# "Cognitive Dysmetria" as an Integrative Theory of Schizophrenia: A Dysfunction in Cortical-Subcortical-Cerebellar Circuitry?

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## Abstract

**Earlier efforts to localize the symptoms of schizophrenia in a single brain region have been replaced by models that postulate a disruption in parallel distributed or dynamic circuits. Based on empirical data derived from both magnetic resonance and positron emission tomography, we have developed a model that implicates connectivity among nodes located in prefrontal regions, the thalamic nuclei, and the cerebellum. A disruption in this circuitry produces "cognitive dysmetria," difficulty in prioritizing, processing, coordinating, and responding to information. This "poor mental coordination" is a fundamental cognitive deficit in schizophrenia and can account for its broad diversity of symptoms.**

**Key words: Cognitive dysmetria, cerebellum, thalamus, prefrontal cortex.**

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The study of the neural mechanisms of schizophrenia has passed rapidly through three phases during the past several decades. During the first phase, the effort was to demonstrate that schizophrenia was a brain disease. This phase was supported primarily through the use of neuroimaging techniques such as computerized tomography (CT), which consistently showed that patients had diffuse nonspecific abnormalities such as prominent sulci or ventricular enlargement (Johnstone et al. 1976; Weinberger et al. 1979*a*; Andreasen et al. 1982, 1990).

The next phase drew on traditions of neurology and neuropsychology; it attempted to localize the anatomic abnormalities and relate specific manifestations of the illness to specific brain regions (Andreasen 1986). This effort received major support from the improved anatomic resolution of magnetic resonance (MR). Some specific relationships that were hypothesized and partially verified include the prefrontal cortex and negative symptoms (Andreasen et al. 1986, 1992), the temporal lobes and auditory hallucinations (Barta et al. 1990; McCarley et al. 1993; Silbersweig et al. 1995), and the planum temporale and thought disorder (Shenton et al. 1992).

The third phase, which is relatively recent, draws on traditions of cognitive psychology, models of distributed parallel processing, and the study of neural circuitry (Rumelhart and McClelland 1986; Goldman-Rakic 1988; Mesulam 1990; Braff 1993). The emphasis of this phase is an attempt to understand schizophrenia as an abnormality in fundamental cognitive processes and distributed circuits. This emphasis contrasts somewhat sharply with earlier efforts, which focused on the relationship between specific symptoms and specific regions. The second phase asked questions such as "Which brain region might explain the schizophrenic experience of spontaneous perceptual phenomena such as 'heard' words and sentences in the absence of an external stimulus?" The third phase asks questions such as "What type of brain abnormality and related disturbance in cognition can explain the diversity of symptoms observed in schizophrenia?" In the third phase, the emphasis has shifted to the development of integrative models. Examples include the exploration of information processing and attention (Braff 1993; Andreasen et al. 1994*a*, 1995*e*), willed action (Frith et al. 1991*b*; Frith 1992), and working memory (Goldman-Rakic 1994).

The third phase will certainly enjoy a peaceful coexistence with the second phase, since much exciting work remains to be done in the effort to map specific cognitive functions in the normal brain and identify subregions that may be abnormal in schizophrenia in relation to specific symptoms. Nonetheless, the integrative approach has some substantial advantages: It is more parsimonious, in

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that it attempts to explain the diversity of schizophrenic symptoms with a single theory or mechanism. It may be more efficient, in that it applies a "top-down" approach that permits the testing of abnormalities in multiple related regions, rather than a piecemeal "bottom-up" approach that examines a single region and a single symptom at a time. It is also more consistent with most current thinking in neuroscience, which maps circuits and assumes distributed parallel processing. And finally, if a defect in a specific cognitive process can be identified, it may permit the development of improved animal models that can be explored in simpler systems than primates, thereby permitting the application of the techniques of molecular biology to the study of schizophrenia. The major disadvantage of the integrative approach is that it can quickly become quite complex and lead to multinodal and multimodal models that are difficult to test in a single experiment.

## Cognitive Dysmetria: The Fundamental Cognitive Deficit in Schizophrenia?

Schizophrenia presents with a diversity of symptoms that represent multiple psychological domains, for example, perception, inference, concept formation, language, volition, motor activity, social interaction, and emotion. Not all patients have symptoms that express all these domains. For example, some patients have no hallucinations, while others have no language abnormalities. In the narrow sense of the word cognition, these abnormalities are not even all cognitive, since they include emotion, motor activity, and sensory systems. Nonetheless, for the sake of simplicity, we will assume that the underlying process producing these diverse symptoms is cognitive in the broad sense of the term: It involves some type of abnormality in receiving and processing information from the external world, relating it to information that has already been processed and stored previously and acting on that information to produce some type of reaction or response.

One model that seems particularly promising assumes that there is a deficit in the underlying system that coordinates the processing, prioritization, and expression of information. This system is sometimes referred to as "executive functions" by neuropsychologists and is thought to be localized in the prefrontal cortex. Based on evidence from both clinical observation and our broad range of MR and positron emission tomography (PET) studies, we hypothesize that the system that is disturbed in schizophrenia is more distributed and complex. The disturbance encompasses not just executive functions, but several forms of memory, attention, emotion, and motor activity. Its underlying neural network is not only cortical, but also subcortical. To express the diversity of the disturbance and to call attention to its subcortical components, we refer to it as "cognitive dysmetria."

