearson's two-tailed correlation).

Two studies have looked at the incidence of cavum septum pellucidum, a structural abnormality of the brain membranes. Degreef et al. (1992) found such abnormalities in 14 of 62 (23%) never-treated individuals with schizophrenia compared to 1 of 46 (2%) controls ($p<0.02$). However, Keshavan et al. (2002), comparing 40 never-treated patients to 59 normal controls, found no difference in the incidence of this structural abnormality between the groups. Finally, Venkatasubramanian et al. (2002b), comparing the corpus callosum in 25 antipsychotic-naïve patients to that of 21 normal controls, reported that the mean area of the corpus callosum was smaller in the patients ($p=0.029$).

Neurological Abnormalities

A wide variety of neurological abnormalities have been reported in individuals with schizophrenia who have never been treated with antipsychotic medications. These include dyskinesias, parkinsonian or extrapyramidal signs, neurological soft signs, and decreased pain perception.

Dyskinesias

Dyskinesias occur spontaneously in individuals with schizophrenia and may also be caused by antipsychotic medications; the latter is called tardive dyskinesia. Dyskinesias in schizophrenia most commonly include involuntary movements of the tongue or mouth (oro-facial dyskinesias) or the upper limbs.

Prior to the introduction of antipsychotic medications, dyskinesias were frequently described as occurring in individuals with schizophrenia. Turner (1989), in a review of the records of over 600 individuals in an English asylum between 1850 and 1890, reported that "movement disorder, often equivalent to tardive dyskinesia, was noted in nearly one-third of schizophrenics." Kraepelin, in his 1919 textbook on schizophrenia, provided an extended description of dyskinesia, and in the ensuing decades other psychiatrists elaborated on it. For example, in 1926, Reiter described 10 cases of schizophrenia with "marked and well-observed motor disturbances" such as "peculiar twitchings of the facial muscles" and "myoclonic jerkings of forearms and hands" (Reiter, 1926). Similarly, Farran-Ridge (1926) noted that "choreiform manifestations" were frequently observed in individuals with schizophrenia: "Of these, by far the commonest are all those spasmodic movements of expression which are grouped together under the heading of 'making faces' or 'grimacing'." In a review of pre–antipsychotic medications–era studies, Casey and Hansen (1984) concluded: "The question is not whether these types of abnormal movements occurred prior to the drug treatment era. They surely did. Rather, it is a question of how much of what is now called 'neuroleptic-induced TD' should actually be attributed to the natural history of psychosis, aging, or other nondrug causes."

Between 1959 and 1984, at least 29 studies assessed the prevalence of dyskinesia in individuals with schizophrenia who had not been treated with antipsychotic drugs. One review of these studies concluded that the prevalence of spontaneous dyskinesias was 4.2 percent (Casey and Hansen, 1984); another review of a subset of these studies came to a

similar conclusion of 5 percent (Kane and Smith, 1982). Much of the variation among studies can be attributed to the use of different scales and thresholds in the measurements.

More recently published studies of dyskinesias in individuals with schizophrenia who had never been treated with antipsychotic medications are summarized in Table 2. The average dyskinesia prevalence rate of 12 percent is modestly above the conclusions of earlier studies, possibly because more older patients were included in the recent studies and it is known that spontaneous dyskinesias increase with age (Fenton, 2000). Another confounding factor is that some of the study patients had been previously treated with ECT and/or insulin shock, including more than half the patients in the Fenton et al. (1997) study. The authors examined this issue and noted that "exposure to such treatments was not significantly related to the presence or absence of movement disorders in these samples." If this study is deleted from the list of recent studies, the average prevalence of spontaneous dyskinesias in the other recent studies is 23/278, or 8 percent.

The rate of tardive dyskinesia in individuals with schizophrenia who have been treated with antipsychotic medications has been estimated to be 15–20 percent in most studies (Casey and Hansen, 1984; Gerlach and Casey, 1988), although it increases over the age of 60. Thus, it appears that one-quarter to one-third of that prevalence is attributable to spontaneous dyskinesias and is not medication-related. The true prevalence of tardive dyskinesia, i.e., related to antipsychotic medications, is therefore no higher than 15 percent. As summarized by Khot and Wyatt (1991): "Not all that moves is tardive dyskinesia."

