

# Neurologic Comorbidities in Schizophrenia

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Brain abnormalities have long been assumed to be involved in the pathophysiology of schizophrenia. Magnetic resonance imaging studies have identified numerous structural and functional imaging abnormalities, such as reduced brain volume, frontal lobe volume, and hippocampal volume, in patients with schizophrenia. Neurologic disorders, such as movement disorders, neurologic abnormalities, and cognitive deficits, are often seen years before the onset of schizophrenia. Many of these abnormalities may be predictive of the development of schizophrenia, but unfortunately, they are usually overlooked. In addition, treatment with antipsychotics may affect brain structure, further complicating the ability to detect changes due to the neuropathology of psychosis. This article reviews the structural and functional imaging abnormalities found in patients with schizophrenia and the neurologic disorders that commonly coexist with the disorder. The role that treatment with atypical antipsychotics may or may not have in contributing to neurologic abnormalities is also discussed. Through increased awareness of these abnormalities, the importance of obtaining a complete neurologic history and examination of patients with schizophrenia at the onset of their illness and before initiating pharmacotherapy will become evident. Such recognition may permit earlier identification and treatment of schizophrenia, thus potentially improving long-term outcome.

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The pathophysiology of schizophrenia (which affects approximately 1% of the general population) has long been assumed to include certain brain abnormalities.<sup>1</sup> Recent neuroimaging and neurophysiologic techniques have demonstrated that schizophrenia has structural and functional impacts on cognitive, emotional, and motivational aspects of human behavior; however, studies using these techniques are often confounded by the heterogeneity of the disease.<sup>1</sup> Antipsychotics can also affect brain structure, which may further confound the ability to identify changes due to the neuropathology of psychosis and may contribute to the therapeutic and adverse event profiles of antipsychotics through their antagonistic effect on dopamine-2 (D<sub>2</sub>) receptors (reviewed by Harrison<sup>2</sup>). In ad-

dition, disease- and drug-induced morphological changes may occur in different structures.<sup>2</sup>

A selective search of the National Library of Medicine's PubMed database between 1998 and 2003 identified numerous articles that have addressed the coexistence of neurologic abnormalities and schizophrenia (Table 1), although the roles that schizophrenia and/or antipsychotics have in the development of abnormalities are not fully recognized in the medical community. In this article, coexistent abnormalities are reviewed in an effort to increase awareness and potentially assist the clinician in the early identification of patients who may be at risk for schizophrenia.

## STRUCTURAL AND FUNCTIONAL IMAGING ABNORMALITIES OF THE BRAIN

### Structural Abnormalities

Structural abnormalities (Table 2) have been found in the brains of patients with schizophrenia using magnetic resonance imaging (MRI). MRI images of the frontal lobe, hippocampus, and ventricles are shown in Figures 1–3. These abnormalities have been extensively reviewed by others,<sup>3–6</sup> and the purpose of this review is to highlight more recent research.

In patients with schizophrenia, the volumes of whole brain and gray matter appear to decrease, with variable changes in white matter volume.<sup>3,4,7,8</sup> In addition to a reduction in volume, the density of gray matter appears to be reduced because of progressive loss with age.<sup>8,9</sup> Age-related changes in patients with schizophrenia are particu-

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**Table 1. Neurologic Abnormalities Comorbid With Schizophrenia**

Structural and functional imaging abnormalities
Movement disorders
Sensory disorders
Neurologic soft signs
Lateral deviations
Epilepsy
Cognitive deficits
Electrophysiologic changes

larly marked in the left amygdala and left hippocampus.<sup>8</sup> Frontal lobe volume is also reduced in schizophrenia,<sup>4</sup> although published reports are inconsistent.<sup>5</sup>

Changes in the temporal lobe appear to be specific for schizophrenia.<sup>10</sup> Compared with that in control subjects, the volume of gray matter of the temporal lobes seems to be reduced. However, temporal volume is low, and specific areas of loss vary between reports<sup>10-13</sup> with no clear correlation between temporal volume and stage of the disorder.<sup>3</sup> Overall temporal lobe reductions averaging approximately 8% have been reported in patients with schizophrenia.<sup>14</sup> The clinical significance of these findings is uncertain, but in 1 study,<sup>13</sup> a smaller temporal lobe gray matter volume at the start of the study was significantly correlated with continued hallucinations.

The hippocampus in patients with schizophrenia is 2% to 3% smaller than in controls, with reductions of 6% in amygdala volume reported,<sup>4</sup> although a more recent study has suggested a reduction of up to 7%.<sup>15</sup> However, a recent small postmortem study<sup>16</sup> failed to show notable reductions in amygdala volume in patients with schizophrenia; thus, further study in this area is warranted.

Total ventricular system volume is reported to be increased by as much as 30% in patients with schizophrenia compared with persons without schizophrenia.<sup>3-5,14</sup> Most of the increase in ventricular system volume occurs in the lateral ventricles, where increases as much as 16% over the volume in controls without schizophrenia have been reported.<sup>4,7</sup> Significant increases are also seen in the third ventricle volume in patients with schizophrenia.<sup>5,7,17,18</sup> A gender difference is suggested because women with schizophrenia had smaller brains but larger third and lateral ventricles.<sup>17</sup> Increases in ventricular system volume were also observed in antipsychotic-naïve patients, indicating that the increase stems from the disorder itself and not from using antipsychotic medications.<sup>6</sup>

The corpus callosum is responsible for transferring information between hemispheres of the brain; therefore, abnormalities in this region might interfere with cognitive function requiring interhemispheric transfer.<sup>19</sup> In patients with schizophrenia, an apparent decrease in area of the corpus callosum may be general<sup>20</sup> or regional.<sup>19</sup> Significant reductions in the corpus callosum area were also seen in patients who had never been treated with antipsychotic medications.<sup>6</sup>

**Table 2. Structural Abnormalities in Schizophrenia**

↓ Brain volume
↓ Frontal volume
↓ Temporal volume
↓ Hippocampal volume
↓ Amygdala volume
↓ Corpus callosum thickness
↓ Thalamic volume
↑ Lateral cerebral ventricle volume
↑ Third ventricle volume

Symbols: ↓ = decreased, ↑ = increased.

