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A sexually dimorphic nucleus in the human brain

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published in
Science
1985

Link to publication in KNAW Research Portal

citation for published version (APA)
Swaab, D. F., & Fliers, E. (1985). A sexually dimorphic nucleus in the human brain. *Science*, *228*, 1112-1115.

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tions is difficult to assess because preferences of the extinct fauna such as dietary habitats, are not known. Cuticle and pollen analyses of the dung material of the giant groundsloth in southern Patagonia, however, reveal links between vegetational shifts and shifts in dietary habits of the extinct groundsloth (Fig. 2). Studies of the North American groundsloth (*21–24*), on the other hand, indicate that in the American Southwest, *Nothrotheriops shastaense* was a browser on xerophytic plants that were available before and after its disappearance, indicating that food resource problems did not cause extinction.

Fifteen samples of dung of the Patagonian groundsloth have been dated from Mylodon Cave (Table 1). To investigate dietary habits and general environmental conditions at the time that *Mylodon* lived in southern Patagonia, cuticle remains and pollen in nine of the samples were analyzed. The data from cuticles (Fig. 2) indicate that these animals were grazers, not browsers, in contrast to their North American counterpart. Their diet consisted of 80 to 95 percent grasses, 5 to 20 percent sedges, and only traces of herbaceous taxa. The pollen data revealed a much greater plant diversity than the cuticle data, reflecting the general environment as well as the diet (*24*). Even though there is considerable variability between the samples (percentage of pollen, pollen concentration, and number of taxa), the major pollen types indicate several paleoenvironmental trends through time. Samples with dates prior to 12,000 B.P. show higher percentages and concentrations of Gramineae and Compositae than the younger samples, which show more *Empetrum*. The youngest sample dated (10,832 ± 400 B.P.) and analyzed for pollen by Salmi (*25*) shows pollen proportions that are quite different from all the other samples, with Compositae and herbaceous taxa dominating and Gramineae low.

This sequence of changes in pollen is similar to the vegetational changes discussed above (Table 2). In all records there is an evident shift between 11,000 and 10,000 B.P. from a cold, mesic environment to a more arid and warmer environment. This change is expressed as a shift from a species-poor grassland to a species-rich shrubby grassland with taxa characteristic for increased aridity. These specific taxa are different at different sites and include *Acaena* and *Berberis* (La Mision), *Empetrum*, *Berberis*, and *Perezia* (Mylodon Cave), and *Ephedra* and Compositae (Fells Cave). The environmental characteristics and contemporaneity of this shift in all records, including the dung material of the extinct fauna, suggests a direct link between vegetation change and dietary response of the fauna.

In conclusion, I propose that the series of paleoenvironmental changes in southern Patagonia and Tierra del Fuego during the time of faunal extinction directly affected the food resources, both in area and in character, and created a stress for the animals that cannot be discounted in extinctions. The additional stress of paleoindian hunters might have been the final blow that led to the extinction of some of the already more decimated beasts, while others such as the guanaco, less specialized in its diet, returned eventually to roam the Patagonian lands again.

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26. We thank J. Bird and P. S. Martin for some of the samples, T. Foppe (Colorado State University, Fort Collins) for cuticle analysis, G. Kruger (Geochron) and A. Long (University of Arizona) for radiocarbon dates, and J. P. Bradbury, D. Grayson, and Ch. Repenning for editorial comments and valuable discussion. Supported by NSF grants ATM-7919771 and ATM-8212836.

22 January 1985; accepted 4 March 1985

A Sexually Dimorphic Nucleus in the Human Brain

Abstract. *A sexually dimorphic cell group is described in the preoptic area of the human hypothalamus. Morphometric analysis revealed that the volume of this nucleus is 2.5 ± 0.6 times (mean ± standard error of the mean) as large in men as in women, and contains 2.2 ± 0.5 times as many cells. Between the ages of 10 and 93 years, the nucleus decreases greatly in volume and in cell number. Although no function has yet been established for this nucleus, it is located within an area that is essential for gonadotropin release and sexual behavior in other mammals.*

