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A Pivotal Role for Glutamate in the Pathogenesis of Schizophrenia, and Its Cognitive Dysfunction

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HIRSCH, S. R., I. DAS, L. J. GAREY AND J. DE BELLEROCHE. *A pivotal role for glutamate in the pathogenesis of schizophrenia, and its cognitive dysfunction.* PHARMACOL BIOCHEM BEHAV **56**(4) 797–802, 1997.—There is mounting evidence of a glutamate dysfunction in schizophrenia, as suggested by the fact that schizophrenia and phencyclidine psychosis are similar and phencyclidine is known to block the *N*-methyl-D-aspartate (NMDA) subtypes of glutamate. Both occur mainly after puberty, suggesting they may share similar underlying developmental processes. Direct evidence is now accumulating from the study of messenger RNA that glutamate receptor deficiencies occur in schizophrenia and are regionally and specifically distributed. These results find support from studies of memory, electrophysiological findings, clinical treatment, and pharmacological studies in mammals and humans. Our recent findings of: a) a marked decrease in pyramidal cell dendritic spines in layer III of the frontal and temporal cortex, and b) a greater than 0.90 correlation between decrease in mRNA for the NMDA glutamate receptor and cognitive deterioration in elderly schizophrenics, present the strongest evidence to date that glutamate dysfunction plays an important role in schizophrenia. © 1997 Elsevier Science Inc.

Schizophrenia NMDA hypofunction Cognitive deterioration Glutamate hypothesis

A POSSIBLE role for glutamate in the pathogenesis of schizophrenia is suggested by the fact that a schizophrenia-like psychosis can be produced by phencyclidine (PCP, Angel Dust) (2), a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist that causes a functional glutamate deficiency by blocking the NMDA glutamate receptor at the MK-801 site (5,47). This psychosis is distinct from that caused by amphetamine (Speed), which causes increased activation of dopamine receptors in limbic and striatal regions due to increased dopamine release and accumulation at the synapse (4).

PCP PSYCHOSIS

The psychosis caused by PCP clinically resembles schizophrenia more closely than the acute paranoid psychosis caused by amphetamines. Normal subjects exposed to PCP become withdrawn, autistic and negativistic, or catatonic, as well as idiosyncratic, with bizarre delusions and hallucinations. They may also show evidence of poverty of speech and thought (2). Interestingly, PCP and another NMDA antagonist, ketamine, are used as anaesthetic agents in children, but are likely to cause psychoses after puberty and are therefore not used in adults. Transient psychosis occurs in up to 50% of adults given PCP anaesthesia (29). The agitation, withdrawal, and hallucinations as well as catatonia, excitation, bizarre behaviour, paranoia, concrete thought, and severe hallucinatory disturbances that occur with PCP may persist beyond the patient's emergence from anaesthesia (2,29). Thus, it appears that a deficit of glutamate function may cause a state resembling schizophrenia both clinically and in developmental terms, as they both occur mainly after puberty. Glutamate is the primary neurotransmitter for cortical–cortical and cortical–basal ganglia and for cortical–limbic connections (4,35). Recent positron emission tomography (PET) studies have implicated abnormal connectivity in the pathogenesis of schizophrenia, as evidenced during PET scanning by a failure to suppress cerebral blood flow (CBF) in the superior temporal lobe during activation of dorsal lateral prefrontal CBF when performing a verbal fluency task; in these circumstances, blood

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flow is suppressed in nonschizophrenics (16). This suggests that a glutamate deficiency may account for abnormal connectivity as part of the pathogenesis of schizophrenic symptoms (28).

RECIPROCAL GLUTAMATERGIC AND DOPAMINERGIC EFFECTS

A role for glutamate becomes more interesting when one considers that there are problems in the dopamine theory of schizophrenia. The clinical antipsychotic effect of neuroleptic dopamine receptor blockers occurs much more slowly than their blocking action on the dopamine receptor itself, which takes place in only minutes. Hence, either dopamine blockade is not the source of this antipsychotic effect or it is only an intermediary process. Moreover, some 25% of patients do not respond to neuroleptics or respond only partially (22), and brain dopamine metabolites have been found to be unchanged or even decreased rather than increased in drug-free schizophrenic brains (4,5,40). As we will see, glutamate dysfunction goes some way toward explaining shortcomings of the dopamine theory.