Parkinsonian signs

Parkinsonian or extrapyramidal motor signs were noted in individuals with schizophrenia for many years before antipsychotic medications were introduced. Kraepelin, in 1919, described patients with rigidity and bradykinesia as well as those with a tremor (Kraepelin, 1919). Similarly, in 1926, Reiter described patients with schizophrenia with a "well-defined parkinsonian syndrome, which overshadows all other symptoms" (Reiter, 1926).

Since 1993, seven studies have been published that assessed parkinsonian motor signs in individuals with schizophrenia who had never been treated with antipsychotic medications (Table 3). Rigidity, bradykinesia, and tremor were assessed using the Simpson-Angus Scale or the Extrapyramidal Symptom Rating Scale. A total of 91 out of 394 patients (23 percent) showed some combination of parkinsonian signs.

Neurological soft signs

It has become customary in neurology to divide neurological abnormalities into "hard" signs, such as the patellar tendon reflex, and "soft" signs, such as being unable to identify a coin in one's hand without looking at it (astereognosis). In the former, it is often possible to specify which part of the brain is affected, while the latter represent more complex brain functions. Heinrichs and Buchanan (1988), in a lucid discussion of neurological soft signs, claimed that they involve impairments in "three higher-order functional areas: the integration of more complex sensory units, the coordination of motor activity, and the sequencing of motor patterns." Neurological soft signs are found in a

variety of central nervous system (CNS) disorders, including dyslexia and attention-deficit/hyperactivity disorder (ADHD), and are less commonly found in individuals with no known CNS disorder.

Eight studies have assessed neurological soft signs in individuals with schizophrenia who had never received antipsychotic medications (Table 4). In the seven studies that included normal controls, the never-treated patients had significantly more soft signs. Five of the studies also compared never-treated and treated patients; in three studies the two groups had approximately the same degree of neurological dysfunction, and in the other two studies the treated patients had higher scores, suggesting that antipsychotic medications also contribute to neurological dysfunction.

These findings are consistent with more than 50 studies that have reported that individuals with schizophrenia who are being treated with medications have significantly more neurological soft signs than normal controls (Sanders and Keshavan, 1998). The present studies suggest that antipsychotic medications are not the main cause of the neurological abnormalities but rather a contributing cause. This confirms previous reports that whether patients were on or off medications at the time of testing had little effect on the presence of neurological soft signs (Manschreck et al., 1982; Kolakowska et al, 1985). It also confirms the schizophrenia twin study by Mosher et al. (1971) that concluded that "total previous drug intake … did not correlate significantly with the two neurologic scores."

Decreased pain perception

Anecdotal accounts of decreased pain perception, occasionally accompanied by self-mutilation, are abundant in historical accounts of schizophrenia from the years before antipsychotic medications were introduced. In the 1798 edition of his textbook, Haslam noted that "in many cases of insanity there prevails a great degree of insensibility, so that patients have appeared hardly to feel … the application of blisters or the operation of cupping" (Haslam, 1798). In the 1809 edition, Haslam added a description of an insane patient who amputated his own penis (Haslam, 1809). Similarly, Esquirol in 1838 described cases of insanity in which "pain may cease altogether, or be changed into a state of well-being. We see mad men frequently commit horrid mutilations with very blunt instruments, sometimes with red hot iron, without exhibiting the least symptom of pain, but, on the contrary, the strongest appearances of pleasure" (anonymous, 1838).

In the 20th century, Kraepelin (1919) observed that "patients often become less sensitive to bodily discomfort … pricks of a needle, injuries, without thinking much about it; burn themselves with their cigar…" Kraepelin's observation was followed by numerous similar reports, and by 1930 it was observed that "nearly every textbook of psychiatry mentions that the reaction to pain in catatonics is incomplete or absent" (Bender and Schilder, 1930). Two studies of psychotic patients who had sustained myocardial infarctions noted that 87 percent (Lieberman, 1955) and 83 percent (Marchand, 1955) of them did not complain of pain. In a study in a large Veterans Administration Hospital, in which 79 percent of the residents were diagnosed with schizophrenia, pain appeared to be absent in 21 percent of patients with an acute perforated ulcer, 37 percent of patients with

acute appendicitis, and 41 percent of patients with a fractured femur. As the authors noted: "The lack of complaint of pain by psychotic patients when afflicted by painful disorders has been an observation of every physician practicing in a mental institution" (Marchand et al., 1959).