As a neurological symptom, dysmetria expresses itself in the coordination of motor activity. It is tested clinically in patients by examining functions such as tandem gait or dysdiadokokinesia. Although patients with schizophrenia have grossly normal motor function, there are many subtle indications of motor impairment. These anomalies are sometimes dismissed as the result of neuroleptic treatment. However, slowing of reaction times is one of the most consistent findings in older psychological studies of schizophrenia, many of which were completed during the preneuroleptic era. Kraepelin et al. (1919) described a variety of motor abnormalities in the preneuroleptic era, and others have as well (Shakow 1926; Shakow and Huston 1936). More recently, studies have also documented the presence of motor system "soft signs" in first-episode neuroleptic naive patients (Gupta et al. 1995). These soft signs include the classical indices of motor dysmetria (e.g., dysdiadokokinesia).

The term dysmetria derives from Greek and means literally "bad" (dys) "measure" or "moderation" (metron). Aristotle's well-known defense of the Golden Mean is based on the Greek proverb "metron ariston" (moderation is best). The word metron refers to taking the measure of time and space; making inferences about interrelationships between them in relation to oneself, others, objects, and memories or concepts; and formulating responses and experiencing feelings as a consequence of this measure-taking. Thus, it is an apt term to refer to an abnormality in cognition as well as motor activity. As a cognitive abnormality, dysmetria would express itself as difficulty in coordinating the processing, prioritization, retrieval, and expression of information. This type of fundamental deficit could express itself as any of the broad range of symptoms of schizophrenia: hallucinations, delusions, disorganized speech, disorganized behavior, alogia, affective blunting or incongruity, avolition, anhedonia, or attentional impairment.

The anatomic substrate of motor dysmetria involves circuitry linking the motor cortex with the cerebellum, joined through nuclei in the pons and thalamus and modulated by the basal ganglia (Holmes 1939; Ito 1984; Middleton and Strick 1994). The anatomic substrate of cognitive dysmetria has recently become the subject of intensive investigation (described below), as a consequence of the growing recognition of the role of subcortical structures—particularly the cerebellum—in cognition. Many nodes are probably linked on this cognitive network. The three nodes that we explore in this particular essay are the prefrontal, thalamic, and cerebellar.

## Nodes of the Cognitive Dysmetria Network

**Prefrontal Cortex.** For many years, researchers have hypothesized that the prefrontal cortex plays a key role in generating the symptoms of schizophrenia. At the beginning of this century, Kraepelin proposed that schizophrenia could be explained by abnormalities in the frontal lobes (Kraepelin et al. 1919). Others later "discovered" the same idea, and for good reason.

First, the prefrontal cortex is phylogenetically important. It is one-third larger in human beings than in other primates, and it contains regions such as areas 44 and 45 that are present only in the human brain and that permit the generation of specifically human functions such as language and speech. Such functions are frequently disrupted in schizophrenia, which is in essence a disease of higher cognitive functions. Second, the prefrontal cortex is anatomically designed to play a key role in complex cognitive processes by virtue of its connectivity. It has afferent and efferent connections to all other cortical regions, as well as to many subcortical regions. Third, many investigations have demonstrated that it plays a key role in decisionmaking, executive functions, regulation of behavior by representational memory, temporal sequencing of perceptions and events, willed action, memory encoding and retrieval, and emotional perception (Nauta 1971; Stuss and Benson 1986; Fuster 1989, 1993; Goldman-Rakic 1990; Frith et al. 1991*b*; Kapur et al. 1994*b*; Tulving et al. 1994*a*, 1994*b*, 1996; Andreasen et al. 1995*e*; Paradiso et al. 1997).

The prefrontal cortex has been extensively studied in schizophrenia using neuropathology, MR, single photon emission computed tomography (SPECT), and PET. While the findings are not completely consistent, they clearly converge on the likelihood that this node of the network is disturbed in schizophrenia.

There are many possible reasons for inconsistent findings. Although we speak of the prefrontal cortex, it consists of many different modules that perform a variety of different functions. Many of these functions have been partially mapped with lesion and animal studies, but the explicit details of prefrontal functions and connectivity are still "works in progress" as imaging data and new anatomic studies of humans and nonhumans increase our informational resources. Adding to the difficulties in interpreting nonreplications, particularly in schizophrenia, are issues such as medication effects, sample size and statistical power, difficulties in measurement techniques with MR, and the nature of the cognitive tasks used in functional imaging studies.