There is strong evidence for a reciprocal function between the glutamatergic and dopaminergic systems (4). For example, spines of pyramidal cells receive dopaminergic synapses as well as glutamatergic ones (46), glutamate receptors are present on terminals of the nigrostriatal dopaminergic pathway (41), and dopamine receptors are located on the terminal projections of glutamatergic cortical striatal neurons (42).

The reciprocal modulatory role of glutamate receptors on dopaminergic neurons and dopaminergic receptors on glutamatergic neurons indicates mechanisms by which a deficiency of the former or an excess of the latter may predispose to psychotic symptoms (4). It has been shown that dopamine stimulates cyclic AMP-dependent phosphorylation, and glutamatergic NMDA receptors can reverse cyclic AMP-stimulated phosphorylation and cause dephosphorylation through calcineurin (20).

At a more general level, Carlsson has advanced the gating hypothesis (the thalamic filter dysfunction hypothesis), which envisages a reciprocal relationship between the role of glutamate stimulation in closing the thalamic gate for the inflow of sensory information to the cortex and dopamine stimulation, which opens the thalamic gate; both functions are mediated by GABAergic interneurons (4). The resulting loss of inhibitory control over inflowing cortical information is a postulated mechanism for thought disorder and bizarre experiences, which Carlsson theorises can be brought about by hypofunction of glutamatergic control or hyperfunction of the dopaminergic system.

GLUTAMATE HYPOFUNCTION MAY LEAD TO PYRAMIDAL CELL LOSS

Olney and Farber have produced a body of evidence that NMDA receptors provide inhibitory tone on a range of pyramidal cell axonal receptors by stimulating inhibitory GABA ergic and noradrenergic interneurons, which in turn inhibit neuropeptide Y-mediated stimulation, acetylcholine-mediated muscarinic (M_3) stimulation, and glutamatergic-mediated stimulation of kainate receptors on pyramidal cell neurons (39). There is also an NMDA-mediated GABA inhibitory feedback loop on the pyramidal cell glutamate terminals. These interactions are illustrated in Fig. 1.

It has been shown that in rats an intraperitoneal injection of MK-801 causes prolonged inhibition of NMDA receptors, which leads to the formation of intracellular vacuoles and, after time, heat shock proteins, which are associated with pyramidal cell death (39). According to Olney and Farber, this neurotoxic effect spreads from the posterior cingulate and retrosplenium to the areas of the brain most closely associated with aberrant cell morphology in histopathological studies of schizophrenia. These are the neocortical and limbic areas, anterior cingulate, piriform cortex, entorhinal cortex, hippocampus, thalamus, and amygdala (14). The results in rats are seen only after puberty, which is consistent with the developmental history of schizophrenia in humans, which mainly occurs after puberty, and a similar age dependency of PCP psychosis, suggesting common mechanisms. Moreover, the postpubertal rat can be protected from this effect by administering sigma, muscarinic, or kainic acid antagonists, or GABA, $alpha_2$ adrenoceptor, or NMDA agonists, any one of which would decrease excitatory overstimulation of the pyramidal cell. Most importantly, some conventional neuroleptics such as thioridazine and haloperidol and the atypical neuroleptics clozapine, olanzapine, and fluspirolene have been found to increase the activity of NMDA receptors by their facilitatory action on the MK-801 site (39), and Olney and Farber have reported that they confer a similar possible effect against toxic pyramidal cell excitation.

Thus, Olney and Farber (39) envisaged a liability of NMDA hypofunction to cause excitatory dyscontrol and destruction of pyramidal cells due to loss of glutamatergic inhibitory control of pyramidal cell neurons. The pyramidal cell necrotizing reaction is due to loss of all inhibitory tone over excitatory receptors on the pyramidal cell. However, opposing this theory is recent evidence that fails to show loss of cell number or necrotizing cell reactions in schizophrenia, which should be predicted from the model (14,43).

