KAVLI LECTURE

Kavli Institute
for Systems Neuroscience

GORAN ŠIMIĆ

Professor of Neuroscience and Anatomy,
Croatian Institute for Brain Research

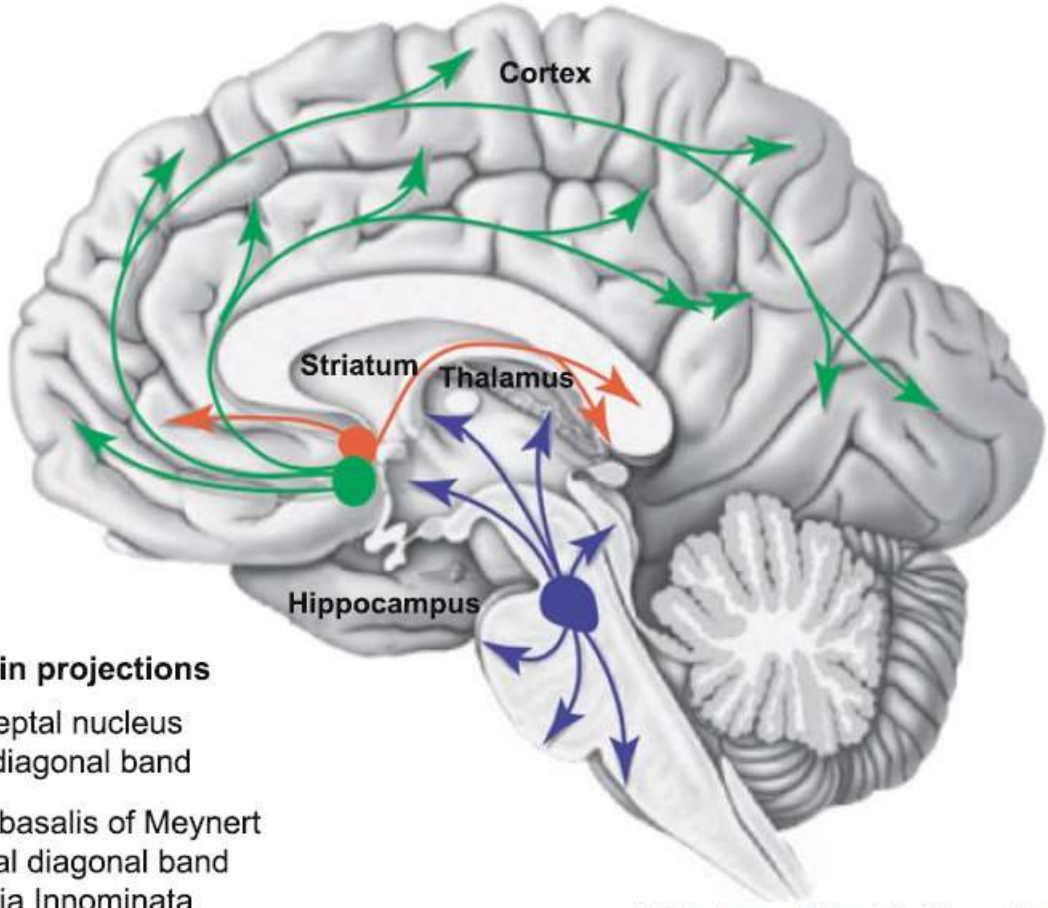
"ROLE OF SUBPUTAMINAL NUCLEUS IN LANGUAGE:
ENIGMA OF PRIMARY PROGRESSIVE APHASIA SOLVED?"

Time:
NOV 12, 2021 10:30 AM

Location:
SEMINAR ROOM 5TH FLOOR OR ZOOM

Organized by
MENNO WITTER

Cholinergic system



Basal forebrain projections

Medial septal nucleus
Vertical diagonal band

Nucleus basalis of Meynert
Horizontal diagonal band
Substantia Innominata

Brainstem cholinergic projections

Laterodorsal pontine tegmental nucleus
Pedunculopontine nucleus

A Review of the Cholinergic System and Therapeutic Approaches to Treat Brain Disorders

Daniel Bertrand and Tanya L. Wallace

Curr Topics Behav Neurosci (2020) 45: 1–28
https://doi.org/10.1007/7854_2020_141
Published Online: 26 May 2020