For ethical reasons, it would not be possible today to do research on the pain threshold of individuals with schizophrenia. Such studies were, however, carried out prior to the introduction of antipsychotic medications. For example, Stengel et al. (1955) studied 13 individuals with schizophrenia and reported that they had decreased pain perception for pin-prick or pressure. Malmo et al. (1951) subjected 17 individuals with schizophrenia to "thermal stimulations" to the forehead, asking each to press a button "when he felt that the stimulus was about to become painful." The individuals with schizophrenia had a much "lower responsiveness to the pain stimulus" than individuals with psychoneuroses or normal controls. Hall and Stride (1954) carried out a similar study of 14 individuals with schizophrenia and also reported that "the overall results for the group show a very high [threshold for] V.R.P. [verbal report of pain] and P.R.P. [pain reaction point]."

The incidence of having a decreased pain threshold in individuals with schizophrenia is unknown. A questionnaire to members of the National Schizophrenia Fellowship in England reported that 16 percent said they had "insensitivity to pain" (Tyler, 1995). Anecdotal evidence also suggests that some individuals with schizophrenia may have the opposite and be unusually sensitive to pain and/or suffer from paresthesias, e.g., a feeling that insects are crawling on one's skin.

The mechanism responsible for decreased pain perception in individuals with schizophrenia is not known but most likely includes the thalamus, for which neuropathological abnormalities have been reported. In recent years, some observers (Fishbain, 1982; Guieu et al., 1994) have suggested that the decreased pain perception is a consequence of antipsychotic medications but, given the previous studies carried out prior to the use of such medications, this is unlikely. Brain endorphins and opiates have also been suggested as being involved. Finally, there is a lively debate whether individuals with schizophrenia do not feel the pain, or feel the pain but underreact; this debate is well summarized by Dworkin (1994).

Neuropsychological Abnormalities

Haslam, in his 1809 *Observations on Madness and Melancholy,* observed that recent memory was often impaired in individuals with insanity:

> In persons of sound mind, as well as in maniacs, the memory is the first power which decays; and there is something remarkable in the manner of its decline. The transactions of the latter part of life are feebly recollected, whilst the scenes of youth and of manhood, remain more strongly impressed. (Haslam, 1809)

Over the ensuing century and a half, anecdotal accounts continued to describe memory and other neuropsychological deficits in individuals diagnosed with insanity, dementia praecox, and schizophrenia.

In the 1940s, Rapaport and his colleagues carried out extensive neuropsychological testing on hospitalized patients with schizophrenia. Their two-volume report concluded that patients with schizophrenia differed markedly both from normal controls and from patients with depression on many neuropsychological tests, including "association thought processes" and "loose sortings, syncretistic, fabulated, or symbolic definitions" (Rapaport, 1946).

In recent years, five studies have reported neuropsychological test results in individuals with schizophrenia never treated with antipsychotic medications (Table 5). Saykin et al. (1994), studying 37 antipsychotic-naïve individuals with schizophrenia, reported "generalized impairment of approximately 2 SD units magnitude relative to healthy controls," with the greatest difference seen on tests of verbal memory and learning. They concluded that "this pattern is evident already in patients experiencing FE [first episode] of psychosis, who have never been exposed to neuroleptics."

Censits et al. (1997), comparing 30 first-episode patients (of which 28 were antipsychotic-naïve) to 30 previously treated patients and 38 normal controls, reported that "patients' neuropsychological performance was equally impaired for first-episode [antipsychotic-naïve] and previously treated patients." The data in this study were reanalyzed by Ragland to include only the 28 antipsychotic-naïve patients in the 30 first-

episode group (Ragland, personal communication 2002); maximum deficits in the patients were seen for tests of abstraction, attention, verbal memory, spatial memory, and language abilities ($p<0.0000$ for each).

McCreadie et al. (1997), comparing 19 antipsychotic-naïve patients to 55 normal controls, reported that memory was most impaired and that the degree of memory impairment correlated with the severity of the patients negative symptoms. Lussier and Stip (2001), comparing 16 antipsychotic-naïve patients to 20 normal controls, found that the patients were "mildly impaired" and that tests of attention were most affected. And Schuepbach et al. (2002), comparing 20 antipsychotic-naïve patients to 21 normal controls, reported that selective attention was significantly impaired in the patients.