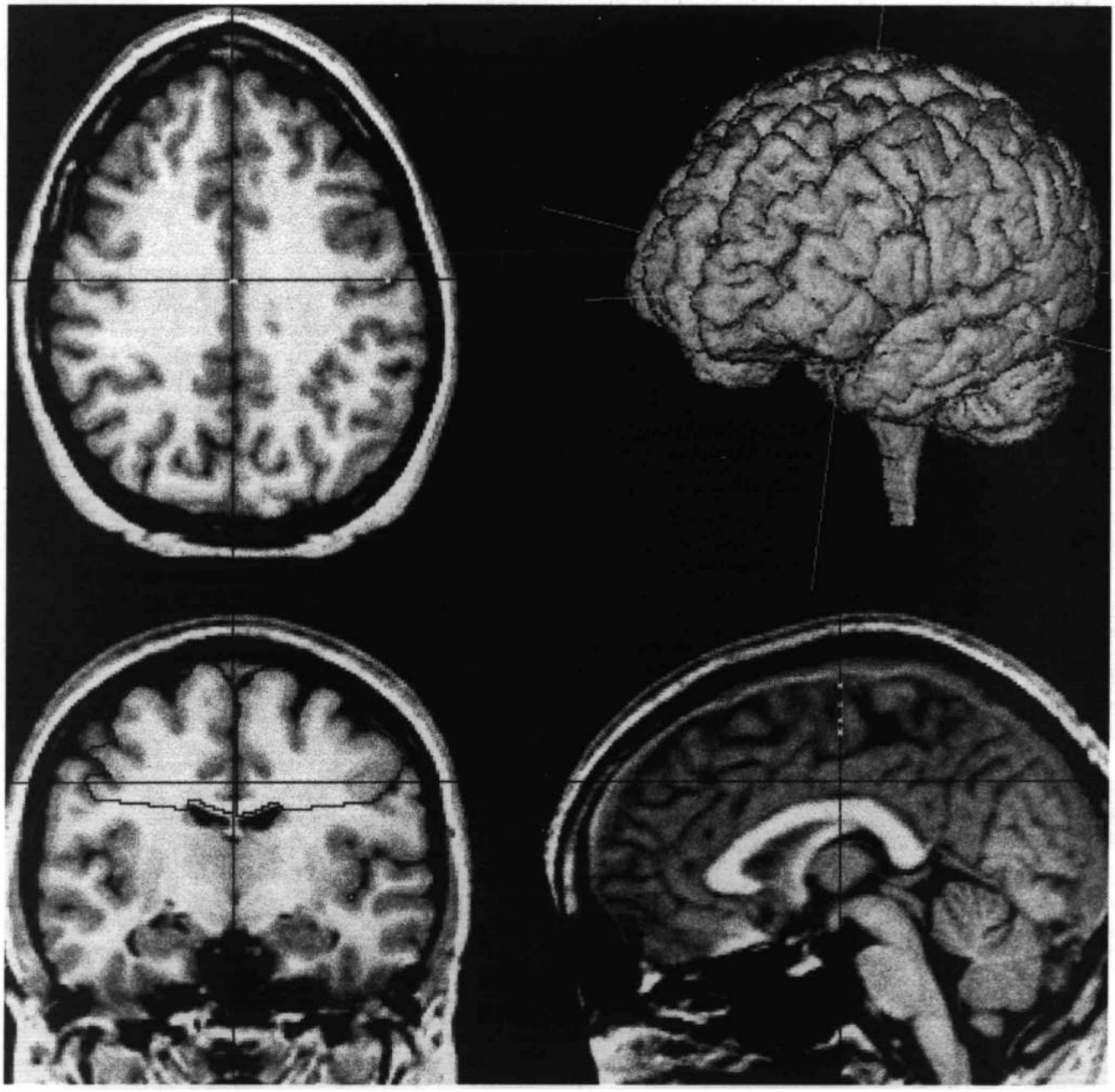
MR studies have attempted to determine whether there are gross differences in frontal lobe size between schizophrenia patients and healthy volunteers. In the first MR study of frontal lobe size and schizophrenia, we reported a decreased frontal and cerebral size, which we postulated might be due to any early developmental abnormality (Andreasen et al. 1986). Although a second study did not confirm these findings (Andreasen et al. 1990), our more recent study with state-of-the-art volumetric measurements has again demonstrated decreased frontal and cerebral size in schizophrenia patients (Andreasen et al. 1994*a*). Further, an examination of first-episode patients has indicated that decreased frontal size is present at the onset of the illness, thereby providing additional confirmation for our original neurodevelopmental hypothesis (Nopoulos et al. 1995). We have now replicated our original 1986 finding of decreased frontal size in a fourth completely independent sample, making this a clearly solid finding (Andreasen, unpublished data).

In retrospect, we believe that the nonreplication in our 1990 study was due to a confound with educational achievement and cerebral size in our controls, who were matched to the patients educationally in the second study (thus, the controls had smaller cerebral size). We have now consistently shown a relationship between intelligence and cerebral size (Andreasen et al. 1993), as have others (Van Valen 1974; Willerman et al. 1991). Although a few negative studies of decreased frontal size using MR have also been reported, they used small samples with inadequate power or did not employ the anatomical precision of three-dimensional visualization of cortical landmarks to delineate frontal lobe size, as in our two recent studies (Kelsoe et al. 1988; Wible et al. 1995) (see figure 1).

Neuropathological studies provide a means to explore specific regional abnormalities in the prefrontal cortex in much greater detail. Because of their technical difficulty, as well as the limited availability of postmortem tissue from patients suffering from schizophrenia, only a few neuropathological studies have been completed. Work by Benes et al. (1986, 1991) found some abnormalities in area 10 and in gamma-aminobutyric acid (GABA)ergic interneurons (Benes et al. 1992). A more recent report by Selemon et al., examining area 9, has found that neuronal density is increased in layers 3–6 in area 9, secondary to increased cell packing of pyramidal and nonpyramidal neurons. Their results suggest that a reduction of neuropil, including dendritic arbors and axons, produces a thinner cortical layer (Selemon et al. 1995). As in other neuropathological studies, no gliosis was noted, suggesting that the underlying process is developmental rather than degenerative.