Simplified schematics of the major cholinergic projections in the human brain

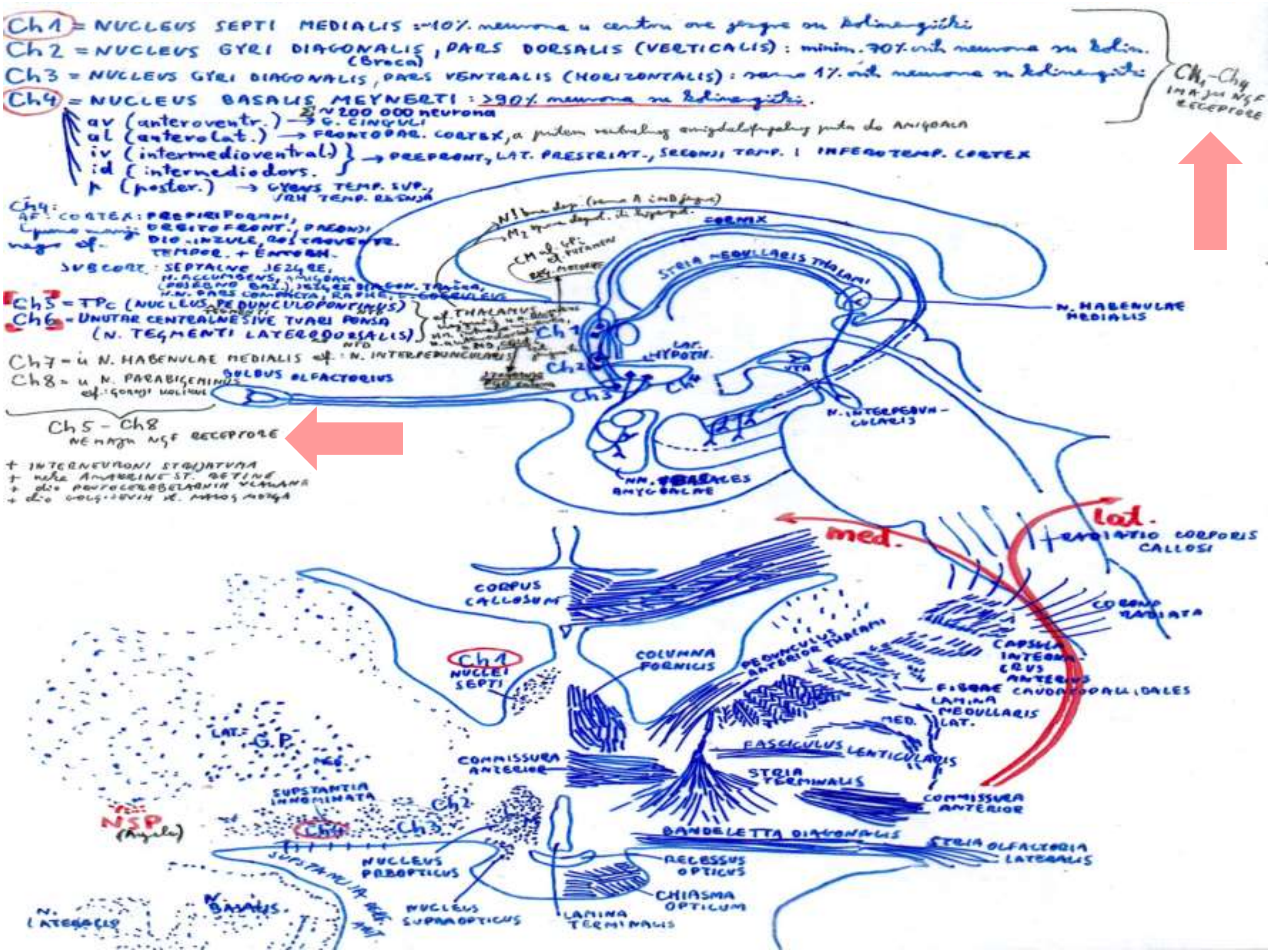
Cholinergic system

- Based on the topographical distribution of ChAT-ir bodies in the rhesus macaque brain, a nomenclature proposed by Mesulam and colleagues was proposed in 1983. Although the human NBM is much larger and more complex, the same terminology has been adopted for human brain

THE JOURNAL OF COMPARATIVE NEUROLOGY 214:170–197 (1983)

Cholinergic Innervation of Cortex by the Basal Forebrain: Cytochemistry and Cortical Connections of the Septal Area, Diagonal Band Nuclei, Nucleus Basalis (Substantia Innominata), and Hypothalamus in the Rhesus Monkey

M.-MARSEL MESULAM, ELLIOTT J. MUFSON, ALLAN I. LEVEY, AND BRUCE H. WAINER



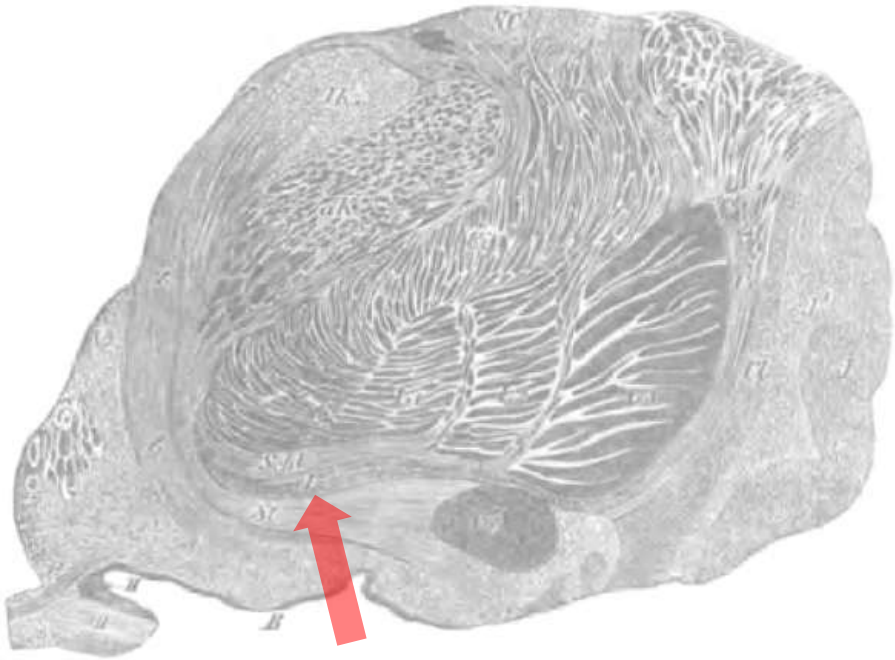
Ch1 = NUCLEUS SEPTI MEDIALIS : ~10% neurona u centru ove jezgre su kolinergički
Ch2 = NUCLEUS GYRI DIAGONALIS (Broca), PARS DORSALIS (VERTICALIS) : minim. 70% ovih neurona su kolin.
Ch3 = NUCLEUS GYRI DIAGONALIS, PARS VENTRALIS (HORIZONTALIS) : samo 1% ovih neurona su kolinergički
Ch4 = NUCLEUS BASALIS MEYNERTI : >90% neurona su kolinergički.
Σ ~200 000 neurona
av (anteroventr.) → G. CINGULI
al (anterolat.) → FRONTOPAR. CORTEX
iv (intermedioventral.)
id (intermediodors.)
→ PREFRONT., LAT. PRESTRIAT., SEKUNDARNI TEMP. I INFEROTEMP. CORTEX
p (poster.) → GYRUS TEMP. SUP.
Ch1–Ch4
IMAJU NGF RECEPTORE
Ch4:
AF: CORTEX:
SUBCORT.: SEPTALNE JEZGRE, N. ACCUMBENS, AMIGDALA
Ch5 = TPc (NUCLEUS PEDUNCULOPONTINUS)
Ch6 = UNUTAR CENTRALNE SIVE TVARI PONSA (N. TEGMENTI LATERODORSALIS)
Ch7 = u N. HABENULAE MEDIALIS
Ch8 = u N. PARABIGEMINUS
Ch5 – Ch8
NEMAJU NGF RECEPTORE
FORNIX
STRIA MEDULLARIS THALAMI
N. HABENULAE MEDIALIS
THALAMUS
Ch1
Ch2
Ch3
Ch4
LAT. HYPOTH.
VTA
BULBUS OLFACTORIUS
N. INTERPEDUNCULARIS
NN. BASALES AMYGDALAE
lat.
med.
RADIATIO CORPORIS CALLOSI
CORPUS CALLOSUM
CORONA RADIATA
Ch1
NUCLEI SEPTI
COLUMNA FORNICIS
PEDUNCULUS THALAMI ANTERIOR
CAPSULA INTERNA CRUS ANTERIUS
FIBRAE CAUDATOPALLIDALES
LAMINA MEDULLARIS
MED.
LAT.
G.P.
LAT.
MED.
COMMISSURA ANTERIOR
FASCICULUS LENTICULARIS
STRIA TERMINALIS
COMMISSURA ANTERIOR
SUPSTANTIA INNOMINATA
Ch2
Ch4
Ch3
NSP
BANDELETTA DIAGONALIS
STRIA OLFACTORIA LATERALIS
RECESSUS OPTICUS
NUCLEUS PREOPTICUS
CHIASMA OPTICUM
N. BASALIS
N. LATERALIS
NUCLEUS SUPRAOPTICUS
LAMINA TERMINALIS

Basal telencephalon and basal nucleus

Theodor **Meynert** was first to analyze human basal forebrain in 1872, when he also described the **nucleus of ansae lenticularis**.

The eponym **n. basalis of Meynert** was given by Rudolf Albert von **Kölliker** in 1896. but it is a misnomer, as Meynert's work does not exactly show this group of cells (as later shown by Mettler in 1968).