The literature of the past century on the possibility of morphological sex differences in the human brain is a mixture of scientific observations and cultural bias, in which male and female "superiority" were alternately contended (*1, 2*). Until recently, however, Mall's conclusion that "each claim for specific [sex] differences fails when carefully tested" (*3*, p. 27) held true with respect to the human brain, apart from the sex difference in overall size of the brain (*1*). A few years ago a sex difference in the shape of the corpus callosum was described (*4*), and recently the shape of the suprachiasmatic nucleus (SCN) was found to be sexually dimorphic (*1*). Yet, to our knowledge, no sex difference in cell number has been reported for any human brain area. On the other hand, since Raisman and Field (*5*) reported sex differences in the synaptic organization of the preoptic area in the rat, reports pertaining to gender-linked differences in many brain components throughout the animal kingdom have increased (*1*). The most conspicuous of these sex differences was described by Gorski *et al.* within the rat brain (*6*), in the preoptic area (POA). A cell group within this area revealed such a clear cytoarchitectonic sex difference that it could even be seen with the naked eye in Nissl-stained sections. We have studied an analog of this sexually dimorphic nucleus (SDN) of the POA in the human brain. Morphometric analysis demonstrates that the SDN-POA is 2.5 ± 0.6 times [mean ± standard error of the mean (S.E.M.)] as large in men as in women and contains 2.2 ± 0.5 times as many cells.

Brains of 13 men and 18 women between 10 and 93 years of age were fixed, generally for 1 month, in Formalin. Serial coronal sections (6 μm) were taken from the hypothalamus and stained with thionin (*7*).

As has been reported for the rat (*6*),

the SDN-POA was characterized by its more intense staining, larger cell bodies, and higher cell density than the rest of the POA. The SDN-POA was located in the medial POA, between the dorsolateral supraoptic nucleus and the rostral pole of the paraventricular nucleus (Figs. 1 and 2). It was generally present in the same sections that contained the suprachiasmatic nucleus, which had been marked by antivasopressin (*2, 8*).

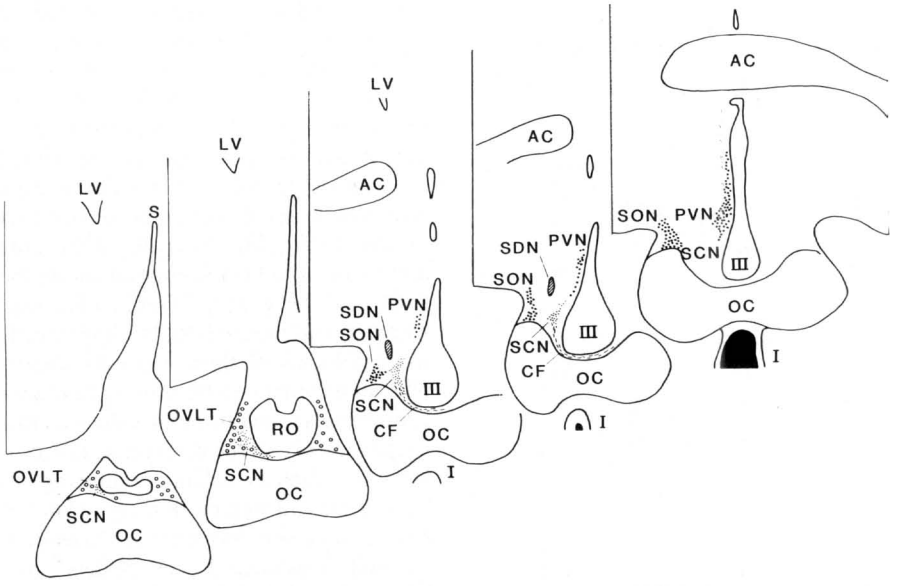
The rostrocaudal axis of the SDN-POA and its maximum cross-sectional surface were measured to describe the shape and to calculate SDN-POA volume (*9*). In addition, cell density was measured (*10*), which, in combination with SDN-POA volume, allowed for calculation of total SDN-POA cell numbers. The SDN-POA measurements were performed on the same side of the brain and in the same subjects as the earlier suprachiasmatic nucleus measurements (*1, 8*).