Approaching the neuropathology of schizophrenia from a different perspective, Akbarian et al. (1995) have also noted an absence of overall neuronal loss in the pre-

**Figure 1. BRAINS software visualization of internal brain structures in three orthogonal planes and surface anatomy**



Operator-controlled tracing of the frontal lobes is evidenced. Coordinates of the traced lines in one view are telegraphed to their corresponding positions on the other views (dots). BRAINS = Brain Research Analysis of Images, Networks, and Systems.

frontal cortex, but a reduction in the activity-dependent expression of messenger ribonucleic acid for glutamic acid decarboxylase, the crucial enzyme in GABA synthesis in the superficial layers of the dorsolateral prefrontal cortex. These and other neuropathological abnormalities (Benes et al. 1992), reflecting a compromise of GABA-mediated transmission in the cortico-cortical associative areas of the dorsolateral prefrontal cortex, could be the outcome of developmental alterations responsible for altered circuit formation in the prefrontal cortex in schizophrenia (Akbarian et al. 1995).

Studies of the frontal cortex using functional imaging techniques are by far the most extensive. "Hypofrontality" was originally reported by Ingvar and Franzen (1974*a*,

1974*b*) using measurements of cerebral blood flow and several different cognitive activation techniques. Hypofrontality was subsequently confirmed with some tasks in a number of SPECT studies (e.g., Mathew et al. 1982; Gur et al. 1983; Devous et al. 1985; Weinberger et al. 1986, 1988; Berman et al. 1987; Wood and Flowers 1990; Andreasen et al. 1992), but not all (e.g., Devous et al. 1985; Berman et al. 1988). Buchsbaum et al. (1982) reported the earliest PET study of reduced prefrontal glucose metabolism.

PET studies provide a somewhat more elegant tool for examining both cognitive operations and specific brain regions, and there has been a steady increase in the sophistication of PET studies examining the prefrontal cortex in schizophrenia. The concept of hypofrontality has been further dissected and defined. Early studies tended to compare patients and controls during a resting condition and to use some type of ratio to generate a "frontal index," usually showing that the activity in the frontal cortex was low relative to a "control region" (e.g., Buchsbaum et al. 1982; Farkas et al. 1984; Wolkin et al. 1985; Volkow et al. 1987). A recent study with a large sample of patients with schizophrenia and normal controls (Gur et al. 1995) found no evidence of hypofrontality in resting cerebral glucose metabolism. Many recent studies have used more sophisticated normalization techniques and employed cognitive challenges of various types, introducing the concept of hypofrontality as a failure of the prefrontal cortex to increase its flow during a targeted experimental task. The Continuous Performance Test, which assesses sustained attention, has been widely used in PET studies, since it is well adapted to the relatively long time window of the fluorodeoxyglucose method (e.g., Buchsbaum et al. 1990).

The most recent studies have exploited the improved temporal resolution of functional magnetic resonance (fMR) or PET with the $^{15}OH_2O$ method. These techniques have permitted investigators to focus more intensively on deficits in specific brain regions in relation to hypothesized cognitive deficits. For example, Frith's hypothesized abnormality in "willed action" has been extensively explored through the use of verbal fluency tasks (Frith et al. 1991*a*, 1991*b*, 1995). Liddle (1987), Liddle and Morris (1991), and Allen et al. (1993) have shown a relationship between impaired verbal fluency and both disorganized symptoms (incoherence) and negative symptoms (psychomotor poverty). Frith and Liddle have both demonstrated that patients with schizophrenia have as many words available in their lexicons as do normal controls, indicating that the impaired fluency performance stems from specific problems in the retrieval of words. Allen et al. (1993) have proposed that patients with psychomotor poverty terminate the search for words prematurely, whereas patients with incoherence commit errors in selecting words for output.

**The Thalamus.** The majority of studies of schizophrenia have focused on the cerebral cortex, in particular on temporal lobe regions such as the hippocampus. The literature on thalamic abnormalities is very small, however, compared with the extensive work that has been done on the prefrontal or temporal cortex.

The many functions of the thalamus are still being explored in basic neuroanatomical studies. Conventionally, it has been thought to serve a role in "gating" stimuli, but Llinás and Welsh (1993) have proposed that it may function more actively and serve as a generator. The thalamus is conventionally divided into relay and diffuse projection nuclei (Kandel et al. 1991). The relay nuclei project to sensory and motor cortical regions and receive projections from the same cortical areas. These recurrent connections may allow the thalamus to modulate sensory and motor input. The diffuse projection nuclei are believed to be part of a system that governs the level of arousal of the brain. Whatever its roles, the thalamus clearly must have a fundamental and important function in human cognition because of its extensive connections to the rest of the brain (Jones 1985).

Several neuropathological studies have reported abnormalities of the thalamus (Stevens 1982; Pakkenberg 1990, 1992; Bogerts 1993). In particular, Pakkenberg (1990) has described substantial cell loss in the medial dorsal nucleus of the thalamus, the nucleus that serves as the major relay station to the prefrontal cortex. In addition to observing a decreased neuronal density, she observes a reduction in volume. As in the prefrontal cortex, no gliosis is observed, consistent with a neurodevelopmental abnormality or injury occurring early in brain development. Unfortunately, other thalamic nuclei have not been investigated neuropathologically, so it is unclear whether the findings in the literature are specific to the medial dorsal nucleus or whether they also involve other thalamic nuclei. This issue is highly relevant, since it would help answer the question of whether thalamic abnormalities represent a specific disruption in thalamic-frontal circuitry or whether the thalamic abnormality is more diffuse.