Kölliker also introduced the term "**basal telencephalon**" and defined **cytological criteria to differentiate these neurons** from others within this region: 1. to be **large**, 2. to be **hyperchromatic** (upon Nissl stain), 3. the **staining to be more pronounced at the periphery of the perikaryon**, 4. **nuclei** to be **pale**, and 5. **nucleolus to be easily seen**.



Reproduction of Meynert's tranparent preparation of an unfixed section from his chapter in Stricker's *Handbook of histology* (1872). The position of **basal nucleus** is denoted in the second layer "**L**" of the four layers of **substantia innominata** (labeled as SchL, L, St and Z).

The relatively **small magnocellular group of cholinergic neurons** located within the **rostrolateral extension of the basal forebrain** was named and described as the **nucleus subputaminalis (NSP)** in the human brain by Giuseppe Ayala in 1915 (Ayala G., *Brain*, 1915).

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Upon detailed analysis of the NSP in 33 normal subjects, we found the human NSP **projects through the external capsule towards the inferior frontal gyrus** and cingulum (it projects to amygdala too), which strongly suggests it is **connected with the cortical speech area** and involved in generation of **P300 event-related potential** (Šimić G. et al., *Neuroscience*, 1999).

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The **larger size of the NSP on the left side** (an observation that still needs a quantitative confirmation), the **most protracted development among all magnocellular aggregations within the basal forebrain** ("albino group", Kračun and Rösner, 1986) and the fact that **anterointermediate and rostral parts of NSP are usually negligible or missing in monkeys** (Rhaganti M.A., Šimić G., et al., 2011) indicates that these neurons are human specific.

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Recent postmortem analysis of NSP of **cases presenting with primary progressive aphasia (PPA) revealed marked loss of cholinergic neurons in NSP regardless of underlying pathology**, providing further evidence for the importance of NSP in language (Hamodat H. et al., *Can. J. Neurol. Sci.*, 2019). Possible role of NSP in other neurological (variants of FTLD), neurodegenerative (AD) and psychiatric disorders (SCH) should be carefully investigated in future studies.

Ad. 1.

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A HITHERTO UNDIFFERENTIATED NUCLEUS IN THE FOREBRAIN *(NUCLEUS SUBPUTAMINALIS)*.[1]

BY GIUSEPPE AYALA, M.D.

Assistant Neurologist, Clinic of Nervous Diseases, Royal University of Rome.

Brain **1915(3-4): 433-448.**

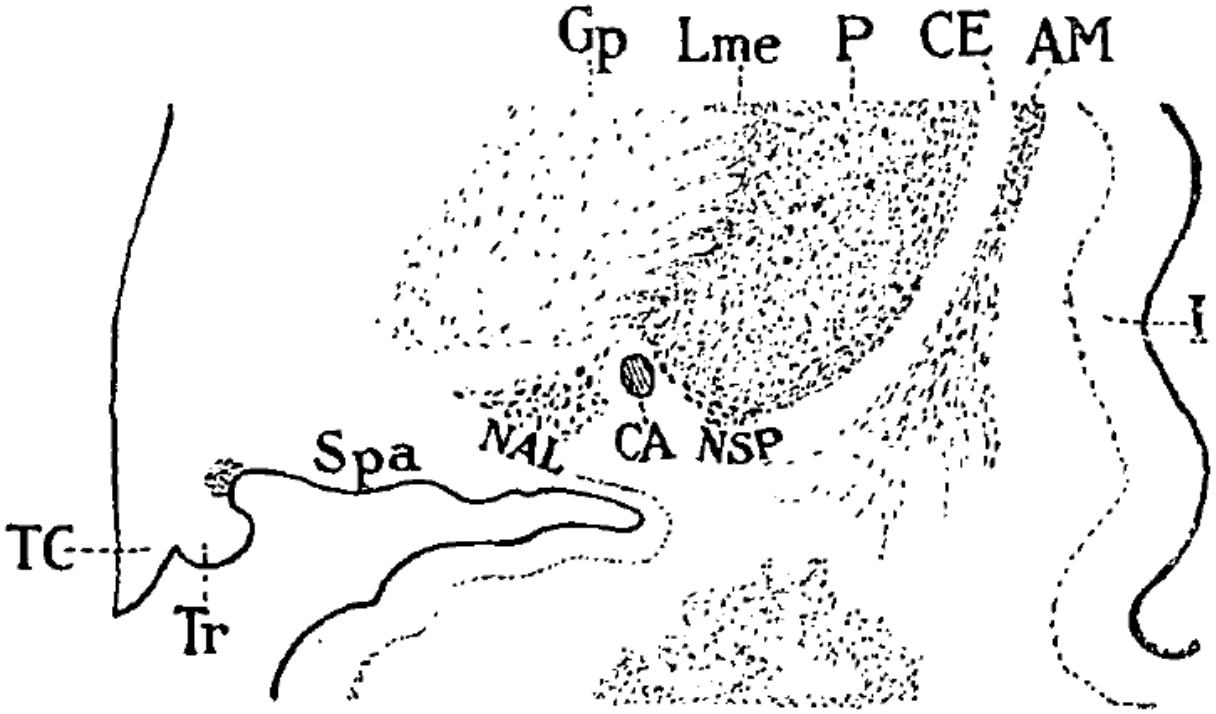

FIG. 3.—Semischematic figure (4 x 1) of a frontal section at the level of the tuber cinereum. Nissl stain—AM = claustrum; CA = commissura anterior; CE = capsula externa; Gp = globus pallidus; I = insula; Lme = lamina medullaris externa nuclei lentiformis; NAL = nucleus ansa lenticularis; NSP = nucleus subputaminalis; P = putamen; Spa = substantia perforata anterior; TC = tuber cinereum; Tr = tractus.