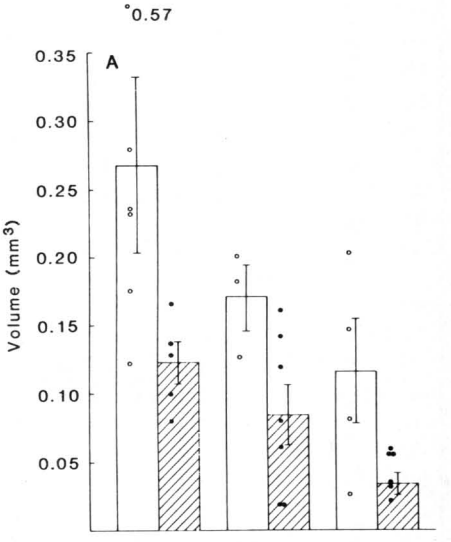
The SDN-POA volumes were, respectively, 2.2 ± 0.6, 2.0 ± 0.6, and 3.3 ± 1.3 times as large in men as in women in the three age groups (Table 1) (*11, 12*). Total cell number was, respectively, 1.74 ± 0.36, 1.96 ± 0.62, and 2.75 ± 0.79 times as large in men as in women (Figs. 2 and 3) (*11*). Also when SDN-POA volume was expressed as a ratio to brain weight, the values were significantly larger in men ($131.3 \pm 18.8 \times 10^{-6}$ mm^3/g) than in women ($63.5 \pm 9.8 \times 10^{-6}$ mm^3/g) (*11*). The maximum cross-sectional area through the SDN-POA was 2.1 ± 0.4 times as large in men as in women (*11*). The SDN-POA attained its maximum cross-sectional area 300 μm caudal to the section containing the maximum area of the SCN in women and 500 μm caudal in men. The values of the Alzheimer's patients were commensurate with their ages and have therefore been included in the study.

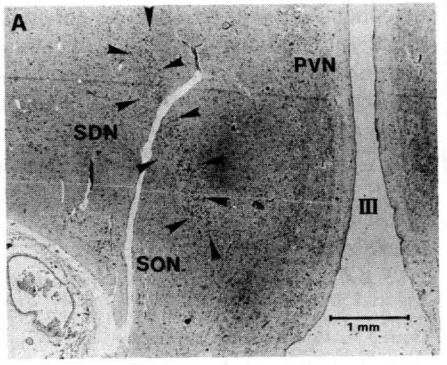
In both sexes SDN-POA volume (in men, to 43 ± 17 percent; in women, to 29 ± 7 percent), cell number (to 46 ± 13 percent and 29 ± 6 percent), and maximum cross-sectional area (to 49 ± 10 percent and 52 ± 9 percent) decreased with advancing age (Fig. 3 and Table 1) (*11*).

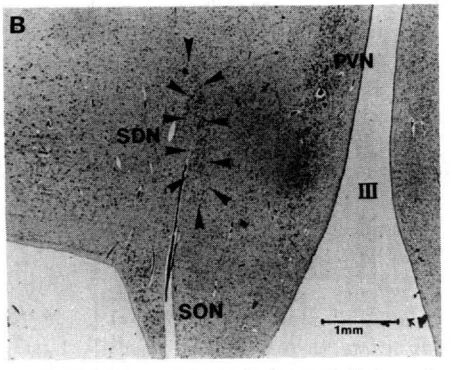
Sex differences in the size of the SDN-POA in the rat are independent of sex hormonal treatment in adulthood (*13*). Our series included the brain of a 46-year-old woman who had been virilized by a tumor of the adrenal cortex (*7*). Her SDN-POA measurements were similar to the other female values, which is in agreement with Gorski's data on the rat (*13*). In our series no information is available with respect to still another SDN-POA property described in the rat—the reversibility of sexual dimorphism by hormonal manipulation in earlier development.