Family members of patients with schizophrenia also have reductions in the volume of the thalamus compared with healthy subjects.<sup>21</sup> Similar decreases were also observed in patients with first-episode schizophrenia who had never been treated with antipsychotic drugs, confirming that the abnormalities are part of the disease process itself and not related to the medication.<sup>6</sup> The volume of the left fusiform gyrus is smaller in patients with schizophrenia, and the asymmetries of the gray matter of the parahippocampal and fusiform gyri seen in most healthy individuals are reversed in the brains of patients with schizophrenia.<sup>22,23</sup> Abnormal gyrus formation in the brains of patients with schizophrenia supports the neurodevelopmental theory of schizophrenia.<sup>24,25</sup>

In summary, there is evidence of structural differences in the brains of patients with schizophrenia compared with those of healthy subjects. However, the extent of this diversity is somewhat variable; therefore, further research is required in this area.

### Cerebral Metabolic Abnormalities

Studies in patients with schizophrenia indicate the presence of low blood flow or a metabolic dysfunction in the prefrontal portion of their brains. In particular, there is decreased activation of the right dorsolateral prefrontal cortex, which is related to working-memory deficit in these patients.<sup>26-32</sup> Dysfunction of the dorsolateral prefrontal cortex occurs in both medication-naïve patients and in those taking antipsychotic medications, supporting the view that the abnormality is caused by the underlying dysfunction and not medication.<sup>26</sup>

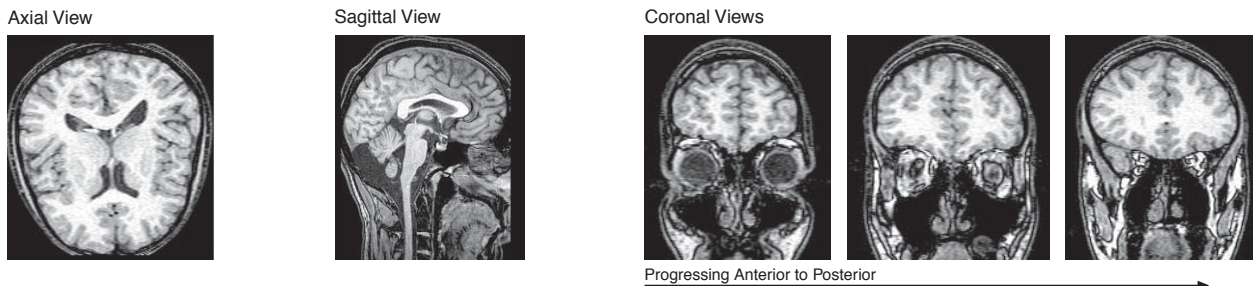
Potkin et al.<sup>33</sup> found that patients with schizophrenia exhibiting predominantly negative symptoms appear to have more metabolic abnormalities in certain areas of their brains than both patients with predominantly positive symptoms and healthy subjects. This finding was particularly shown by a lower glucose metabolic rate in the right dorsolateral prefrontal cortex.<sup>33</sup>

### Minor Physical Anomalies

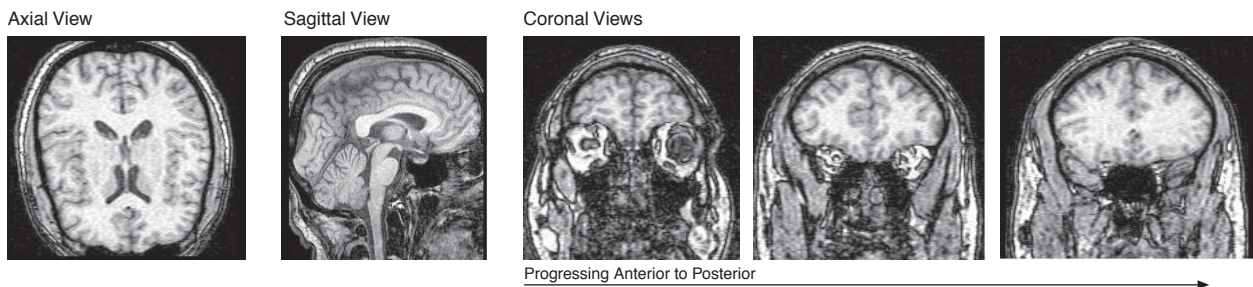
A number of minor physical anomalies (MPAs), such as anomalies of the mouth, head, extremities, and face, commonly occur in patients with schizophrenia (Table 3).<sup>34,35</sup> A high-steeped palate is often seen in patients with

Figure 1. Axial, Sagittal, and Coronal Views of the Frontal Lobe of a Patient With Schizophrenia; No ACPC Squaring<sup>a</sup>