In addition to these four neuropsychological studies utilizing exclusively antipsychotic-naïve patients, two other studies included a subset of antipsychotic-naïve patients and reported that this subset did not differ on neuropsychological testing from patients who had been treated with medications. Mohamed et al. (1999) included 77 antipsychotic-naïve patients with 21 others who had received medications and compared them to 305 normal controls on a broad neuropsychological test battery. The patients displayed "substantial impairments in most aspects of cognition," especially on tests of memory, speeded cognitive tasks, attention, social cognition, and executive skills (e.g., sequencing, organization, and flexibility). Similarly, Riley et al. (2000) included 15 antipsychotic-naïve patients with 25 other first-episode patients and compared them to 22 matched controls. The patients showed "significant impairment on tasks of executive

function, verbal learning, delayed recall from non-verbal memory, and psychomotor speed."

It should be noted that these neuropsychological studies of individuals with schizophrenia who have never been treated with antipsychotic medications yield results remarkably similar to neuropsychological studies of patients who have been treated with antipsychotic medications for varying lengths of time. Between 1980 and 1997, 204 such studies were published, covering 7,420 individuals with schizophrenia and 5,865 normal controls. In their analysis of these studies, Heinrichs and Zakzanis (1998) reported that deficits of memory, attention, and executive function were most prominent. Studies of medicated, previously medicated, and never medicated patients thus yield similar results, suggesting that antipsychotic medications have relatively little effect on most neuropsychological functions. This conclusion is also consistent with Mortimer (1997), who noted that "the effects of conventional neuroleptics on cognition in schizophrenia are minor according to numerous studies."

Electrophysiological Abnormalities

The most common way to assess electrophysiological function in individuals with schizophrenia is with an electroencephalogram (EEG). EEGs have been used for psychiatric research since the early 1930s. Between 1941 and 1954, five EEG studies of individuals with schizophrenia were carried out in which normal control groups were also

included. An additional study by Colony and Willis (1956) is not included in this analysis because it is unclear whether or not the patients with schizophrenia were being medicated and also because the "control" group consisted of other psychiatrically hospitalized patients, including those diagnosed with schizoid personalities and paranoid states.

Evaluation of EEG tracings is somewhat subjective. Thus, estimates of abnormal EEGs among groups of normal controls done at that time ranged from 5 to 20 percent (Ellingson, 1954). As summarized by Chamberlain and Russell (1952): "In general, while the proportion of subjects with abnormal EEGs varies with the group selected for study, it probably does not exceed 15 percent in the general population, and 10 percent probably is a fair approximation."

All five controlled studies of EEGs on individuals with schizophrenia carried out prior to the introduction of antipsychotic medications reported significantly more abnormal EEGs in the patients. As shown in Table 6, the rate of abnormal EEGs in these studies ranged from 23 to 44 percent. It is noteworthy that no single pattern of abnormality was found. A 1952 study of 100 patients with schizophrenia of varying degrees of severity reported that "abnormal electroencephalograms were quite definitely more frequent in the group of cases in which the psychopathologic process was most severe" (Kennard and Levy, 1952).

In addition to the above EEG studies using scalp electrodes, at least two groups carried out studies using deeply implanted electrodes in the years before the introduction of antipsychotic medications. Heath and his colleagues studied 26 patients with schizophrenia and reported spike abnormalities in the septal region and secondarily in the hippocampus

and amydgala; such spikes were not found in nonpsychotic patients being treated for conditions such as chronic pain or Parkinson's disease (Heath and Walker, 1985). Similarly, Peterson et al. (1953) used depth electrodes on four individuals with schizophrenia and reported abnormal electrical activity in the "deep frontal" and "subthalamic" regions.

In more recent years, many researchers have reported abnormal EEG activity in individuals with schizophrenia, but in almost all cases, they had been treated previously with antipsychotic medications. One exception to this was a sleep EEG study carried out on 8 individuals with schizophrenia and 16 normal controls. Compared to the controls, the patients showed diminished slow-wave sleep that was inversely "correlated with the severity of negative symptoms" (Ganguli et al., 1987).

Cerebral Metabolic Abnormalities

The measurement of cerebral 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 (Loeber et al., 2002), it is important to use individuals who have not been treated, whenever possible.