The differences with respect to age and sex are unlike those observed for the









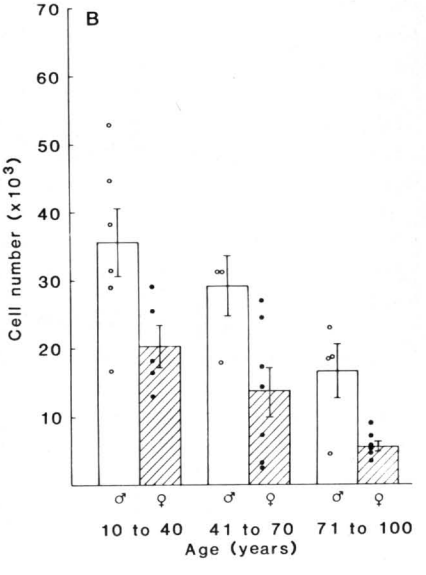


Fig. 1 (top left). Topography of the human hypothalamus. Abbreviations: AC, anterior commissure; CF, commissural fibers of the suprachiasmatic nucleus; I, infundibulum; LV, lateral ventricle; OC, optic chiasm; RO, recessus opticus; OVLT, organum vasculosum of the lamina terminalis; PVN, paraventricular nucleus; S, septum; SDN, sexually dimorphic nucleus of the POA; SCN, suprachiasmatic nucleus; SON, dorsolateral supraoptic nucleus; III, third ventricle. Fig. 2 (bottom left). Thionin-stained frontal sections (6 μm) of the hypothalamus of (A) a 28-year-old man and (B) a 10-year-old girl. Arrows show the extent of the SDN. Fig. 3 (right). (A) Volume and (B) cell number of the human SDN-POA (means and S.E.M.'s). Points represent individual values.

Table 1. Individual data for men and women separately (N.D., not determined).

Men						Women				
				SDN-POA					SDN-POA	
Age group	Age (years)	Body height (cm)	Brain weight (g)	Volume (mm^3)	Cell number ($\times 10^3$)	Age (years)	Body height (cm)	Brain weight (g)	Volume (mm^3)	Cell number ($\times 10^3$)
10 to 40	16	180	1940	0.570	52.87	10	N.D.	1270	0.166	29.15
	19	191	1900	0.123	16.70	15	179	1480	0.129	18.06
	22	190	N.D.	0.233	44.54	30	165	1460	0.081	16.36
	27	180	1560	0.177	31.85	35	174	1200	0.137	25.50
	28	189	1510	0.280	38.12	38	154	1360	0.101	13.00
	31	173	1330	0.234	29.21					
$\bar{X}$ ± S.E.M.	23.8 ± 2.4	183.8 ± 3.0	1648 ± 118	0.270 ± 0.064	35.55 ± 5.15	25.6 ± 5.6	168.0 ± 5.5	1354 ± 54	0.123 ± 0.015	20.41 ± 2.99
41 to 70	43	176	1260	0.128	31.22	46	181	1360	0.142	24.63
	59	177	1350	0.201	17.96	52	173	1370	0.061	7.57
	61	177	1400	0.183	31.60	57	164	1220	0.072	14.36
						60	160	1110	0.161	27.17
						64	169	1090	0.019	2.36
						70	165	780	0.019	3.12
						70	N.D.	1210	0.120	17.20
$\bar{X}$ ± S.E.M.	54.3 ± 5.7	176.7 ± 0.3	1337 ± 41	0.171 ± 0.022	26.93 ± 4.48	59.9 ± 3.4	168.7 ± 3.1	1163 ± 76	0.085 ± 0.022	13.77 ± 3.75
71 to 100	74	172	1410	0.027	4.58	72	165	1200	0.007	9.21
	83	178	1280	0.082	18.87	88	160	1030	0.033	5.94
	85	165	1400	0.203	23.26	90	160	1110	0.058	7.31
	87	N.D.	1275	0.148	18.53	90	N.D.	1300	0.057	4.49
						91	160	1060	0.033	4.96
						93	165	1020	0.022	3.67
$\bar{X}$ ± S.E.M.	82.3 ± 2.9	171.7 ± 3.8	1341 ± 37	0.115 ± 0.038	16.31 ± 4.06	87.3 ± 3.1	162.0 ± 1.2	1120 ± 45	0.035 ± 0.008	5.93 ± 0.83

SCN in the same brain material. In the latter area a sex difference was found only in shape (for example, in the length of the rostrocaudal axis) but not in volume or cell number. In addition, no decline in volume and cell number in the SCN was observed until after the age of 80 years (*8*). This result demonstrates that the sex and age differences reported for the human SDN-POA are not part of a general effect on the hypothalamus but are localized.

The preoptic area plays a role in gonadotropin release and sexual behavior in many species (*14*). Transplantation of the POA from newborn males to the same area in female littermates enhances masculine and feminine sexual behavior in adulthood (*15*). In the male monkey, changes in neuronal activity in the medial POA are related to the initiation of sexual behavior, penile erection, and the refractory period following ejaculation (*16*).