A. Large



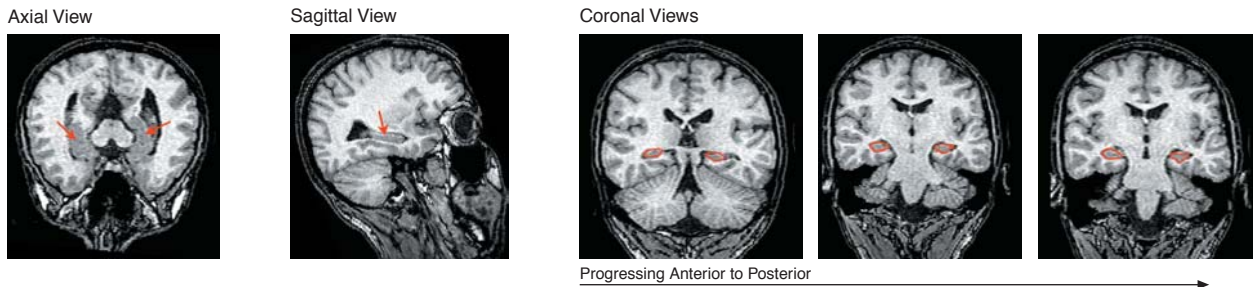
B. Small



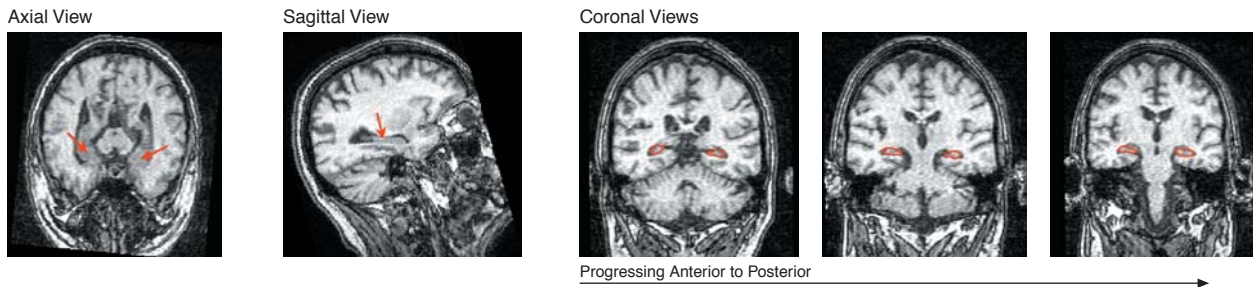
<sup>a</sup>Images on file, University of Cincinnati Center for Imaging Research, Cincinnati, Ohio (S. Strakowski, M.D., Director). Large = regarded as larger than average by radiologists; Small = regarded as smaller than average by radiologists. Abbreviation: ACPC = anterior commissure–posterior commissure.

Figure 2. Axial, Sagittal, and Coronal Views of the Hippocampus of a Patient With Schizophrenia; Obliquely Squared to Left Arm of Hippocampus<sup>a</sup>

A. Large



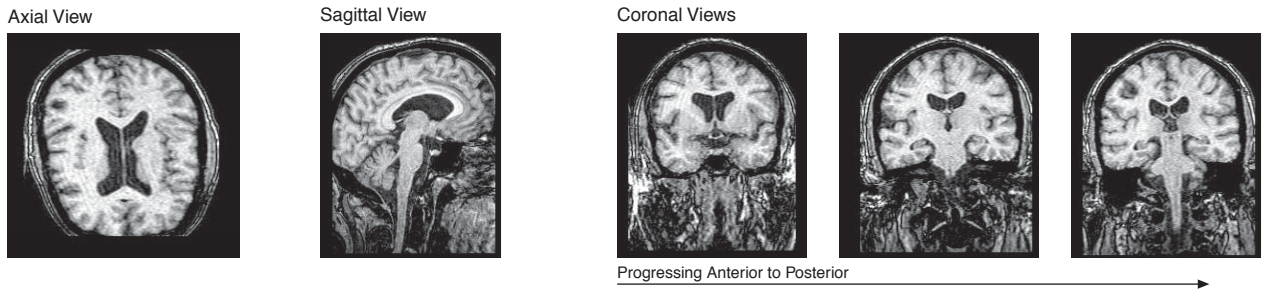
B. Small



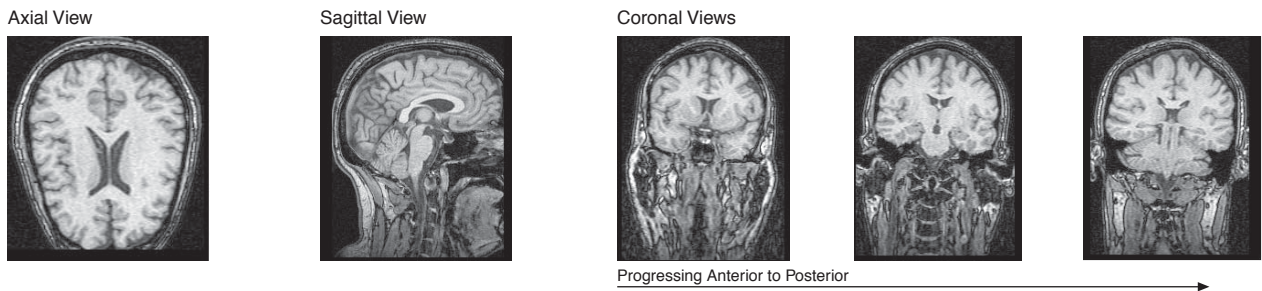
<sup>a</sup>Images on file, University of Cincinnati Center for Imaging Research, Cincinnati, Ohio (S. Strakowski, M.D., Director). Large = regarded as larger than average by radiologists; Small = regarded as smaller than average by radiologists.

Figure 3. Axial, Sagittal, and Coronal Views of the Lateral Ventricles and Third Ventricle of a Patient With Schizophrenia; No ACPC Squaring<sup>a</sup>

A. Large



B. Small



<sup>a</sup>Images on file, University of Cincinnati Center for Imaging Research, Cincinnati, Ohio (S. Strakowski, M.D., Director). Large = regarded as larger than average by radiologists; Small = regarded as smaller than average by radiologists. Abbreviation: ACPC = anterior commissure–posterior commissure.