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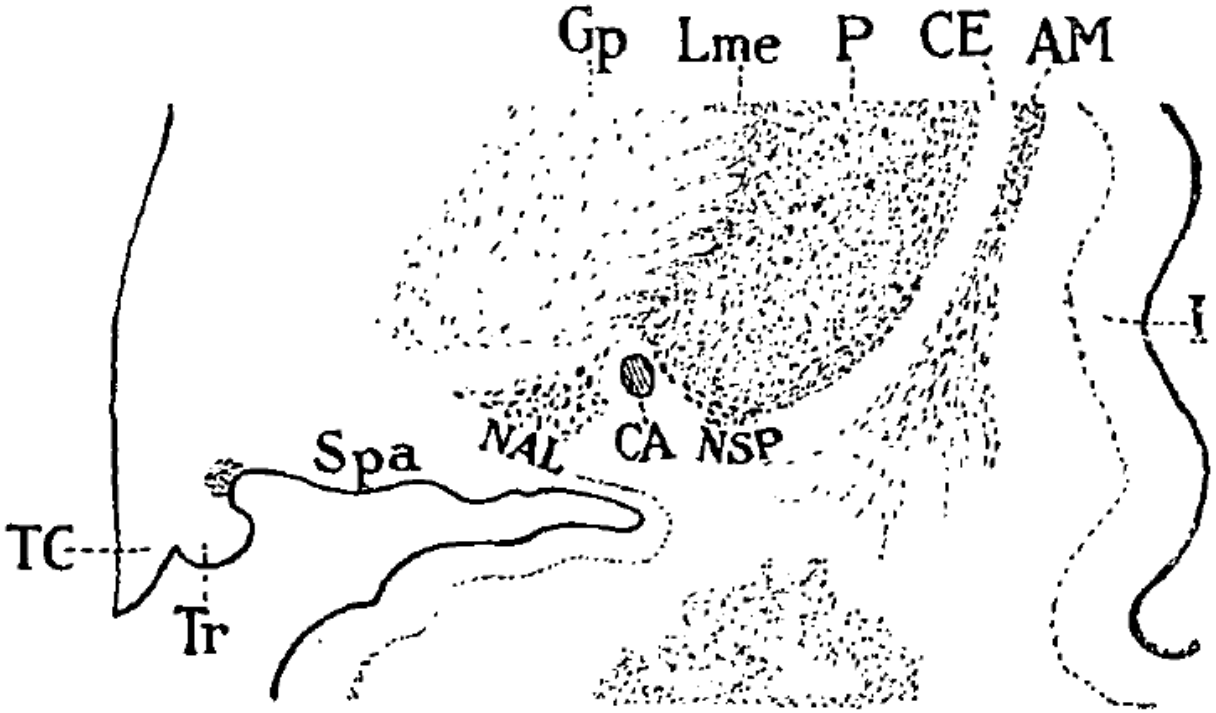

While studying the structure of the different formations of the substantia perforata anterior in man in relation to the overlying ganglion mass of the nucleus lenticularis, a group of nerve-cells of considerable size was observed which I shall call *nucleus hypolenticularis*, or more exactly, *nucleus subputaminalis*. An attempt to justify this appellation is given below.

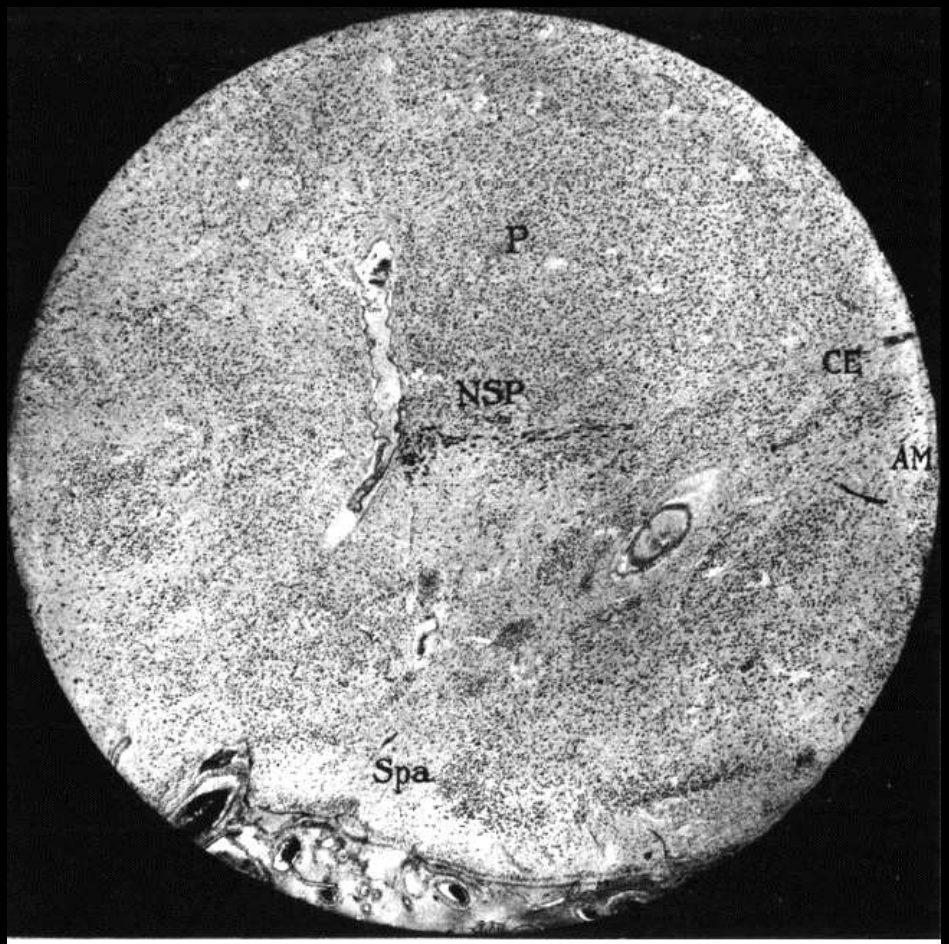

FIG. 1.—Photomicrograph from a frontal section of the right hemisphere at the level of the portio media of the commissura anterior. The proximal part of the nucleus subputaminalis is seen. AM = claustrum; CE = capsula externa; P = putamen; Spa = substantia perforata anterior.

FIG. 2.—Photomicrograph from a frontal section of the right hemisphere at the level of the pars anterior of the tuber cinereum. The nucleus subputaminalis (NSP) is formed by two groups of cells—one medial (a), and the other lateral (b). Other lettering as in fig. 1.

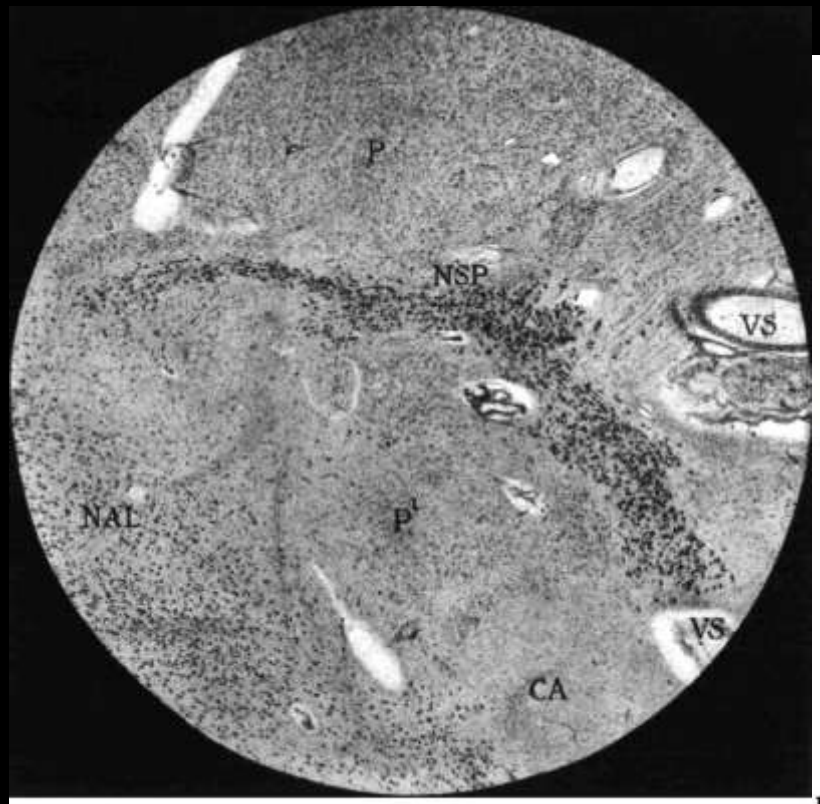

FIG. 7.—Photomicrograph of a horizontal section immediately below the ventral face of the globus pallidus.