Nevertheless, this model has important implications for treatment. Crow and others have reported that first-episode schizophrenics who had gone without treatment for longer than 6 months had a significantly worse prognosis than those with a short interval between expression of the illness and introduction of neuroleptics (6,34). Olney and Farber's model would provide an explanatory basis for deterioration in the early phases of the disease postpuberty if, indeed, there was evidence for a pyramidal cell necrotizing reaction due to NMDA hypofunction in severe schizophrenia.

OTHER EVIDENCE TO SUPPORT A GLUTAMATERGIC DEFICIT IN SCHIZOPHRENIA

The Effect of Glycine and Polyamines, Glutamatergic Agonists

Glycine and the polyamines spermine and spermidine have been shown to have an allosteric modulatory affect on the NMDA receptor such that either glycine or spermine would be expected to increase NMDA receptor function (49). This mechanism would explain the findings of Hirsch et al. (23), who found a selective dose-dependent modulatory effect of spermine and spermidine on amphetamine- and apomorphine-induced hyperactivity in rats. This is believed to be mediated by the mesolimbic system, and polyamines do not effect striatal-mediated behaviour. Das et al. (8) in our unit have found that increased levels of plasma polyamines are found during neuroleptic treatment of schizophrenic patients, suggesting that this may be one of the mechanisms by which neuroleptics exert their delayed antipsychotic effect. Clozapine showed a similar effect in drug-resistant schizophrenic patients (7).

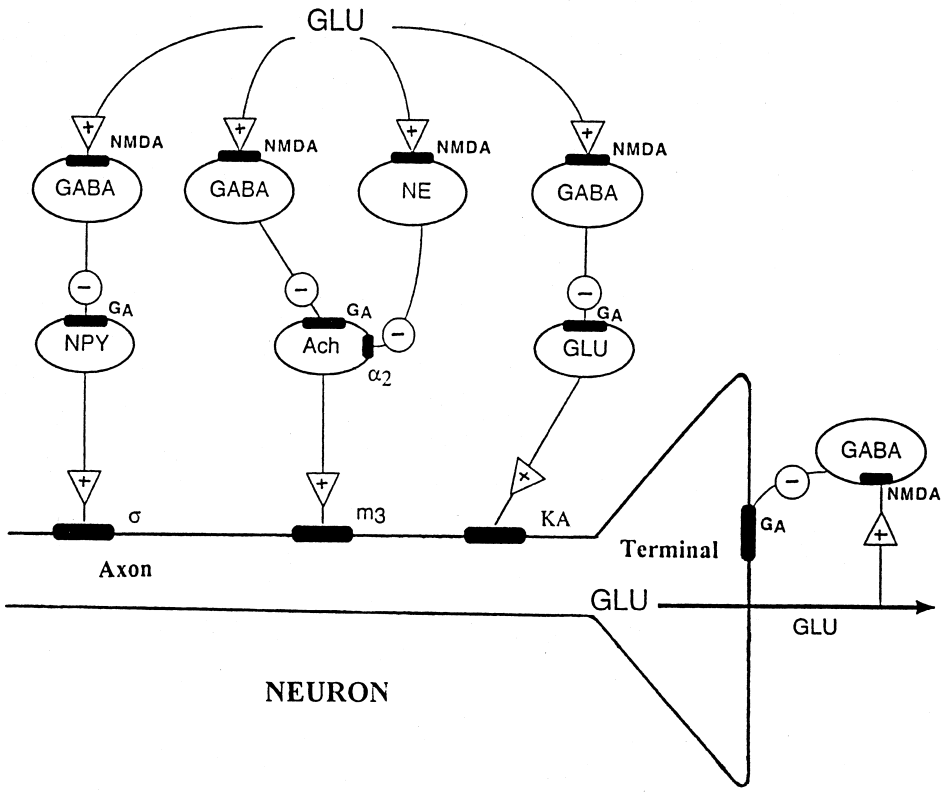

FIG. 1. Schematic representation of neurotransmitter interactions to explain how hypofunction of the NMDA receptor system can cause dysfunction of neuronal circuitry in the brain. Glutamate (Glu) acts on NMDA receptors on γ-aminobutyric acid (GABA) and norepinephrine (NE) neurons to maintain tonic inhibition over three excitatory inputs ("+" signs) to the neuron. Subsequent blockade of the NMDA receptors can cause disinhibition of all three excitatory inputs. The neuron regulates its own firing through the presence of a collateral circuit using Glu as a transmitter that acts on a GABAergic neuron. Ach, acetylcholine; NPY, neuropeptide Y; σ, sigma receptor; α_2, α_2 subtype of adrenergic receptor; G_A, $GABA_A$ subtype of GABA receptor; m_3, m_3 subtype of muscarinic cholinergic receptor; KA, kainic acid subtype of Glu receptor; NMDA, NMDA subtype of Glu receptor; "−" sign indicates inhibitory input. [Adapted from Olney and Farber (39).]