Table 3. Minor Physical Anomalies Frequently Seen in Schizophrenia<sup>a</sup>

- Low-set or malformed ears
- Curved fifth finger
- High-steeped palate
- Partial syndactyly of the 2 middle toes

<sup>a</sup>Based on Ismail et al.<sup>35</sup>

schizophrenia and may be associated with midline brain anomalies.<sup>35,36</sup> Higher rates of furrowed tongue, flat occiput, and ears with primitive shape also have been reported in more patients with schizophrenia than in healthy individuals.<sup>36</sup> MPAs lend support to the neurodevelopment theory of schizophrenia because they are strong indicators of neuroembryonic development.<sup>34,36–39</sup>

Prenatal complications in schizophrenia (e.g., maternal infection, dietary deficiency, hypoxia, rubella, bleeding, and drug use) may contribute to the development of MPAs.<sup>34,38,40–42</sup> An excess of MPAs (abnormalities of the feet, macroencephaly, and microencephaly), noted in patients with schizophrenia but not in their siblings, may represent a nongenetic neurodevelopmental cause of schizophrenia.<sup>39,41</sup> Patients with velocardiofacial syndrome (characterized by mild cognitive impairment, learning disabilities, cardiac malformations, cleft palate, and a characteristic facial appearance) have reduced total brain volume and abnormal temporal lobe and hippocam-

Table 4. Cognitive Deficits and Impairment in Schizophrenia<sup>a</sup>

- Attention
- Memory
  - Verbal and visual recognition
  - Recall
- Executive functions
  - Goal-directed behavior
  - Planning
  - Flexibility
  - Self-monitoring
  - Insight
- Language

<sup>a</sup>Based on Kuperberg and Heckers<sup>45</sup> and Riley et al.<sup>47</sup>

pal development similar to those seen in schizophrenia, suggesting that these patients may be at high risk of developing schizophrenia.<sup>43,44</sup>

**COGNITIVE DEFICITS IN SCHIZOPHRENIA**

In patients with schizophrenia, cognitive decline is observed before the onset of the initial psychotic episode.<sup>45–48</sup> Cognitive deficits in attention, memory, executive function, and language are observed early in the course of the disease (Table 4).<sup>45,47</sup> Studies of cognitive function in first-episode schizophrenia are important because the results show that these deficits are a consequence of the disease and not of antipsychotic treatment or institutionalization.<sup>47</sup>

The degree of cognitive dysfunction is a powerful indicator of long-term outcome in schizophrenia.<sup>46,49–52</sup> For example, verbal memory and executive function are predictive of long-term functional outcome.<sup>52,53</sup> Executive functioning, working memory, verbal learning and memory, and vigilance are predictors of vocational outcome.<sup>53</sup> Good verbal and visual memory performance are predictive of positive clinical, but not social, outcomes.<sup>54</sup>

Various cognitive deficits may occur in schizophrenia, but certain functions are usually spared. Deficits are seen in cognitive functions controlled by frontotemporal processes. Lussier and Stip<sup>48</sup> found that antipsychotic-naïve patients with schizophrenia evidently have decreased ability to sustain attention measured with a continuous performance test. Deficits on this test are stable indicators of schizophrenia.<sup>55</sup>

Poor verbal memory in patients with schizophrenia is attributed to prefrontal and hippocampal dysfunction.<sup>56</sup> Patients with schizophrenia show a reduced ability to use redundant or predictive features of cognitive tasks. Patients with impaired performance on verbal predictive tasks also show deficiencies on certain redundant motor tasks.<sup>57</sup> Patients with schizophrenia have more difficulty recalling the first items in a list compared with control subjects<sup>58</sup> and show impaired object recognition and identification.<sup>59</sup> Recall and recognition of words and factual information, which comprise declarative memory, are also impaired.<sup>60</sup> When compared with control subjects, patients with schizophrenia have impaired retrieval capabilities. However, nondeclarative memory, which is based on prior exposure, is intact in patients with schizophrenia.<sup>60</sup> Differences in memory impairment can be explained by underlying structural impairment.

Impaired working memory has many of the cognitive and clinical features observed in patients with schizophrenia<sup>61,62</sup> and is related to a number of cognitive deficits seen in this disease.<sup>63,64</sup> The observed visual working memory deficits involve both spatial and object working memory dysfunction.<sup>64,65</sup>

The lack of awareness of illness often seen in patients with schizophrenia has been linked to deficits in executive function and coping style. Poor illness insight is the result of deficits in awareness.<sup>66</sup> Perseveration errors and poor insight seem closely related.<sup>67</sup> Impairments of certain executive/attentional cognitive dysfunctions—that is, in selective attention and verbal fluency—may be vulnerability markers in patients with schizophrenia.<sup>68</sup> Executive function deficits observed in patients with first-episode schizophrenia may be associated with hippocampal abnormalities. A dysfunction of the system that links the frontal and mesiotemporal lobe regions thus appears evident.<sup>69</sup>

Dysfunction in language processing is present in patients with schizophrenia at early stages of auditory processing and during higher stages of semantic development.<sup>70</sup> Studies of childhood-onset schizophrenia indicate

that language impairment is the result of abnormal development in language-related regions of the brain.<sup>71</sup> Patients with schizophrenia typically show significant impairment of both semantic and letter fluency.<sup>72</sup>

A greater incidence of schizophrenia is seen in populations with mental retardation and learning disabilities.<sup>73–75</sup> David et al.<sup>73</sup> found that low intellectual ability (IQ < 96) is associated with an increased risk of schizophrenia. Results of some studies indicate that cognitive deficits may be the cause of the higher frequency of schizophrenia observed in patients with learning disabilities. Among patients with learning disabilities, cognitive deficits may be the result of undiagnosed schizophrenia.<sup>75</sup> Amygdala-hippocampal hypoplasia appears to be a risk factor for schizophrenia in patients with mental retardation.<sup>74,75</sup>

### COGNITIVE DEFICITS AND ATYPICAL ANTIPSYCHOTICS

The number of variables in study design makes interpreting studies of the effects of atypical antipsychotics on cognition complex. Variables include stage of disease, level of treatment resistance, duration and dosage of treatment, and type of assessment made. Still, some observations can be made.