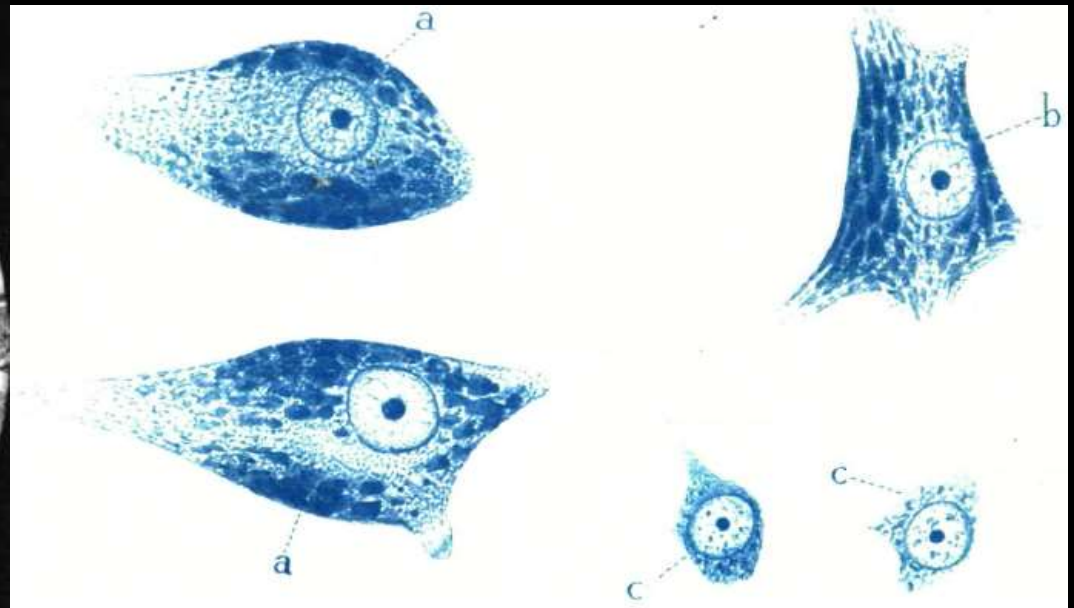

FIG. 8.

a = Nerve-cells of the nucleus subputaminalis.

b = Nerve-cell of the n. ansa lenticularis.

c = Nerve-cells (middle size) of the putamen.

Preparations from the brain of a patient dead of lobar pneumonia, fixed in alcohol and stained with toluidin blue. Drawn by artificial light. Objective $\frac{1}{12}$, ocular 6 (Leitz).

For the above reason it seems justifiable, from a descriptive point of view, to differentiate the one from the other, and to individualize the nucleus subputaminalis as a distinct anatomical formation. It is here intended by the term "nucleus subputaminalis" simply to indicate the topographical situation and to leave open the question of its morphological significance and functional value.

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Pergamon

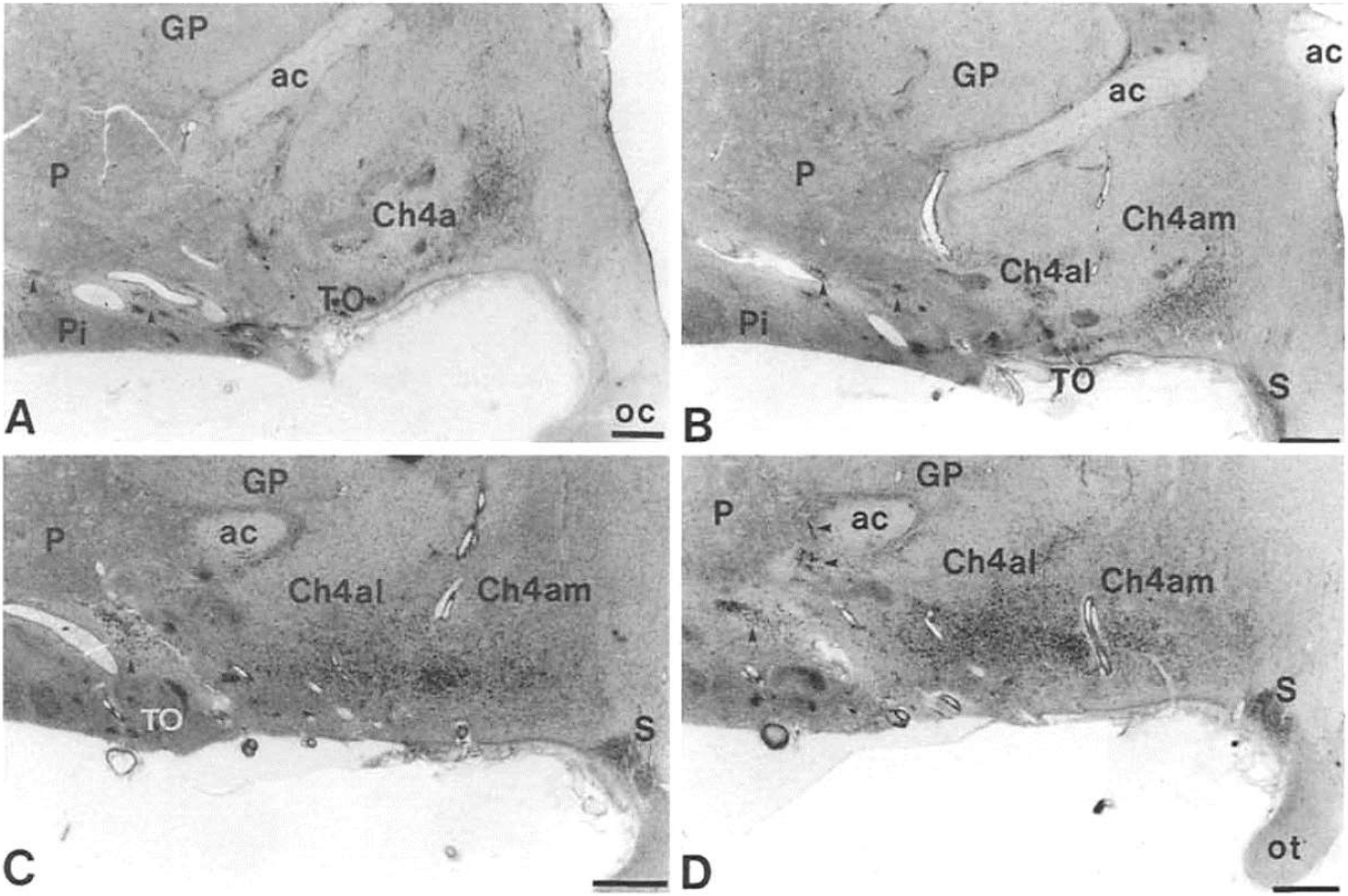
Neuroscience Vol. 89, No. 1, pp. 73–89, 1999

