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Stevens J R. An anatomy of schizophrenia? *Arch. Gen. Psychiat.* 29:177-89, 1973.
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Based on the then-emergent dopamine hypothesis of schizophrenia and the similarity of many symptoms of schizophrenia to the auras of temporal lobe epilepsy, this paper proposed that the nucleus accumbens and adjacent striatum-like nuclei constitute a *limbic striatum*. This second dopamine-biased striatal "filter" system receives projections from major limbic sites and is, except for differences in inputs and outputs, remarkably similar in organization to the neocortical-neostriatal (caudate putamen) system. Disturbed function in this limbic striatal "gate" or "filter" may be a site of pathology in schizophrenia. [The *SCI*® and *SSCI*® indicate that this paper has been cited in over 425 publications.]

Dopamine-Biased Striatal "Filters" and Schizophrenia

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My first ideas for "An anatomy of schizophrenia?" were generated in 1972, while I was flying back to Boston from a neurology meeting in New Orleans. I had left the meeting early, as the organizers, threatened with picketing and violence by antipsychosurgery groups, had cancelled a presentation by Professor Robert G. Heath, who was to have spoken about his pioneering investigations of brain electrical activity in schizophrenia. Sitting next to me on the flight back to Boston was the eminent Massachusetts Institute of Technology neuroanatomist, Professor Walle Nauta. After deploring the suppression of the afternoon's speaker, we talked about new developments in neuropsychiatry.

Three giant steps had taken place in neuropharmacology and neuroscience during the preceding two decades that were transforming the field of psychiatry to a more rigorous discipline closely tied to the anatomy and physiology of the brain: (1) the introduction of chlorpromazine, the first major antipsychotic agent, in 1952; (2) the demonstration by Carlsson and others that chlorpromazine blocks dopamine (DA) receptors in the brain; and (3) the demonstration by Andén, Dahlstrom, Fuxe, and Ungerstedt that previously unknown anatomical pathways carry monoamine transmitters DA, norepinephrine, and serotonin from brain stem to areas of the cerebrum. The DA hypothesis of schizophrenia, suggesting over-activity of DA in one or more DA systems, was born.

To me, as a neurologist, the similarity of symptoms during the auras of temporal lobe epilepsy to the subjective experiences of patients with schizophrenia was striking and suggested that the same medial temporal structures must be involved in schizophrenia. During the three-hour flight from New Orleans to Boston, I discussed these ideas with Nauta. He is a proficient tennis player and our dialogue was like playing tennis with a pro; every symptom and sign of schizophrenia I served elicited an unerring anatomical return.

The following morning I woke with a clear image of projections from the broad expanse of neocortex like the folds of a fan toward its handle. In a parallel ventral fan, amygdala and hippocampal efferents converge on limbic striatum and are then relayed to the pallidal-like cells beneath the anterior commissure.

I hypothesized that overactivity of DA in the limbic striatal "gate" might permit the mnemonic and emotional stores locked in hippocampus and amygdala abnormal passage or distortion en route to consciousness and behavior. To test this hypothesis, we attempted an experimental model of psychosis in the cat, directed toward enhancing DA activity in limbic striatum by blocking the negative feedback pathway with the GABA blocking agent bicuculline.[1] Cats so treated appeared to hallucinate, retreated fearfully from familiar persons, and, perhaps best of all, developed abnormal spike activity in nucleus accumbens similar to that described by Heath in acutely psychotic man.[2] In the meantime "An anatomy of schizophrenia?" had been sent to Daniel X. Freedman, editor of the *Archives of General Psychiatry*, accompanied by original black-and-white line drawings by Nauta. Freedman treated the manuscript generously but commented that "no one knew where the nucleus accumbens was" and could I please clarify Nauta's line drawings. Accordingly, I had a commercial artist redo the original drawings with simpler if less accurate brush paintings.

Neuroanatomy and neuropathology have again, largely due to development of neuroimaging, become major aspects of psychiatric research. Although much important information about these anatomical systems has been added, the original concept of the two parallel DA-biased subcortical "filters" has in general been sustained. Recent anatomic studies point to abnormalities in medial temporal lobe and internal pallidum in schizophrenic patients,[3] lending support to the 1973 hypothesis that denervation supersensitivity or aberrant regeneration in DA-biased limbic striatal projection sites may underlie the schizophrenic process.[4]

1. **Stevens J, Wilson K & Foote W.** GABA blockade, dopamine and schizophrenia: experimental studies in cat. *Psychopharmacologia* 39:105-19, 1974. (Cited 100 times.)
2. **Tulane University, Department of Psychiatry and Neurology. Heath R G, chairman.** *Studies in schizophrenia: a multidisciplinary approach to mind-brain relationships.* Cambridge, MA: Harvard University Press, 1954. 619 p.
3. **Bogerts B, Meertz E & Schonfeld-Bausch R.** Basal ganglia and limbic system pathology in schizophrenia. *Arch. Gen. Psychiat.* 42:784-91, 1985. (Cited 65 times.)
4. **Stevens J R.** Epilepsy, psychosis and schizophrenia. *Schizophrenia Res.* 1:79-89, 1988.

13-2