Treatment Effects

If PCP and ketamine produce a schizophrenic-like psychosis by causing NMDA hypofunction, then we can predict that NMDA co-agonists such as glycine and its prodrug D-cyloserine should improve symptoms of schizophrenia. In fact, there is modest evidence that glycine (30,51) and D-cycloserine (18) produce modest improvements of negative but not positive symptoms in 15–20% of the small groups of patients tested. Glycine, D-cycloserine, and milacemide, another glycine prodrug, have also been reported to improve deficient memory (18).

EFFECTS ON MEMORY

Glutamate has been shown to have an important role in long-term potentiation (LTP), which is thought to be important in a model of learning and memory (3,15). Similarly, NMDA antagonists impair LTP and spatial memory performance in mice (37). Drugs that increase glutamatergic activity tend to improve performance in memory tasks by mice and humans (16,38). Experiments with rats suggest that glutamate content in the brain diminishes with age, though this is not conclusive (36). The controversial evidence that glutamate deficiency is responsible for the memory defect in Alzheimer's disease has been reviewed elsewhere (15,36). A reduction of NMDA and kainic acid receptor binding in very old nondemented women compared with controls, as well as a further significant reduction in Alzheimer-diseased brains, has been reported by some (44) but not all authors. In addition, Fonnum et al. (15) found a 40% bilateral reduction in a marker of glutamate uptake, D-aspartate, following transection of the temporal entorhinal cortical connections that are thought to involved in memory. Evidence of glutamate receptor deficiency in other degenerative diseases has been reviewed by Olney and Farber (39). Given the persuasive evidence that glutamate may play an important role in schizophrenia, this preliminary evidence of a role of NMDA glutamate receptor function in a range of disorders that affect memory may point to an important link with schizophrenia insofar as it has been found to have an association memory disorder that worsens in old age (19,28).

ELECTROPHYSIOLOGICAL EVIDENCE OF AN NMDA DEFICIT IN SCHIZOPHRENIA

There is well established evidence of a deficit in P3 event-related potential (ERP) in schizophrenia that is independent of clinical improvement or medication status. The P3 wave occurs when subjects are presented with a novel "odd ball" stimulus after a sequence of repetitive, standard stimuli, and therefore requires a short-term memory of previously pre-