Comparative studies have shown improvement in some reported cognitive deficits with atypical antipsychotics, but not with conventional antipsychotic drugs (Table 5).<sup>76–84</sup> In studies evaluating treatment-resistant patients with schizophrenia,<sup>76,78,82</sup> significant improvement in cognition has been observed with olanzapine, risperidone, and clozapine compared with haloperidol. In a study conducted by Bilder et al.,<sup>76</sup> > 50% of patients had clinically significant improvement with olanzapine and risperidone compared with haloperidol. Pallanti et al.<sup>78</sup> suggest that clozapine appears to be superior to conventional antipsychotics in enhancing insight in patients with schizophrenia. Olanzapine, in particular, has shown significantly greater improvement in general cognitive index and measures of memory compared with conventional antipsychotics.<sup>77,80,82</sup> Quetiapine has also shown significant improvement in general cognitive index and measures of memory compared with conventional antipsychotics.<sup>81,83,84</sup> In addition, in a preliminary, 6-month study,<sup>81</sup> quetiapine has been associated with some improvement in executive skills and visuomotor tracking, but not at a statistically significant level.

Noncomparative studies also suggest that atypical antipsychotics are associated with beneficial effects in improving cognitive deficits. In a study of patients with first-episode schizophrenia who were treated with atypical antipsychotics (quetiapine, clozapine, risperidone, and olanzapine), significant improvements were seen in intellectual function, auditory and visual memory, and working memory and on some measures of executive function.<sup>85</sup>

Table 5. Comparative Antipsychotic Studies Evaluating Cognitive Deficits in Patients With Schizophrenia

Clinical Trial	N	Diagnosis	Type of Study	Duration	Treatment Group (dosage, mg/d)	Cognitive Effects
Bilder et al, 2002 <sup>76</sup>	101	Schizophrenia/schizoaffective disorder, treatment refractory	Double-blind	14 wk	Clozapine (200–800); olanzapine (10–40); risperidone (4–16); haloperidol (10–30)	Global cognitive performance: olanzapine and risperidone > haloperidol ( $p < .05$ ); neither olanzapine nor risperidone significantly different from each other or clozapine
Cuesta et al, 2001 <sup>77</sup>	38	Schizophrenia, partially responsive	Naturalistic	6 mo	Olanzapine (5–20); control <sup>a</sup>	Verbal memory: olanzapine > control ( $p \leq .03$ ); risperidone > olanzapine (WCST; $p \leq .02$ ); risperidone > CONV (WCST; $p \leq .05$ )
Pallanti et al, 1999 <sup>78</sup>	22	Schizophrenia, treatment refractory	Crossover	6 mo	Clozapine (347.7) <sup>b</sup> ; CONV (197.8) <sup>b</sup>	Amplitude of P300 component of the auditory-evoked potential increased significantly after treatment with clozapine; clozapine > CONV in improving insight
Potkin et al, 2001 <sup>79</sup>	27	Schizophrenia, inpatients	Double-blind, placebo-controlled, crossover	6 wk	Clozapine (300–500); haloperidol (adjusted based on target plasma level 10–20 $\mu\text{g/mL}$ )	Neurocognitive performance: clozapine and haloperidol > placebo; clozapine > haloperidol on Trails B ( $p = .01$ ), verbal fluency ( $p = .02$ ), delayed recall ( $p = .01$ ), and recognition on verbal list learning ( $p = .05$ )
Purdon et al, 2000 <sup>80</sup>	65	Schizophrenia, stable outpatients within 5 years <sup>c</sup>	Double-blind	54 wk	Olanzapine (5–20); risperidone (4–10); haloperidol (5–20)	General cognitive index: olanzapine > haloperidol ( $p < .001$ ); olanzapine > risperidone ( $p = .004$ ); no significant difference between risperidone and haloperidol
Purdon et al, 2001 <sup>81</sup>	25	Schizophrenia	Double-blind	6 mo	Quetiapine (300–600); haloperidol (10–20)	No improvement with haloperidol on cognitive skills; at 6 mo, quetiapine ( $N = 8$ ) showed significant improvement vs baseline on general cognitive index ( $p = .003$ ) and verbal reasoning/fluency ( $p < .001$ ) and a trend toward improvement on executive skills/visuomotor tracking ( $p = .014$ ) and immediate recall ( $p = .022$ )
Smith et al, 2001 <sup>82</sup>	33 <sup>d</sup>	Schizophrenia, treatment refractory	Double-blind; open-label	8 wk (double-blind); 3 mo (open-label)	Olanzapine (5–20) <sup>e</sup> ; haloperidol (5–40)	Double-blind: olanzapine and haloperidol not significantly different in verbal and visual memory; open-label: significant improvement in verbal and visual memory with olanzapine vs baseline
Velligan et al, 2002 <sup>83</sup>	58	Schizophrenia, stable outpatients	Double-blind	24 wk	Quetiapine (300 or 600); haloperidol (12)	Quetiapine 600 > haloperidol in overall cognitive function ( $p < .02$ ), attention ( $p < .03$ ), and verbal memory ( $p < .02$ )
Velligan et al, 2003 <sup>84</sup>	40	Schizophrenia, stable outpatients	Double-blind, rater-blinded	6 mo	Quetiapine (319) <sup>b</sup> ; CONV (348) <sup>b</sup>	Quetiapine > CONV in cognitive function summary score ( $p < .023$ ), verbal fluency ( $p < .013$ ), and verbal memory ( $p < .02$ )

<sup>a</sup>Patients in the control group received risperidone (1.5–9.0 mg/d) or a conventional antipsychotic (dose range not specified).