To date, ten studies have examined metabolic abnormalities in individuals with schizophrenia never treated with antipsychotic medications (Table 7). All except two of the studies reported statistically significant differences. Six of the studies used PET, three used fMRI, and one used SPECT. Representative of these studies is that by Barch et al. (2001), in which 14 antipsychotic-naïve individuals with schizophrenia, compared to 12 normal controls, failed to activate the dorsolateral prefrontal cortex (DLPFC) in response to neuropsychological tasks. The authors conclude "that DLPFC deficits are present at the onset of the first acute exacerbation in this illness and are not due to current or previous medication effects."

Discussion

This review of 65 studies, carried out on individuals with schizophrenia who had never received antipsychotic medications, indicates that the brains of these individuals have abnormalities in both brain structure and function that are inherent in the schizophrenia disease process, not medication-related. As such, schizophrenia is a disease of the brain in the same sense that Parkinson's disease and multiple sclerosis are diseases of the brain. Amariah Brigham (1844), a founding member of the American Psychiatric Association, expressed this clearly in 1844:

> Insanity is a chronic disease of the brain, producing either derangement of the intellectual faculties, or, prolonged change of the feelings, affections, and habits of an individual.

The best indicators of schizophrenia as a brain disease appear to be neurological and neuropsychological measures, since these studies are the most numerous and generally show the greatest differences between individuals with this disease and normal controls. Structural differences, as measured by CT or MRI, and cerebral metabolic differences, as measured by fMRI, PET, or SPECT, have been more highly publicized, but the differences between patients and normal controls are less impressive. Electrophysiological measures also show significant differences, but most of the antipsychotic-naïve studies were done in the early 20th century, when research methodology was less rigorous.

The importance of neurological and neuropsychological measures as indicators of adult schizophrenia is also consistent with findings from prospective studies of children who later develop schizophrenia. Compared to controls, the children who later develop schizophrenia have delayed developmental milestones such as walking and talking (Isohanni et al., 2001); "poorer fine and gross motor coordination" from ages 0 to 5 (Walker and Lewine, 1990); lower educational test scores at age 8 (Jones et al., 1994); and deficits in gross motor skills, in verbal memory and attention, and "cognitive and neurointegrative deficits" at ages 7 to 12 (Fish et al., 1992; Cannon et al., 1999; Erlenmeyer-Kimling et al., 2000). Thus, the neurological and neuropsychological deficits seen in adults with schizophrenia are adult manifestations of deficits that were apparent

premorbidly, many years before the symptoms became manifest or the individuals received any antipsychotic medications.

It should be emphasized, however, that there is no single abnormality in brain structure or function that is pathognomonic for schizophrenia. All deficits cited above can be found in some other brain diseases and, occasionally, in normal individuals, although statistically they occur more frequently in individuals with schizophrenia. Thus, we do not yet have a specific diagnostic test that points conclusively and exclusively to schizophrenia as the diagnosis.

It is also apparent from reviewing studies of individuals with schizophrenia who were antipsychotic-naïve that the schizophrenia disease process is not confined to a single part of the brain. Structural studies suggest involvement of the periventricular area, caudate, thalamus, and gray matter in general; MRI studies of individuals who were not antipsychotic-naïve have also implicated the medial temporal lobe, superior temporal gyrus, prefrontal and orbitofrontal cortex, inferior parietal lobule, corpus callosum, and cerebellum. Neurological studies of antipsychotic-naïve patients point to the basal ganglia (dyskinesias and extrapyramidal symptoms) and thalamus (decreased pain perception), although cortical structures are probably also involved. Neuropsychological studies of antipsychotic-naïve patients suggest dysfunction of the prefrontal and medial temporal areas; depth electrophysiological studies implicate the medial temporal and septal areas; and cerebral metabolic studies point toward the prefrontal cortex. It should be emphasized that these various structures are extensively interconnected and function as part of complex circuits, not as discrete brain areas.

It may also be asked whether the same individuals have abnormal findings in each of the five measures of brain structure and function. There are correlations between some findings in the same patients, such as neurological soft signs and Parkinsonian signs (Gupta et al., 1995), but not between others, such as neurological soft signs and ventricular enlargement (Kolakowska et al., 1985) or cerebral metabolism (Rubin et al., 1994). Overall, the correlations between abnormal findings in the same patients are not impressive, suggesting that abnormalities in brain structure and function are probably present in a large percentage of individuals with schizophrenia and not merely in a small subset. What this percentage is remains to be ascertained.