Nearly all the work examining thalamic abnormalities in schizophrenia with MR has been completed in our laboratory. In our first MR study (Andreasen et al. 1986), we measured thalamic size and found it to be significantly decreased in patients, but did not report it because of a concern that the finding could be due to partial voluming with the enlarged ventricles and the limitations of measurement with a single midline slice. In our second large MR study (Andreasen et al. 1990), we did report decreased thalamic size. As in our 1986 study, we sug-

gested that the observed brain abnormalities could be due to a neurodevelopmental defect.

In the process of conducting these two studies, we also serendipitously noted some unusual developmental anomalies. The most striking was an increased incidence of partial or complete agenesis of the corpus callosum (Andreasen 1988; Swayze et al. 1990). Since most patients with callosal dysgenesis or agenesis tended to show very poor response to neuroleptic treatment, we hypothesized that they had a disruption in midline neuronal circuitry that could not be reversed by chemical means. Other patients with less severe disruptions might, however, have a better treatment response, depending on the degree to which neurodevelopmental anomalies disrupted crucial connections. We have also observed an increased incidence of cavum septi pellucidi (Nopoulos et al. 1996) and the occurrence of brain matter heterotopias (Nopoulos et al. 1995), which are also consistent with a neurodevelopmental mechanism. Others have also noted an increase in midline abnormalities (Lewis and Mezey 1985; Lewis et al. 1988; Degreef et al. 1992). In a third MR study of 102 new patients (to our knowledge the largest MR study completed to date), we again found smaller thalami in patients suffering from schizophrenia than in the normal controls ($n = 87$) (Flaum et al. 1995).

These three studies relied on manual tracing to generate area or volume measurements. In a fourth study, we took advantage of advances in MR technology and software development to obtain measurements more empirically and efficiently. Using the locally developed software Brain Research Analysis of Images Networks and Systems (BRAINS) (Cohen et al. 1992; Andreasen et al. 1993, 1994*b*; Arndt et al. 1994; Cizadlo et al. 1994), we transformed all brains into the same stereotactic space, using a 6-point linear transformation. We then produced an image of an "average schizophrenic brain" and an "average normal brain," and then subtracted the two average brains from one another and displayed the result as an effect size map. In this study, we again observed that the thalamus was a major area of difference between the two groups, and we observed a difference in white matter projections to the prefrontal cortex (Andreasen et al. 1994*a*). This series of MR studies yielded a substantial array of evidence for thalamic abnormalities in schizophrenia, suggesting that they may be due to some type of midline developmental anomaly.

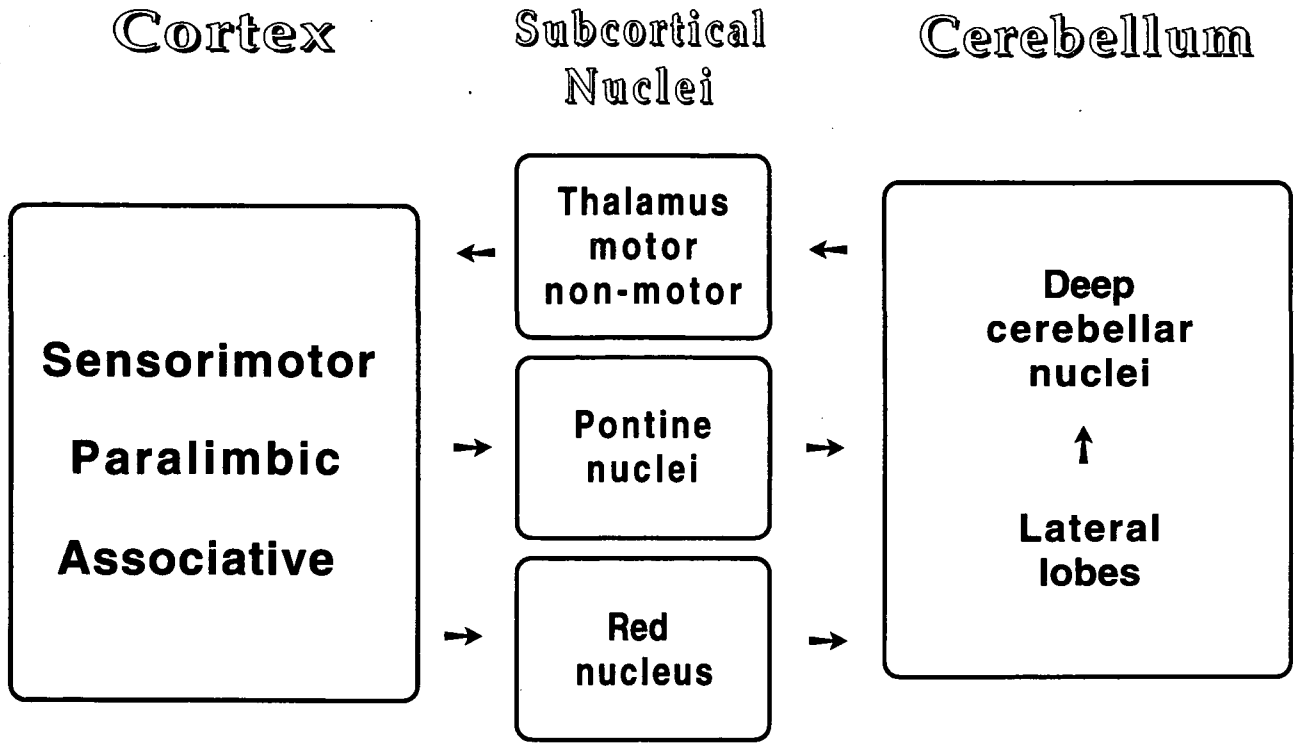
Several recent PET studies, also assessed with functional methods, have now confirmed thalamic abnormalities. The thalamus was one of the regions observed by Silbersweig et al. (1995) to be abnormally activated when patients suffering from schizophrenia experienced auditory hallucinations. Using fluorodeoxyglucose, Buchsbaum et al. (1996) have also observed thalamic abnormalities in PET studies of patients suffering from schizophrenia. This study of 20 never-medicated patients showed a diminished metabolic rate in the right cerebellum, with loss of the normal right-greater-than-left asymmetry. The left anterior region of the thalamus was also significantly smaller in the patients with schizophrenia. These reports support the possibility that the sensory filtering role of the thalamus is disrupted in patients with schizophrenia.