In addition, neurons of the POA concentrate androgens and estrogens (*17*), a function presumed to be instrumental in the development of sex differences in this area. The function of the SDN-POA, on the other hand, is unknown both in the rat and in humans. Lesions restricted to this nucleus in the rat failed to reveal a role in male sexual behavior for this part of the POA (*18*). Sexually dimorphic areas have also been identified within the POA's of the gerbil, ferret, guinea pig, hamster, and mouse (*19*), but interspecific homologies of these sexually dimorphic areas remain to be shown. Immunocytochemistry might be of value for this purpose, since in the rat intense innervation by cholecystokinin-containing fibers, a lack of innervation by serotonin fibers, and a sex difference for neurotensin and substance P cell bodies have been reported (*20*). In addition, immunocytochemistry seems to be a potent technique for studying the exact chemical nature of the SDN-POA sex differences and the cell types in which the changes with aging occur.

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7. Brains of 31 patients (13 men and 18 women)

were obtained at autopsy. Subjects had no neurological disease, except for one man and two women who had been diagnosed clinically and pathologically as suffering from senile dementia of the Alzheimer's type. One 46-year-old woman had suffered during at least 1 year from a tumor of the adrenal cortex, which induced high concentrations of androstenedione and testosterone in the blood. At autopsy, male brains weighed 1467.9 ± 66.3 g (mean ± standard error of the mean) and female brains weighed 1201.7 ± 41.5 g (18.1 percent smaller) (Table 1). Brains were fixed in 10 percent formaldehyde at room temperature generally for 30 days. The hypothalamic area was subsequently dissected, dehydrated, and embedded in paraffin. Serial 6-μm frontal sections were cut on a Leitz microtome, mounted on chromium aluminum sulfate–coated slides, hydrated, brought to phosphate-buffered saline, and stained with thionin.

8. D. F. Swaab *et al.*, in *Topics in Aging Research*, D. L. Knook *et al.*, Eds. (Eurage, Brussels, 1984), vol. 2, pp. 71–78.
9. The rostrocaudal length of the SDN-POA was determined by staining every 25th section from the lamina terminalis to the caudal end of the optic chiasm with thionin. The rostral and caudal borders of the SDN-POA were assessed by subsequent staining of every fifth section in the most rostral and the most caudal parts and by determining the sections in which the first and last SDN-POA cells were present. Area measurements of the cross-sectional SDN-POA and the cell nuclei were performed by means of a Calcomp digitizer, through the use of a Zeiss microscope with ×10 and ×40 (plan) objectives, respectively, and ×12.5 plan oculars. The maximum cross-sectional SDN-POA area is presented as a separate measure. The volume of the SDN-POA was determined by integrating area measurements from the first to the last SDN sections [C. G. Van Eden *et al.*, *Dev. Brain Res.* **12**, 146 (1984)], 11 ± 3 sections (mean ± standard error of the mean) being measured per subject.
10. The number of SDN cells per (unit) volume (cell density) was estimated through the use of a discrete "unfolding" procedure [E. R. Weibel, *Stereological Methods*, vol. 1, *Practical Methods for Biological Morphometry* (Academic Press, New York, 1979)], which included the modification for classification proposed by L. M. Cruz-Orive [*J. Microsc.* **112**, 153 (1978)] and a correction for section thickness (6 μm). The nuclear profiles of 132 ± 6 cells (mean ± standard error of the mean) per SDN-POA were measured per subject for this procedure in the section containing the maximum SDN-POA area. The computer program for these procedures was developed in our institute by R. W. H. Verwer.
11. The influence of age and sex on SDN-POA length, maximum area, cell density, and cell number were tested by means of two-way analysis of variance ($\alpha = 0.05$). Significant sex (main) effects were found for maximum area [$F(1, 25) = 18.21$; $P < 0.001$], volume [$F(1, 25) = 12.17$; $P = 0.002$], cell number [$F(1, 25) = 15.97$; $P = 0.001$], and the ratio of SDN-POA volume to brain weight [$F(1, 25) = 11.63$; $P = 0.002$]. Significant age (main) effects were found for the decline in maximum area [$F(2, 25) = 6.61$; $P = 0.005$], volume [$F(2, 25) = 5.52$; $P = 0.001$], cell number [$F(2, 25) = 9.44$; $P = 0.001$], and the ratio of SDN-POA volume to brain weight [$F(1, 25) = 5.29$; $P = 0.012$], while no significant interactions between the effects of age and sex on these variables were found ($P > 0.25$). As in the rat (*12*), there was no statistically significant sex difference either in the length of the rostrocaudal axis ($P = 0.162$) or in cell density ($P = 0.937$) of the SDN-POA. In addition, no significant effects of postmortem delay ($P > 0.05$) or duration of fixation ($P > 0.05$) were found.
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18 September 1984; accepted 14 February 1985