What are the limitations of this review of antipsychotic-naïve patients? The main limitation is that some of the patients, especially those in studies carried out prior to the introduction of antipsychotic medications, had been treated with somatic therapies (e.g., ECT or insulin coma therapy) or were being treated with sedatives or other medications. Studies that took this into account reported no differences between patients who had and had not been so treated. In most of the studies done in more recent years, however, the individuals with schizophrenia were experiencing their first episode of illness and had received no treatment whatsoever.

Now that schizophrenia is firmly established as a disease of brain structure and function, the next challenge is to identify the predisposing genes and biological insults that interact to cause the damage. This is the challenge for emerging molecular psychiatry, which, by focusing on the brain areas apparently affected in schizophrenia, will increase knowledge regarding the nature of the disease process and elevate our understanding of

schizophrenia's etiology to another level. With such understanding should come new and better medications.

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Table 1. Pneumoencephalography Studies of Individuals with Schizophrenia Never Treated with Antipsychotic Medications

Year	Investigator(s)	Enlargement of Cerebral Ventricles	
1927	Jacobi and Winkler	18/19	95%
1933	Moore et al.	25/60	42%
1935	Lemke	50/100	50%
1949	Donovan et al.	16/19	84%
1957	Huber	131/195	67%

Table 2. Recent Studies of the Prevalence of Dyskinesia in Individuals with Schizophrenia Never Treated with Antipsychotic Medications

Year	Author(s)	Country	Prevalence
1985	Rogers	England	3/8 (38%)
1989	Chorfi and Moussaoui	Morocco	0/50 (0%)
1994	McCreadie and Ohaeri	Nigeria	0/12 (0%)
1995	Chatterjee et al.	United States	1/89 (1%)
1996	Fenn et al.	Morocco	3/22 (14%)
1996	McCreadie et al.	India	8/21 (38%)
1997	Fenton et al.	United States	22/94 (23%)
1998	Gervin et al.	Ireland	5/49 (10%)
1999	Puri et al.	England	3/27 (11%)
Total			45/372 (12%)

Table 3. Recent Studies of the Prevalence of Parkinsonian Signs in Individuals with Schizophrenia Never Treated with Antipsychotic Medications

Year	Author(s)	Country	Prevalence
1993	Caligiuri et al.	United States	5/24 (21%)
1995	Chatterjee et al.	United States	15/89 (17%)
1996	McCreadie et al.	India	5/21 (24%)
1998	Kopala et al.	Canada	9/41 (22%)
1999	Puri et al.	England	1/27 (4%)
2002	Honer et al.	Multicenter International	47/167 (28%)
2002	Cortese et al.	Canada	9/25 (36%)
Total			91/394 (23%)

Table 4. Studies of Neurological Soft Signs in Individuals with Schizophrenia Never Treated with Antipsychotic Medications

Year	Author(s)	Country	Results
1992	Schröder et al.	Germany	On a 17-item scale, compared 17 never-treated patients to 33 receiving treatment and 34 normal controls. The patient group had significantly more soft signs than controls ($p<0.0001$), and the scores of the never-treated patients "did not differ from that of the remaining patients."
1994	Rubin et al.	Denmark	Compared 12 never-treated patients to 33 receiving treatment and 24 normal controls. The never-treated group had a significantly higher total neurological abnormality score than the controls ($p=0.03$) and was virtually identical to the group receiving treatment.
1994	Sanders et al.	United States	On a 27-item scale, compared 17 never-treated patients to 15 normal controls. The former had significantly more neurological abnormalities ($p=0.0001$).
1995	Gupta et al.	United States	On a 13-item scale, compared 26 never-treated patients to 126 receiving treatment and 117 normal controls. Compared to the controls, the never-treated patients had more soft signs (23% vs. 0%) and developmental reflexes (19% vs. 0%). The treated patients had even more soft signs (46%).
2000	Browne et al.	Ireland	On a 26-item scale, compared 35 never-treated patients to 31 receiving treatment. Sixty-three percent (63%) of the never-treated patients had at least two abnormal soft signs, and they did not differ significantly from those receiving treatment.