PII: S0306-4522(98)00304-2

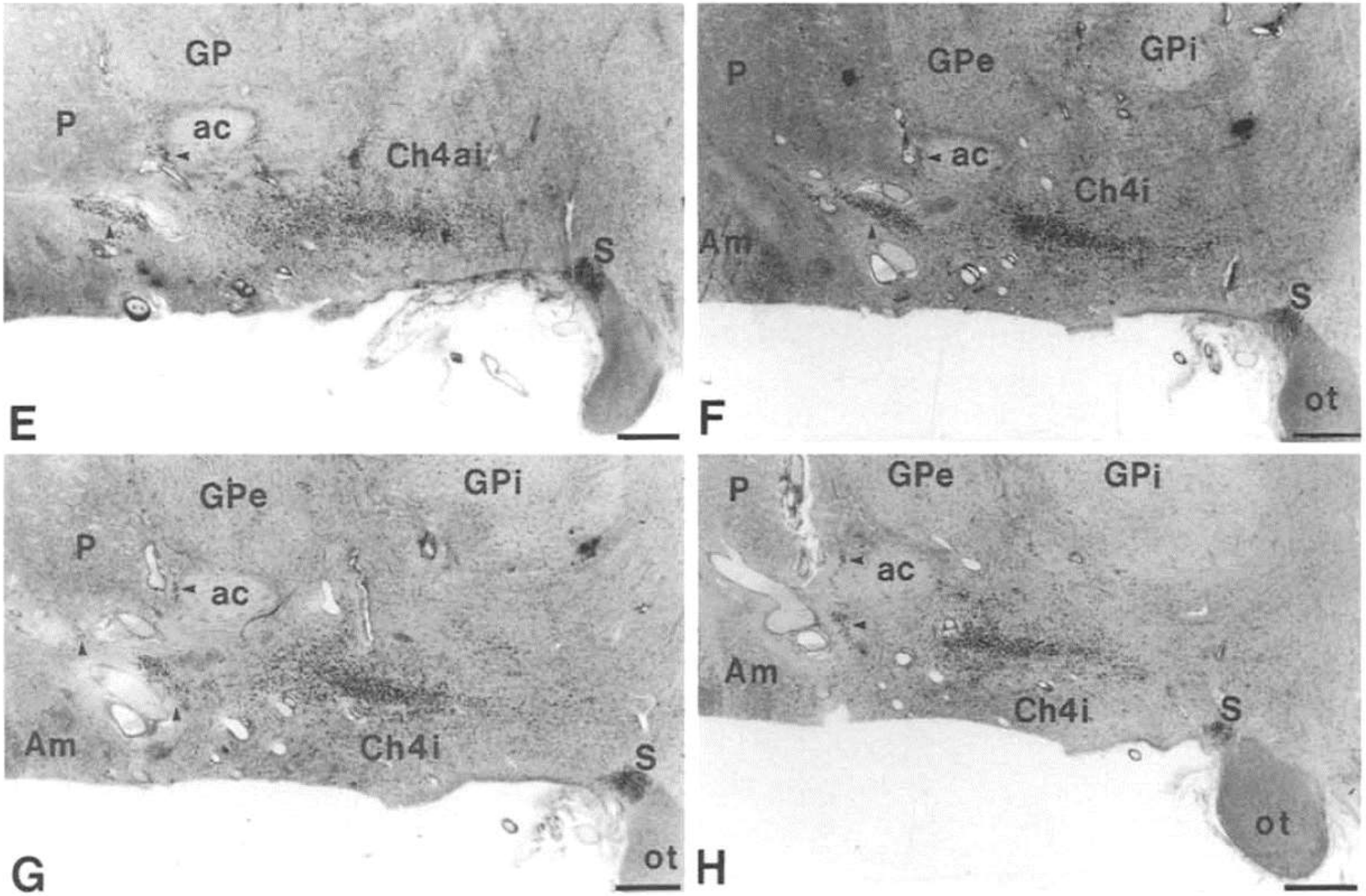
NUCLEUS SUBPUTAMINALIS (AYALA): THE STILL DISREGARDED MAGNOCELLULAR COMPONENT OF THE BASAL FOREBRAIN MAY BE HUMAN SPECIFIC AND CONNECTED WITH THE CORTICAL SPEECH AREA

G. ŠIMIĆ,*§¶ L. MRZLJAK,† A. FUČIĆ,‡ B. WINBLAD,§ H. LOVRIĆ* and I. KOSTOVIĆ*

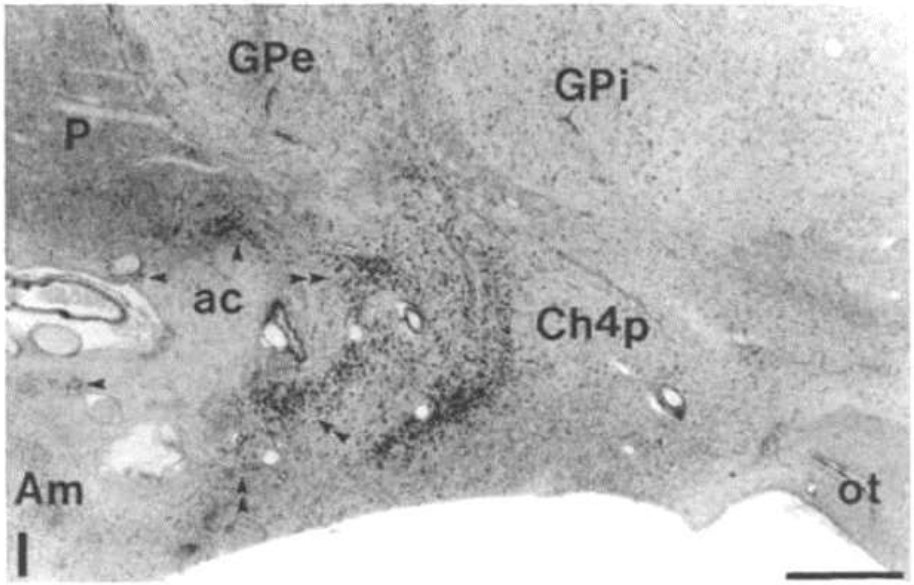
NSP at anterior (septal-chiasmatic) level (Nissl)