Loss of M2 Muscarine Receptors in the Cerebral Cortex in Alzheimer's Disease and Experimental Cholinergic Denervation

Abstract. *Cerebral cortex samples from patients with Alzheimer's disease and from rats after experimental cholinergic denervation of the cerebral cortex exhibited reductions in the presynaptic marker choline acetyltransferase activity and in the number of M2 muscarine receptors, with no change in the number of M1 receptors. These results are in keeping with evidence that M2 receptors function in cholinergic nerve terminals to regulate the release of acetylcholine, whereas M1 receptors are located on postsynaptic cells and facilitate cellular excitation. New M1-selective agonists and M2-selective antagonists directed at post- or presynaptic sites deserve consideration as potential agents for the treatment of the disease.*

Large reductions in choline acetyltransferase (CAT) activity are found in postmortem samples from the cerebral cortices of patients with senile dementia of the Alzheimer's type (SDAT) (*1–5*). Cortical cholinergic deficits result from the degeneration of cell bodies located in the nucleus basalis of Meynert (*6*). However, all but two (*7, 8*) of many studies have indicated no change in the numbers of receptors for acetylcholine ("muscarine" receptors) in samples of SDAT cerebral cortex and hippocampus (*9–11*). The absence of major changes in the number of receptors has been taken as evidence that muscarine receptors are located postsynaptically. We have reexamined this situation because of evidence that there are two basic subtypes of muscarine receptors in the brain, M1 and M2 (*12*), and that the M2 receptors may function primarily to regulate the release of acetylcholine from cholinergic nerve terminals (*13*). We report that M2 receptors are lost in advanced SDAT and are diminished (in proportion to the reduction of CAT activity) after experimental cholinergic denervation of the cerebral cortex in rats. The number and affinity of postsynaptic M1 receptors remain unchanged.

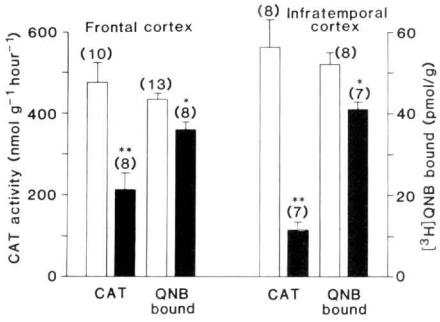

Fig. 1. Changes in CAT activity and in the total number of muscarine receptors in cortical samples from patients with SDAT (filled bars) as compared with controls (open bars). The numbers in parentheses are the numbers of tissue samples assayed as described in the text. Data are expressed per gram of wet tissue weight, and values are means ± the standard errors of the mean. Statistical significance of the differences was judged by Student's *t*-test: $*P < 0.05$; $**P < 0.001$.

Brain tissue was obtained from deceased persons with and without SDAT and from rats with nucleus basalis lesions (*14*). Frontal and infratemporal cortical samples were obtained at autopsy from neurologically normal individuals (mean age, 71 years) and patients with SDAT (mean age, 74 years) within 12 hours of death (mean delay, 8 hours). One SDAT patient had been receiving low doses of phenobarbital, and two SDAT patients had received Thorazine; except for those, none of the patients had been receiving drugs that affect the central nervous system. Phenobarbital and Thorazine are not known to affect muscarine receptors or CAT activity. The diagnosis of SDAT was made histologically on the basis of the widespread distribution of neurofibrillary tangles and neuritic plaques. No brain showed other significant neuropathology. For the animal experiments, male Sprague-Dawley rats weighing 200 g each were injected with 10 μg of ibotenic acid unilaterally into the ventral and medial aspects of the globus pallidus 72 hours before neurochemical assays of the frontoparietal cortex.

CAT activity was estimated by the