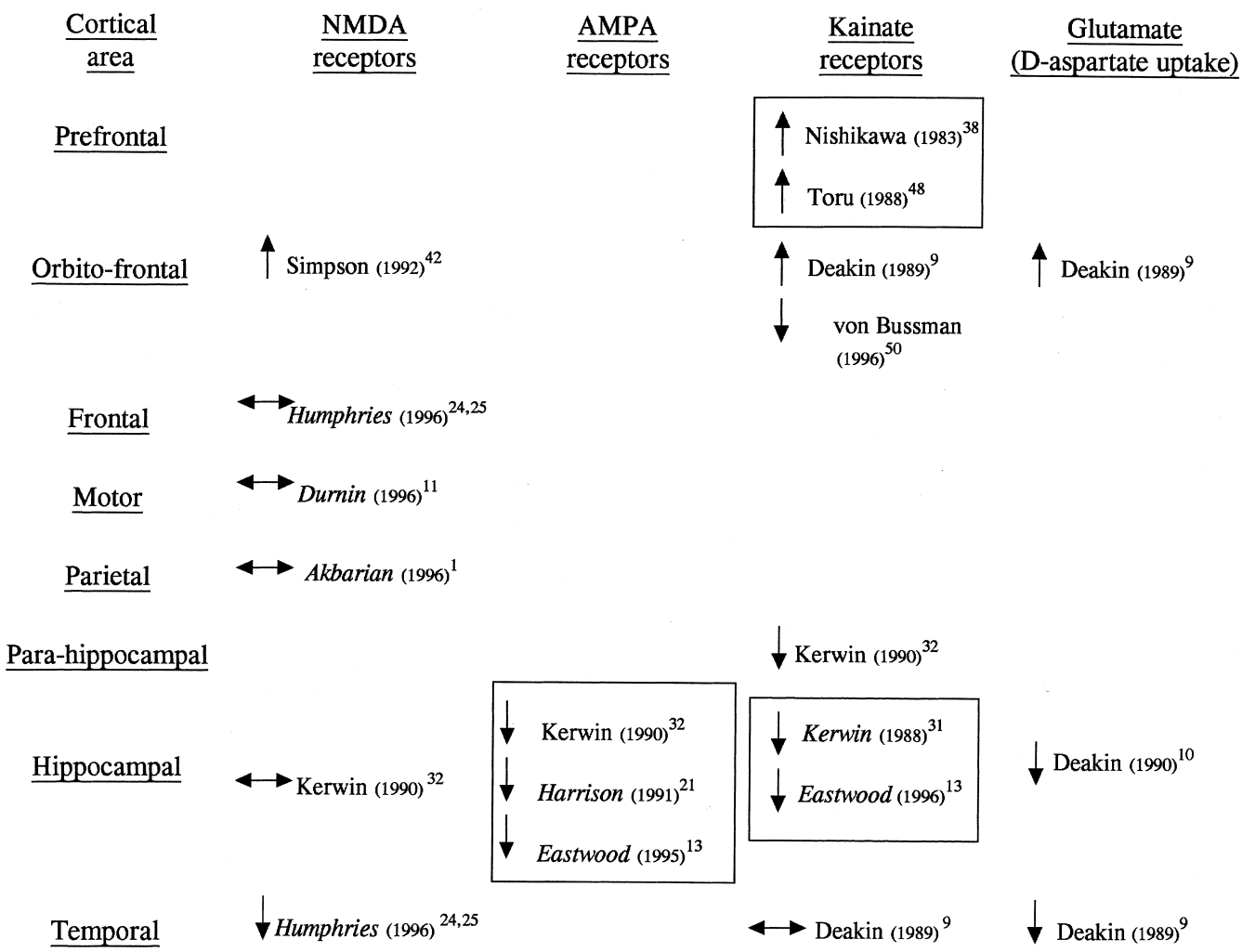

FIG. 2. Evidence of glutamatergic abnormalities in schizophrenia. Ligand binding studies shown in plain text, and mRNA analysis shown in *italics*.

sented stimuli as well as an alertness to the "odd ball." Schizophrenics show a decreased amplitude of the P3 response that correlates with thought disturbance and negative symptomatology (27). The ERP consists of an early short response at 50 ms called mismatch negativity (MMN), which is thought to reflect preattentive detection of stimulus change, and a later N2 200-ms component, followed by the P component at 300 ms. They are thought to correspond, respectively, to detection, analysis, and response phases to unexpected stimulus change, which require memory and recognition of previously experienced signals. The amplitude but not the latency of MMN was shown to be significantly decreased in schizophrenics and independent of treatment or symptom status. This deficit was correlated with a similar deficit in the later N2 and P3 component (26).

Intravenous injection of MK-801, a phencyclidine-like NMDA calcium channel blocker, into nonhuman primates selectively abolished the MMN response of the auditory ERP (26). We suggest this could be related to deficits in auditory short-term memory function, supporting evidence for NMDA-mediated glutamate dysfunction in schizophrenia.

DIRECT EVIDENCE OF GLUTAMATERGIC ABNORMALITIES IN SCHIZOPHRENIA

Early interests in a glutamate deficiency in schizophrenia followed Kim et al.'s report of low glutamate levels in cerebral spinal fluid of schizophrenic patients (33). Various authors have studied glutamate concentrations in a number of brain regions, but the approach is unreliable because results reflect both metabolic and neurotransmitter levels of glutamate. A number of groups, including Kerwin's (32), Deakin's (10), Nishikawa's (38), and others, have studied glutamate uptake labelled by [^{3}H]D-aspartate and non-NMDA glutamate receptor binding using [^{3}H]kainate (40). In general, there is evidence to support decreased messenger RNA for non-NMDA glutamate receptors in the temporal cortex, amygdala, and hippocampus (21), as well as evidence of an increase in kainate binding sites in prefrontal, orbital frontal, and medial frontal sites. The results of binding studies and studies of messenger RNA are summarised in Fig. 2, which indicates which receptors have been shown to be increased or decreased and in which area of the brain. Boxed author names indicate findings that have been replicated by more than one group for a particu-