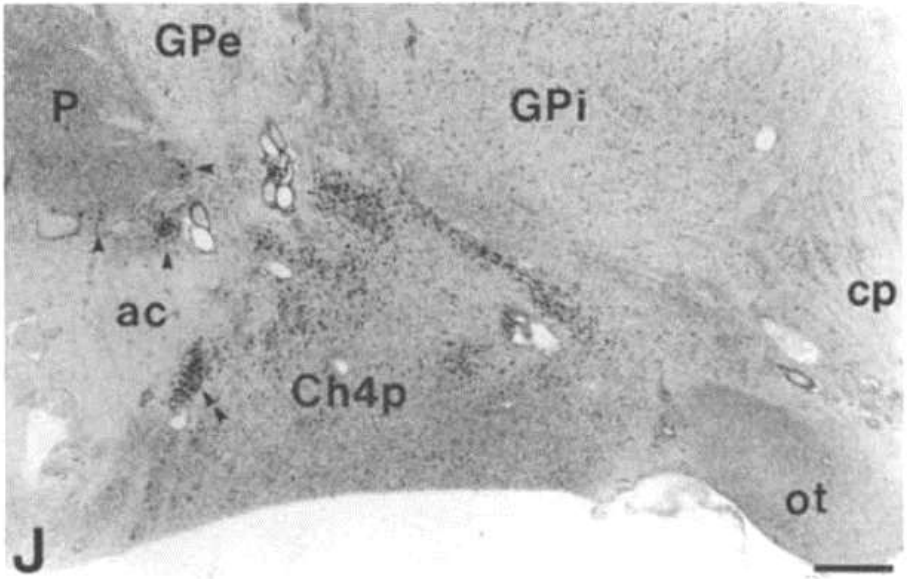


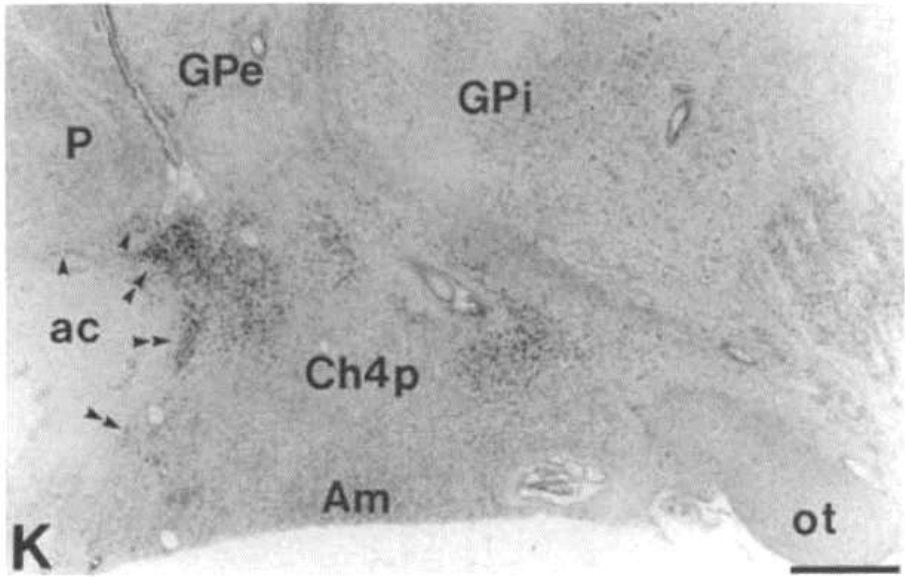
NSP at intermediate (tubero-infundibular) level



NSP at posterior (premammillary-mammillary) level (Nissl)

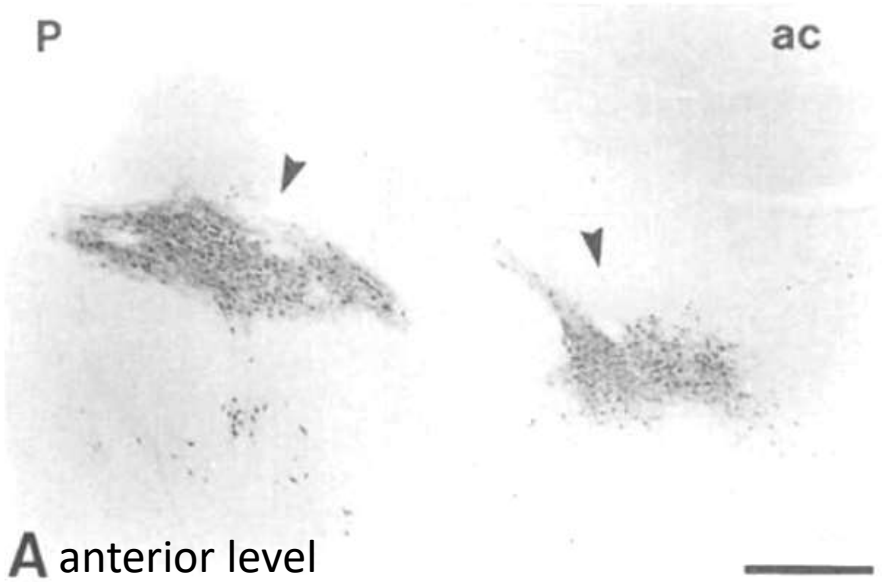




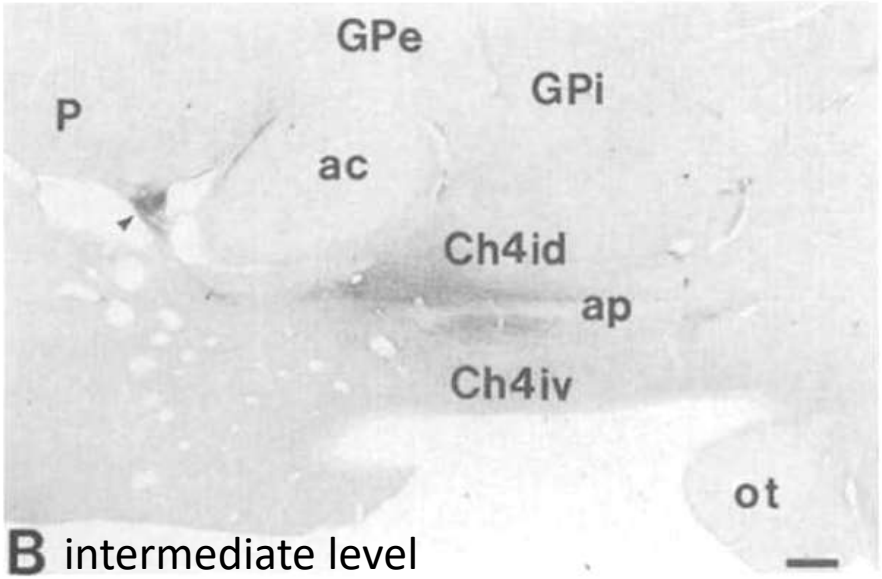


ac	anterior commissure
Am	amygdala
ap	ansa peduncularis
C	claustrum
cp	cerebral peduncle
Ch1	cholinergic cell group 1 (medial septal nucleus)
Ch2	cholinergic cell group 2 (nucleus of the vertical limb of the diagonal band of Broca)
Ch3	cholinergic cell group 3 (nucleus of the horizontal limb of the diagonal band of Broca)
Ch4a	anterior division of cholinergic cell group 4
Ch4ai	anterointermediate division of cholinergic cell group 4
Ch4al	anterolateral division of cholinergic cell group 4
Ch4am	anteromedial division of cholinergic cell group 4
Ch4i	intermediate division of cholinergic cell group 4
Ch4id	intermediodorsal division of cholinergic cell group 4
Ch4iv	intermedioventral division of cholinergic cell group 4
Ch4p	posterior division of cholinergic cell group 4
CN	caudate nucleus
GP	globus pallidus (i, internal segment; e, external segment)
I	insular cortex
ic	internal capsule
lv	lateral ventricle
NSP	nucleus subputaminalis
oc	optic chiasm
ot	optic tract
P	putamen
Pi	piriform (primary olfactory) cortex
S	supraoptic nucleus
TO	tractus opticus