<sup>b</sup>Mean dose; dose of conventional antipsychotics based on chlorpromazine equivalent units.

<sup>c</sup>Patients were within 5 years of their exposure to neuroleptic treatment and had at least mild symptom severity.

<sup>d</sup>Twenty-nine patients participated in the open-label phase of this study.

<sup>e</sup>Maximum dose of olanzapine during the open-label phase of the study was 40 mg/d.

Abbreviations: CONV = conventional antipsychotics, WCST = Wisconsin Card Sorting Test.

Unfortunately, the study design did not allow for differentiation of the atypical antipsychotics in this patient population. Good et al.<sup>86</sup> found that first-episode patients have significant improvement in verbal fluency, attention, and executive function after 6 months and 1 year of quetiapine treatment. In patients with treatment-refractory schizophrenia, clozapine has been observed to significantly improve verbal fluency ( $p = .03$ ), set shifting ( $p = .033$ ), and general memory ( $p = .003$ ) compared with baseline levels.<sup>87,88</sup> Manschreck et al.<sup>87</sup> have noted that 65% of treatment-resistant patients improved enough to be discharged from the hospital during treatment with clozapine for up to 1 year. In an open-label study,<sup>89</sup> patients with chronic schizophrenia showed improvement in explicit memory, selective attention, and alertness following 6 months of risperidone treatment. Additionally, a 6-week open-label study of 19 patients with chronic schizophrenia showed significant improvement with quetiapine in working memory ( $p = .04$ ), attention ( $p = .02$ ), and fine motor performance ( $p = .02$ ).<sup>90</sup>

A recent study that utilized positron emission tomography and functional MRI<sup>15</sup> has determined that hippocampal volume is reduced in patients with schizophrenia treated with antipsychotics and that this reduction is associated with an impaired ability to identify novel items on an old-new recognition memory test. The authors also determined that a reduction in hippocampal volume is not associated with a global reduction in hippocampal function.<sup>15</sup> Further studies on the relationship between structure and function, and the effect of treatment, clearly are required.

### MOVEMENT DISORDERS IN DRUG-NAIVE PATIENTS WITH SCHIZOPHRENIA

A number of movement disorders related to schizophrenia are seen in patients who have never taken antipsychotic medications,<sup>6</sup> including dyskinesias, parkinsonism, and gait abnormalities.

Dyskinesias occur spontaneously in a small percentage of patients with schizophrenia or, more often, may be an adverse event of antipsychotic drugs. Drug-induced dyskinesia is referred to as *tardive dyskinesia*.<sup>6</sup> Spontaneous dyskinesias occur most frequently as involuntary movements of the tongue or face (orofacial dyskinesias) and upper extremities of the body, and are often mistaken for tardive dyskinesia. In studies conducted in antipsychotic-naive patients to identify dyskinesias caused by schizophrenia, prevalence rates were reported to be as high as 38%, with a mean of 12%.<sup>6,91-98</sup> Dyskinesias appear to increase with age and duration of disease. Tardive dyskinesia resulting from antipsychotic drug usage is estimated to occur in an average of 15% to 30% of patients with schizophrenia.<sup>99,100</sup>

Parkinsonism, which is characterized by rigidity, tremor, and bradykinesia, is frequently observed in patients

with schizophrenia, even in those who have never taken antipsychotic medications.<sup>96</sup> The high prevalence of parkinsonism or extrapyramidal motor signs (up to 38%) reported in studies of drug-naive patients with schizophrenia suggests that parkinsonism is the result of the disease process of schizophrenia and is not drug induced.<sup>6,91,96,98,101-104</sup>

Gait abnormalities in which movements are awkward and uncoordinated are commonly seen in patients with schizophrenia and may be apparent years before clinical schizophrenia emerges.<sup>105</sup> In a study conducted in 100 patients with severe psychiatric illness,<sup>97</sup> 48% of the patients reported  $\geq 1$  abnormality in gait, including slow, shuffling, and stiff-legged gait.

### MOVEMENT DISORDERS AND ATYPICAL ANTIPSYCHOTICS

Among the atypical antipsychotics, clozapine is considered to be an effective agent in the treatment of psychosis associated with Parkinson's disease and has an anti-dyskinetic effect, while quetiapine may be a suitable alternative.<sup>106</sup> However, clozapine is associated with agranulocytosis, which limits its use.<sup>106</sup> Investigation of fine extrapyramidal motor symptoms (e.g., reduction of handwriting area)<sup>107</sup> found a significant correlation between D<sub>2</sub>-receptor occupancy and reduced handwriting area, suggesting that Parkinson-like symptoms may respond better to atypical antipsychotics than typical antipsychotics. Olanzapine has demonstrated an antidyskinetic effect but often worsens symptoms of parkinsonism. In a double-blind placebo-controlled study of 9 patients with idiopathic Parkinson's disease and levodopa-induced dyskinesia,<sup>108</sup> olanzapine (mean dosage, 3.6 mg/day; range, 2.5–6.0 mg/day) showed significant improvement in objective and subjective ratings for dyskinesia compared with placebo. However, adverse events, including increased parkinsonism, increased "off" time, and increased drowsiness, were more commonly reported with olanzapine than with placebo. During poststudy follow-up, the worsening of parkinsonism was reported to occur at doses as low as 1.25 mg every other day, and at least 3 patients required discontinuation of therapy.<sup>108</sup> In first-episode patients, risperidone at doses above 5 mg/day have been reported to be associated with the development of extrapyramidal symptoms, including akathisia and parkinsonian rigidity.<sup>109</sup> However, when compared with haloperidol, a randomized, controlled, flexible-dose study involving 555 patients with first-episode schizophrenia<sup>110</sup> indicates that risperidone (1–6 mg/day) is associated with less parkinsonism and fewer reports of extrapyramidal symptoms and emergent dyskinesia compared with equivalent dosages of haloperidol.