**The Cerebellum.** Unlike the prefrontal cortex or even the thalamus, the cerebellum has largely been ignored in studies of schizophrenia. Cerebellar size was visually inspected or measured semiquantitatively in a few early CT or MR studies, with inconclusive results (Heath et al. 1979; Weinberger et al. 1979*b*; Yates et al. 1987; Nasrallah et al. 1991). As discussed in two review papers, the cerebellum is a brain region of potential interest in schizophrenia for a variety of reasons (Taylor 1991; Martin and Albers 1995).

As noted by Passingham (1975), the cerebellum is phylogenetically interesting. Like the prefrontal cortex, it is one-third larger in human beings than in nonhuman primates, and it also has substantial anatomic connections with the prefrontal cortex, suggesting that it could perform cognitive as well as motor functions in humans. Several investigators have pointed out that it is well suited to perform massive parallel processing because of the nature of its cellular array (Leiner et al. 1989, 1991, 1995; Bowen 1995). It has a large surface area condensed into a small volume, permitting it to pack large numbers of cells in a columnar array. Leiner et al. have pointed out that its structure is the biological equivalent of modern microprocessor chips. It is constructed of narrow modules that are aligned perpendicular to the cortical surface and parallel to each other, making it beautifully designed to conduct distributed parallel processing. Further, the anatomical connectivity appears to obey the same type of modular specificity that is observed in the neocortex, although its connectivity is still being worked out in both the nonhuman primate brain and the human brain.

Figure 2 shows the general schematic organization of cerebellar circuitry. Projections from the cerebral cortex sweep down to the pons, where they typically cross before synapsing on cerebellar neurons. The cerebellar Purkinje cells are massively branched, making them ideally suited for efficient processing. Output from the cerebellum passes through the thalamus before projecting on to various neocortical regions, including the prefrontal cortex. The entire system appears to be a reciprocally connected circuit with modular specificity. Cerebro-cerebellar connections have been established for motor, sensory, and limbic regions, as well as for parts of prefrontal and parietal association cortices (Brodal 1981; Brodal

**Figure 2. Diagrammatic representation of the neuroanatomical connectivity linking the cerebral cortex with the cerebellum**




Corticopontine projections carry sensorimotor and high-order information from the cerebral cortex to the pontine nuclei of the ventral pons. A ponto-cerebellar pathway conveys this information to the cerebellar cortex. A second major output pathway from the cerebral cortex synapses at the level of the red nucleus, where neurons give rise to axons (central tegmental tract) that connect to the inferior olivary nucleus (not shown). From here a fiber system reaches the cerebellum. The cortex receives information processed by the cerebellum as follows: The cortical projections reach the deep cerebellar nuclei, from which cerebello-thalamic projections originate. The bulk of the cerebello-thalamic projections originate in the dentate nucleus, but there is evidence that fastigial and interpositus nuclei contribute as well (Brodal 1981). Motor and nonmotor thalamic nuclei then project to the cerebral cortex and close the circuit. The traditionally motor thalamic nuclei send information to the motor cortex. They also send efferents to supplementary motor areas, prefrontal areas, and posterior parietal and multimodal temporal regions. Thalamic intralaminar and medial dorsal nuclei project to association and limbic cortices and receive afferents from the deep cerebellar nuclei.

and Brodal 1981; Glickstein et al. 1985; Schmahmann and Pandya 1987; Middleton and Strick 1994; Schmahmann 1996).

This anatomical and phylogenetic evidence suggests that the cerebellum could play a role in cognition, but skeptics have questioned this hypothesis, based largely on the fact that gross cognitive deficits are not observed in patients with large cerebellar lesions. More recently, however, evidence from neuropsychology and functional imaging has led many to modify their view of the cerebellum and to suggest that it may perform cognitive functions.

Lesion studies of the cerebellum have reported mutism and dysarthria (van Dongen et al. 1994), abnormalities in verbal associative learning and visual spatial skills (Akshoomoff and Courchesne 1992; Akshoomoff et al. 1992), agrammatic speech (Silveri et al. 1994), impaired memory (Appollonio et al. 1993), impaired procedural learning (Pascual-Leone et al. 1993), decreased general intelligence as measured by IQ tests (Berent et al. 1990), abnormalities in representation of temporal information (Ivry et al. 1988; Ivry and Keele 1989), impaired cognitive planning (Grafman et al. 1992), and impaired nonmotor learning and error detection (Fiez et al. 1992).