2000 & 2002	Krebs et al. Krebs et al.	France	Compared 54 never-treated patients to 51 receiving treatment and 48 normal controls on a 23-item scale. The mean scores of the groups were 10.8 for never-treated, 13.7 for treated, and 5.0 for normal controls. Using their data, we compared the never-treated and normal controls by t test ($p<0.0001$).
2002	Shibre et al.	Ethiopia	On a 26-item scale, compared 200 never-treated patients to 78 normal controls. The median scores of neurological abnormalities were 5.0 for patients and 1.5 for controls ($p=0.000$).
2002a	Venkatasubramanian et al.	United States	Compared 25 never-treated patients to 21 normal controls on a Neurological Evaluation Scale. The patients had more soft signs ($p=0.006$).

Table 5. Studies of Neuropsychological Function in Individuals with Schizophrenia Never Treated with Antipsychotic Medications

Year	Author(s)	Results
1994	Saykin et al.	Thirty-seven (37) patients, compared to 131 normal controls, had marked impairment in tests of verbal memory and learning ($p<0.001$).
1997	Censits et al., reanalyzed by Ragland to include only the antipsychotic-naïve patients	Twenty-eight (28) patients, compared to 38 normal controls, showed generalized impairment that was most marked for tests of abstraction, attention, verbal memory, spatial memory, and language abilities ($p<0.0000$ for each).
1997	McCreadie et al.	Nineteen (19) patients, compared to 55 normal controls, performed more poorly on some memory tests including memory quotient ($p=0.008$) and digit span ($p=0.0009$).
2001	Lussier and Stip	Sixteen (16) patients, compared to 20 normal controls, showed the greatest deficits on tests of attention ($p<0.001$).
2002	Schuepbach et al.	Twenty (20) patients, compared to 21 normal controls, showed significant deficits on the Stroop test for selective attention ($p<0.01$).

Table 6. EEG Studies of Individuals with Schizophrenia Never Treated with Antipsychotic Medications

Year	Authors	Number of individuals with schizophrenia	Percent abnormal EEGS (schiz)	Number of controls	Percent abnormal EEGs (controls)	Statistical significance
1941	Finley and Campbell	500	28%	215	7%	$p<0.001$
1944	Greenblatt	465	23%	240	10%	$p<0.001$
1952	Chamberlain and Russell	45	44%	43	12%	$p<0.001$
1952	Hill	147	35%	138	20%	$p<0.01$
1954	Ellingson	53	28%	1,000	16%	$p<0.02$

Table 7. Studies of Cerebral Metabolic Abnormalities in Individuals with Schizophrenia Never Treated with Antipsychotic Medications

Year	Author(s)	Measure	Results
1991	Cleghorn et al.	PET	Eleven (11) patients, compared to 8 normal controls, showed significantly altered glucose metabolism in the striatum ($p=0.02$), superior temporal ($p=0.02$), and posterior frontal ($p=0.02$) regions.
1992	Buchsbaum et al.	PET	Eighteen (18) patients, compared to 20 normal controls, showed significantly reduced glucose metabolism in the frontal regions ($p=0.03$) and basal ganglia ($p<0.05$).
1998	Shihabuddin et al.	PET	Seven (7) patients, compared to 24 controls, had a lower metabolic rate in the right putamen ($p<0.05$).
1999	Laruelle et al.	SPECT	Seven (7) patients, compared to 36 normal controls, showed significant increase in dopamine displacement in response to amphetamine challenge ($p<0.001$).
2001	Barch et al.	fMRI	Fourteen (14) patients, compared to 12 normal controls, showed deficits in activation of the prefrontal cortex in response to neuropsychological tasks ($p=0.007$).
2001	Clark et al.	PET	Twenty-six (26) patients, compared to 32 normal controls, had lower glucose metabolism in all 27 brain regions, but the results did not achieve statistical significance.
2002	Braus et al.	fMRI	Twelve (12) patients, compared to 11 normal controls, showed reduced activation in the right thalamus and right prefrontal cortex in response to visual and auditory stimuli ($p<0.01$).

2002	Brewer et al.	fMRI	Eight (8) patients, compared to an unspecified number of normal controls, failed to activate the anterior cingulate in response to neurospsychological tasks.
2002	Karlsson et al.	PET	Ten (10) patients, compared to 10 normal controls, did not differ significantly in D-1 dopamine receptor binding.
2002	Tauscher et al.	PET	Fourteen (14) patients, compared to 14 normal controls, showed significantly increased serotonin 5-HT1A receptor binding ($p=0.02$).