Several studies suggest that quetiapine does not worsen parkinsonism and may be useful in Parkinson's-related movement disorders. In a 12-month investigator-blinded

trial,<sup>111</sup> quetiapine (mean dosage, 400 mg/day) demonstrated significantly greater improvement in patients with established tardive dyskinesia than haloperidol (mean dosage, 8.5 mg/day). In this study, the effect was sustained, with response rates at 6 and 12 months of 64% and 55% with quetiapine and 37% and 28% with haloperidol, respectively.<sup>111</sup> The use of quetiapine (25–600 mg/day) in patients with Parkinson's disease and drug-induced dyskinesia have yielded inconsistent results; some reports indicate no change in dyskinesia,<sup>106,112</sup> whereas others indicate the potential for improvements in general motor functioning.<sup>113,114</sup> Two-year data from Kopala et al.<sup>115</sup> have demonstrated that quetiapine (mean dosage, 540 mg/day at year 1 and 605 mg/day at year 2) administered to patients with schizophrenia spectrum disorder and first-episode psychosis improves preexisting abnormal motor function as assessed by the Extrapyramidal Syndrome Rating Scale. In this open-label study, improvements in akathisia were significant ( $p = .047$ ) during year 1 and approached significance ( $p = .057$ ) at year 2.<sup>115</sup>

### ELECTROPHYSIOLOGIC ABNORMALITIES

Previous studies in patients with schizophrenia showed varied prevalence rates (range, 9%–60%) of abnormalities on electroencephalograms (EEGs).<sup>116–119</sup> In first-episode, never-medicated patients with schizophrenia, EEG recordings indicated that a loosening of the functional connectivity of some processes in the brain may be linked to working memory dysfunction.<sup>120</sup> Imbalances in the level of coordination of the determinants of functional states of the brain lead to the cognitive-emotional and behavioral changes seen in schizophrenia.<sup>121</sup>

P50 auditory evoked potentials in EEGs are related to sensory gating mechanisms.<sup>122</sup> In patients with schizophrenia, abnormalities of the P50 component of the auditory evoked potential have been associated with deficits in attention.<sup>123</sup> The amplitude of the auditory P300 component of the event-related potential of the brain is reduced in patients with schizophrenia compared with that in control subjects,<sup>124–127</sup> suggesting that this reduction may be caused by reduced volume of cortical gray matter. The reduction in P300 amplitude may also be related to the negative and possibly the positive symptoms of schizophrenia and cognitive dysfunction.<sup>128–131</sup>

Patients with schizophrenia seem to have disturbed sleep continuity, slow-wave sleep (SWS) deficits, and shortened rapid eye movement sleep latency.<sup>132,133</sup> These abnormalities may be caused by increases in ventricular system volume reported in patients with schizophrenia.<sup>133</sup> However, others have suggested that sleep disturbances might be the result of residual antipsychotic medications and a relationship between SWS and ventricular system volume not seen in schizophrenia.<sup>132</sup> Further studies are warranted to reach more definite conclusions.

Drug-induced EEG slowing resulting from treatment with clozapine may be related to improvement in negative and positive symptoms and positive outcomes. Similar improvements were not observed with conventional antipsychotics.<sup>134</sup> In contrast to conventional antipsychotic medications, atypical antipsychotics have been shown to increase P50 suppression and increase P300 wave amplitudes and thereby improve symptoms and cognitive function in patients with schizophrenia.<sup>135,136</sup>

### EPILEPSY

Patients with schizophrenia develop seizures more often than the general population.<sup>137,138</sup> One thought is that schizophrenia may impose secondary risks, similar to closed-head injuries or substance abuse, that result in an increased incidence of seizures.<sup>137</sup> Makikyro et al.<sup>138</sup> found an 11-fold increase in the risk of developing epilepsy in patients with schizophrenia.

In patients with epilepsy, estimates of the occurrence of comorbid psychiatric disorders ranged from 20% to 50%.<sup>139,140</sup> Psychotic disturbances are overrepresented among patients with epilepsy compared with the general population (2.5%–8% vs. 1%, respectively).<sup>139</sup> Patients with epilepsy are reported to have more hallucinations and delusions than inappropriate affect, motor retardation, and conceptual disorganization.<sup>140,141</sup> Patients with frontal lobe epilepsy develop schizophrenia-like psychosis (SLP) at higher than expected rates.<sup>141</sup> The part of the brain where seizure activity begins plays an important role in the manifestation of psychiatric symptoms in patients with epilepsy.<sup>141</sup> Temporal lobe abnormalities in patients with epilepsy could be responsible for the emergence of SLP.<sup>137,139,141</sup> Anecdotal reports from Christodoulou et al.<sup>142</sup> and Tebartz van Elst et al.<sup>143</sup> suggest that neurodevelopmental pathology involving the mesial temporal structures may contribute to postictal psychosis.