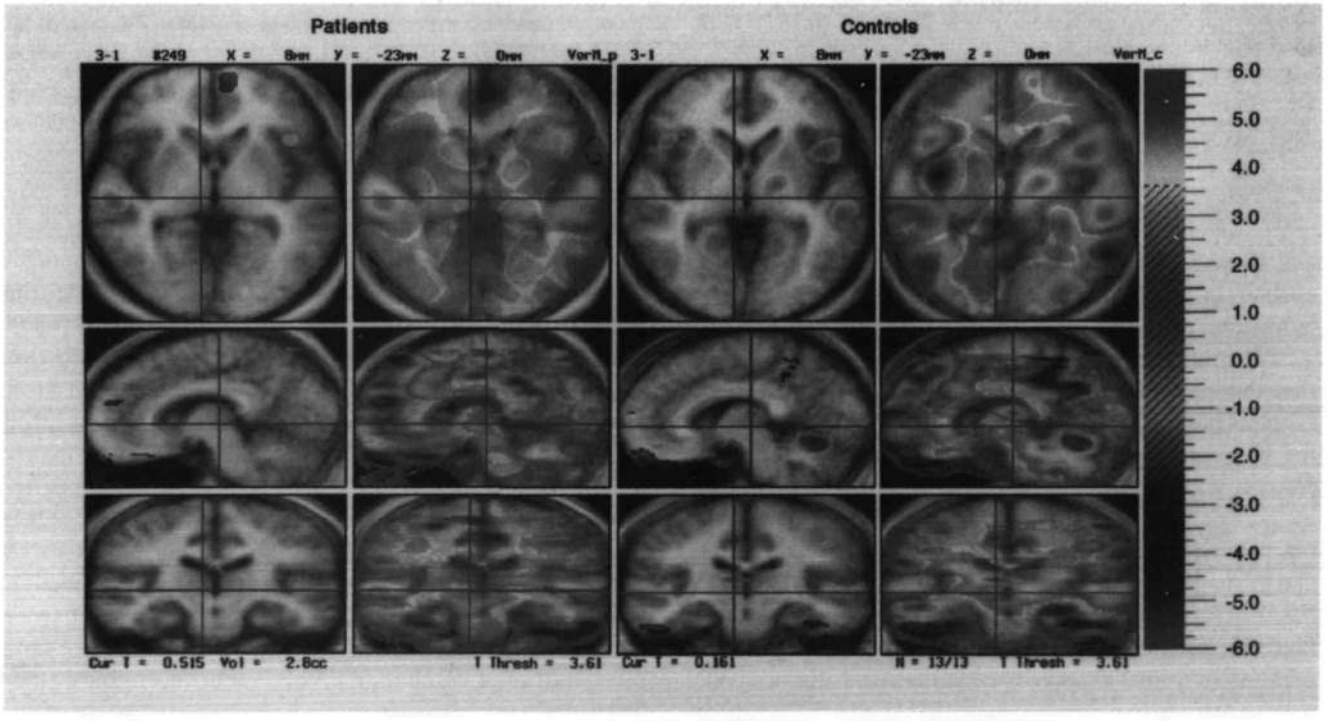
Functional imaging studies have added to the data base. An early SPECT study indicated that the cerebellum participates in mental activity (Decety et al. 1990). PET studies of word generation and the effects of practice have also indicated cerebellar involvement in cognition and

memory (Raichle 1994; Raichle et al. 1994; Nyberg et al. 1995). Grasby et al. (1993) and Haxby et al. (1994) have also demonstrated increased cerebral blood flow in the cerebellum and the thalamus during memory tasks using PET, while George et al. (1993), Mayberg and Solomon (1995), and Paradiso et al. (1997) have observed activations of the cerebellar vermis during mood induction studies. Kim et al. (1994) have also shown activation of the dentate nucleus during cognitive processing with fMR.

Our own PET studies of normal individuals have produced impressive cerebellar activations during a wide range of cognitive tasks, and these activations appear in many studies to be independent of motor activity. For example, in our studies of long- and short-term memory of word lists, we observed a robust cerebellar activation that appeared to be closely linked in size to activations in the contralateral prefrontal cortex, reflecting its well-known cross-hemispheric connectivity (Andreasen et al. 1995*a*). A similar pattern of frontal-cerebellar activation was also noted in the companion study involving facial recognition (Andreasen et al. 1997). Subsequent memory studies confirmed this pattern of activation using recall memory tasks with many different types of memory conditions: episodic memory, novel and practiced recall of complex narratives, novel and practiced recall of word lists, and verbal fluency (Andreasen et al. 1995*b*, 1995*c*, 1995*d*). Further, we observed a similar pattern of frontothalamic cerebellar activation, following classic cross-hemispheric anatomical patterns, using a verbal fluency task. Figure 3 shows a sample image from one of these PET studies.