lar brain area. These results indicate widespread but specific changes in NMDA receptor function, with replication of the findings of decreased NMDA receptors in the hippocampal area, increased kainate receptors in the prefrontal and orbitofrontal areas, and decreased kainate receptors in the hippocampus.

Results from the Charing Cross/Wiesloch Prospective Postmortem Study

Our group was the first to report an association of a biochemical defect with a particular clinical characteristic in a schizophrenic population (24,25) that had been assessed clinically and histochemically to rule out Alzheimer's and other serious neurological diseases. Patients were well characterised clinically, having consented to tissue donation prior to death. mRNA for the NMDA subunit NR-1 was measured in tissue homogenates of superior temporal cortex and found to be significantly reduced—by 30%—in cognitively impaired schizophrenic cases compared with control cases, but not reduced in cognitively preserved cases matched for age. Patients with histological evidence of Alzheimer's disease were excluded from the study. Moreover, the NR-1 NMDA receptor mRNA deficit was significantly correlated with the patients' general cognitive function, rated premorbidly with the Global Deterioration Scale ($r = 0.91$, $p < 0.001$) and the Mini Mental State Examination ($r = 0.66$, $p < 0.01$), and the premorbid IQ as determined by the National Adult Reading Test (NART) ($r = 0.95$, $p < 0.01$). No significant correlation of NR-1 mRNA concentration was found with age, sex, tissue pH, or postmortem delay in the control group or the schizophrenia group when analysed separately or combined (25). As yet unpublished work from our laboratory has not found NR-1 mRNA in the parietal lobe to be affected, and we found only a slight reduction in the frontal lobe. Thus, the finding appears to be specific to the temporal and hippocampal area within patients, thereby controlling for drug effects, and is symptom-specific, being reduced only in patients with severe cognitive deterioration within an elderly schizophrenic cohort.

The strong correlation between the NART score and expression of NR-1 is surprising. The NART is used as a measure of premorbid IQ because it depends on vocabulary skills developed during childhood. Because there was no correlation of NR-1 with age, medication, or duration of illness, the correlation of low NART score with low NR-1 levels suggests that an early developmental defect occurs and is expressed well before the onset of the illness.

We also studied the distribution of dendritic spines on pyramidal neurons of layer III of human cortex in 16 schizophrenic patients and 17 nonschizophrenic patients (17). As for the mRNA studies, autopsies were obtained within less than 24 h after death. Blocks from multiple cortical areas were impregnated using the rapid Golgi method, and spines were counted on the dendrites of pyramidal neurons of which the soma was in layer III, i.e., those that take part in cortical–cortical connectivity. All measurements were made blind to diagnosis. The average spine count in all cortical areas studied in control brains was 243 (SD 137.5) per mm of dendrite and in the schizophrenics 108 (SD 62.8) per mm ($p < 0.0002$). Tissue from the temporal and frontal association cortices showed an even greater reduction in spine number, with 296 per mm in the temporal cortex of controls and 107 in schizophrenics, and 272 and 117, respectively, in the frontal cortex. There was no correlation of spine loss with age at death, but there was a suggestion that males may be more severely affected than females. Because glutamate receptors are known to be located on dendritic spines, and given the role of pyramidal cells in connecting different areas of cortex, this finding suggests a glutamate deficiency that could account for decreased connectivity, as reported in PET studies (16), without loss of cell number.

We are looking forward to obtaining a broader and more systematic profile of glutamate dysfunction across the cerebral cortex, and we are studying other cortical neurotransmitters. We will continue to correlate localised tissue abnormalities with symptoms and syndromes identified with a clinical assessment prior to death.

The evidence that glutamate dysfunction plays a pivotal role in the pathogenesis of schizophrenia is now of increasing interest.

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