In a retrospective study,<sup>144</sup> the effects on EEG patterns in patients treated with quetiapine ( $N = 22$ ), olanzapine ( $N = 37$ ), or haloperidol ( $N = 22$ ) were compared with a group of healthy subjects ( $N = 30$ ). EEG abnormalities were observed in patients receiving olanzapine (13/37) and haloperidol (5/22), but rarely in patients treated with quetiapine (1/22), compared with healthy subjects (2/30). In addition, epileptiform activity was observed in 4 of 37 patients treated with olanzapine but not in the other treatment groups.

### SENSORY ABNORMALITIES

A number of patients with schizophrenia do not sense or complain of pain and seem indifferent to it. Anecdotal reports of reduced pain perception have been described since the 1800s, before the introduction of antipsychotics, indicating that apparent analgesia is part of schizophrenia



**Table 6. Neurologic Soft Signs in Patients With Schizophrenia<sup>a</sup>**

Mental status
Attention deficits
Unawareness of illness
Speech problems
Right/left confusion
Perseveration
Bizarre response
Decreased motor activity
Retardation
Poverty of movements
Stupor
Posturing
Cooperation
Opposition
Autonomic obedience
Ambitendency
Increased motor activity
Restlessness
Excitement
Tremor
Stereotype/mannerisms
Impulsive movements

<sup>a</sup>Based on Torrey,<sup>6</sup> Dazzan and Murray,<sup>146</sup> Boks et al.,<sup>148</sup> Cuesta et al.,<sup>149</sup> Chen et al.,<sup>150</sup> Egan et al.,<sup>151</sup> and Ismail et al.<sup>152</sup>

and not drug induced.<sup>6,145</sup> However, findings conflict. Guieu et al.<sup>145</sup> reported no differences in pain perception between a group of 10 patients with schizophrenia and 10 healthy controls. Yet a review of the literature indicates that patients with schizophrenia showed insensitivity to pain associated with myocardial infarction, perforated ulcers, burns, appendicitis, and bone fractures.<sup>6</sup> Because studies on pain perception in schizophrenia were done before the introduction of most antipsychotic medications, the insensitivity to pain may be the result of neurologic abnormalities in schizophrenia, action of a drug, or an increased threshold for pain.

### NEUROLOGIC SOFT SIGNS

Neurologic abnormalities in schizophrenia can be divided into hard neurologic signs (e.g., patellar tendon reflex) and neurologic soft signs (NSSs; alterations in sensory and motor performance),<sup>6</sup> which are identified by clinical assessment. Hard neurologic signs can identify specific areas of the brain that are affected. However, NSSs are the result of more complex abnormalities and indicate nonspecific cerebral impairment in sensory and motor performance.<sup>6,146</sup> The neurologic abnormalities of schizophrenia appear to be focused in 3 functional areas: motor coordination, motor sequencing, and the integration of sensory function.<sup>6,146,147</sup>

Neurologic soft signs that involve impairment in mental status or motor activity are listed in Table 6.<sup>6,146,148–152</sup> Patients with psychosis score higher on examinations of NSSs than control subjects, and cognitive performance of psychotic patients is also impaired, suggesting that NSSs

reflect neurocognitive dysfunction.<sup>149</sup> Although there is no clear pattern of NSSs that conclusively identifies patients with schizophrenia, NSSs are good predictors of cognitive dysfunction in patients with psychosis.<sup>149</sup> Among the NSSs, motor coordination alterations reportedly are the most specific for schizophrenia.<sup>148</sup> In many instances, motor dysfunction emerges before the onset of the clinical symptoms of schizophrenia.<sup>105</sup>

Sensory NSSs in patients with schizophrenia that are caused by abnormalities in the cortical area of the brain include agrophesthesia (failure to recognize numbers written on the palm), astereognosis (failure to recognize shapes of objects when held in the hand), and topognosis (inability to localize tactile stimuli).<sup>59,153,154</sup> In patients with schizophrenia, primitive (developmental) reflexes are present, such as gaze reflex, grasp reflex, palmomental reflex, snout reflex, and sucking reflex.<sup>148,154</sup> These involuntary movements normally are present early in life and disappear by adulthood but persist throughout adulthood in patients with schizophrenia, suggesting that the brain dysfunction is the result of a neurodevelopmental, not a neurodegenerative, abnormality.<sup>154,155</sup>

### AMBIGUOUS LATERALITY

In schizophrenia, reductions or even reversals of right/left hemispheric asymmetry<sup>14,156</sup> seem to occur most often in the left hemisphere.<sup>14,157</sup> Abnormal left-hemisphere activation can cause attention deficits and positive symptoms, such as hallucinations or hallucination-like processes.<sup>158</sup> In general, a more leftward asymmetry is associated with a later age at onset of the disease. However, women who generally have a later age at onset for any value of asymmetry, regardless of age at onset, have more rightward frontal lobe asymmetry.<sup>157</sup> Patients with schizophrenia also have increased left-handedness that is associated with decreased cognition and mixed-handedness<sup>156,159</sup> and possibly increased mixed eye and foot preferences.

### CONCLUSION

A number of comorbid neurologic disorders often occur years before patients are treated for schizophrenia. Most neurologic comorbid disorders are consistent with and supportive of neurodevelopmental, rather than neurodegenerative, theories of schizophrenia. Although antipsychotics may contribute to the development of neurologic abnormalities, their role seems to be mostly positive. Studies with atypical antipsychotics, in particular, have shown positive benefits on cognitive deficits related to schizophrenia, although there are differences between agents in this class.

Thus, it is essential that clinicians obtain a complete neurologic history and examination of patients with schizophrenia at the onset of illness and before initiating

pharmacotherapy. Increased recognition of the neurologic abnormalities discussed in this article may assist the clinician in identifying and treating patients with schizophrenia earlier, potentially improving long-term outcome.

*Drug names:* chlorpromazine (Thorazine and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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