This work provides the basis for our examination of cognitive dysmetria in schizophrenia with PET (Andreasen et al. 1996). We have now evaluated practiced and novel recall of complex narrative material in a sample of 14 schizophrenia patients who were withdrawn from neuroleptic medication for 3 weeks. The schizophrenia patients failed to show prominent activation of the frontal-thalamic-cerebellar circuit. Statistical analysis using randomization techniques confirmed that the two groups differed significantly in all three regions for both the practiced and the novel task. The specific areas included the frontal opercula, the thalamus, and large regions of the cerebellum. This particular study was designed to remove the confound of poor performance that renders many functional imaging studies of schizophrenia difficult to interpret. Patients were extensively rehearsed for one of the conditions, the practiced recall task, so they performed at the same level as the normal subjects. Consequently, we could conclude that their failure to activate the frontal-thalamic-cerebellar circuit was not due to poor task performance. The observation of a similar pattern of abnormality for the novel recall task, where the patients did perform less well, indicates that this circuit is disrupted across both difficulty levels, thereby confirming that the physiological differences observed during the practiced task were not due to a "ceiling effect."

**Figure 3. Sample image from one of the positron emission tomography studies**



## Other Nodes

Other nodes may also be involved in this overall network. For example, it is likely that the basal ganglia play a prominent role in modulating cortical activity (Middleton and Strick 1994). Both the anterior and the retrosplenial cingulate gyrus also appear, from functional imaging studies, to play a role in memory functions and other cognitive activities (e.g., Kapur et al. 1994*a,* 1994*b*; Shallice et al. 1994; Tulving et al. 1994*a*, 1994*b*, 1996; Andreasen et al. 1995*e*; Fletcher et al. 1995). Several recent PET studies of schizophrenia have shown the anterior cingulate to be related to auditory hallucinations (Silbersweig et al. 1995) or to impaired cognitive function (Dolan et al. 1995). Several recent studies of the effects of medication on cerebral blood flow have implicated the anterior cingulate and the cerebellum as regions that emerge as more active when patients are withdrawn from medication (Holcomb et al. 1996; Miller et al. 1997*a*, 1997*b*).

## Summary and Conclusion

Developing a neuroanatomic model that can explain the multiple and diverse symptoms of schizophrenia is a fundamental problem in schizophrenia research. We have proposed one that we consider to be heuristic: a model where the diverse symptoms of schizophrenia reflect abnormalities in connectivity in the circuitry that links prefrontal and thalamic regions and where cerebro-cerebellar connectivity may also be disrupted. We assume that the abnormality is neurodevelopmental in origin, based on the early theories of Fish (1977; Fish et al. 1992) and Feinberg (1982), our own early empirical work suggesting the occurrence of dysgenesis (Andreasen et al. 1986), and other evidence that has been summarized in more recent reviews and reports (e.g., Lewis et al. 1987; Murray and Lewis 1987; Weinberger 1987; Waddington 1990; Walker and Lewine 1990; Castle and Murray 1991; Jones and Murray 1991; Waddington and Torrey 1991; Bloom 1993; McNeil et al. 1993).

Given that brain development continues into early adulthood and is characterized by considerable plasticity, the developmental injury could occur at any time between conception and early adulthood. This particular presentation of the model does not specify the time or mechanism of the injury, but rather considers these factors to be related and important empirical questions. Likewise, the level at which connectivity could be disturbed could involve abnormalities at multiple levels: neuronal migration, cellular alignment, apoptosis, dendrite and spine formation or pruning, or synapse formation or deletion. Again, at present, the type of abnormality in connectivity is also an empirical question being addressed by many avenues of research.

Evidence for this model of schizophrenia comes from a variety of converging sources: studies of neuroanatomy, neural circuitry, and cerebral physiology. The existing empirical data derive from basic anatomy, developmental anatomy, MR, SPECT, and PET. First, a number of investigators have previously suggested that there may be a deficit in midline regions modulating information processing. A large number of studies using techniques of neurophysiology and experimental psychology have implicated defects in sensory gating in schizophrenia (Broadbent 1958; McGhie and Chapman 1961; Holzman et al. 1976; Braff 1993; Swerdlow and Geyer 1993). Second, previous neuropathological studies have reported abnormalities in frontal, thalamic, or pontine regions (e.g., Stevens 1973; Pakkenberg 1990; Benes et al. 1991; Bogerts 1993; Karson et al. 1993). As reviewed above, an increasing number of imaging studies are also implicating the importance of these regions in cognitive activities and in schizophrenia. Finally, abnormalities in this circuit are consistent with hypotheses concerning disruptions in the chemical anatomy of the brain, since the major neurotransmitter systems arise in midline regions (Carlsson and Carlsson 1990).

We have called the clinical abnormality produced by the putative neuroanatomic disruption "cognitive dysmetria." This concept is intended to highlight the importance of explaining the multiple symptoms of schizophrenia by identifying basic cognitive mechanisms. It is also intended to highlight the importance of examining cortical-subcortical circuitry in schizophrenia and examining the role of the thalamus and cerebellum in more detail. The concept is intended to be heuristic: to provide a model that is experimentally testable and can be confirmed or disconfirmed through studies using various techniques from cognitive psychology, animal models, neuropathology, and imaging studies. Other neurocognitive models, such as those presented by Goldman-Rakic (1994), Braff (1993), and Frith (1992), are important alternative efforts to pursue this same basic strategy. None of these models is likely to be completely confirmed or rejected in the near future. The existence of multiple competing models is certain, however, to advance our knowledge of the neural mechanisms of schizophrenia.

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