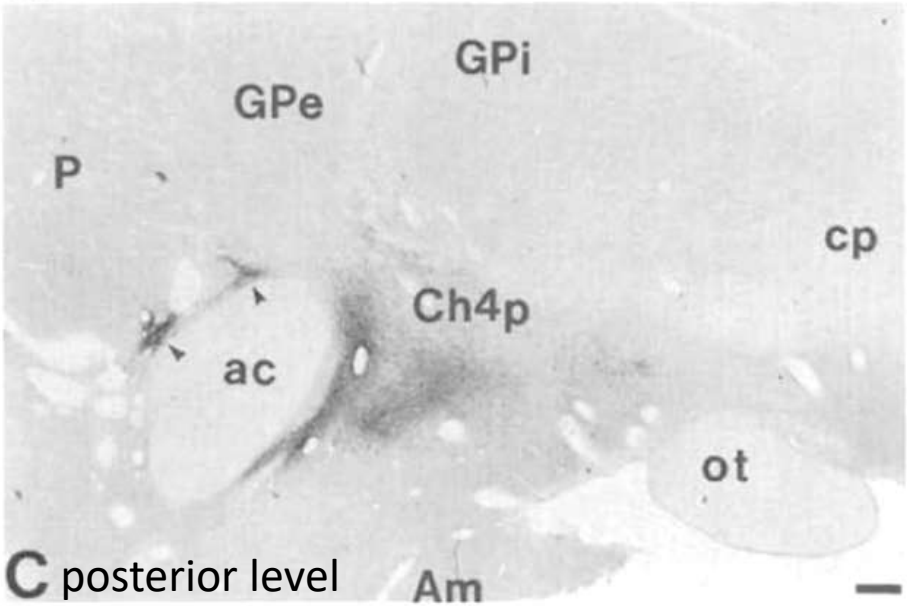
NSP at three aforesaid levels (NGFr-ir)



A anterior level

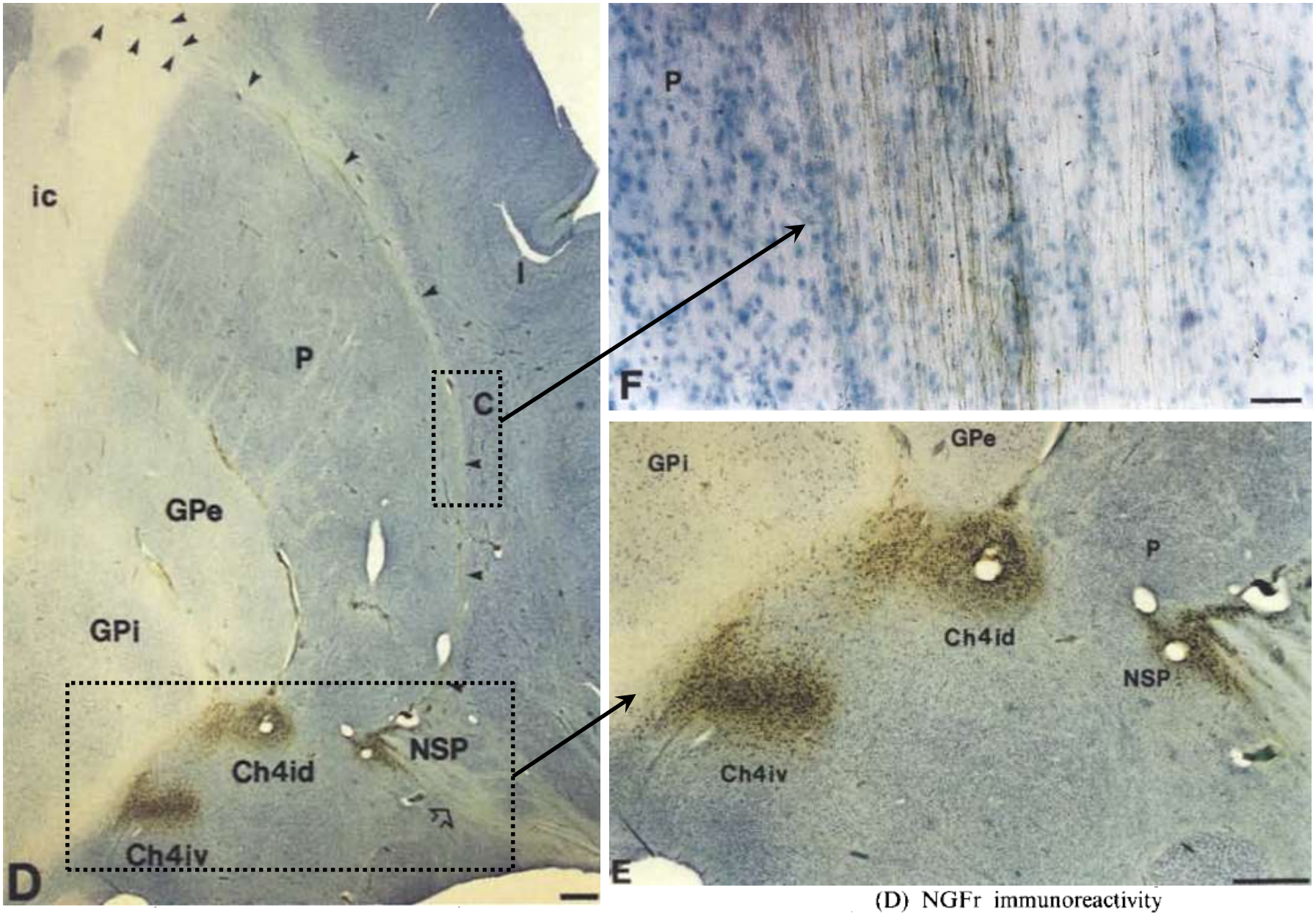


B intermediate level

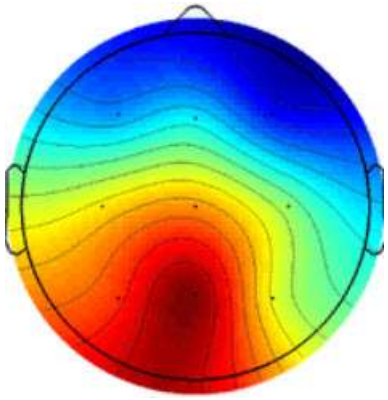


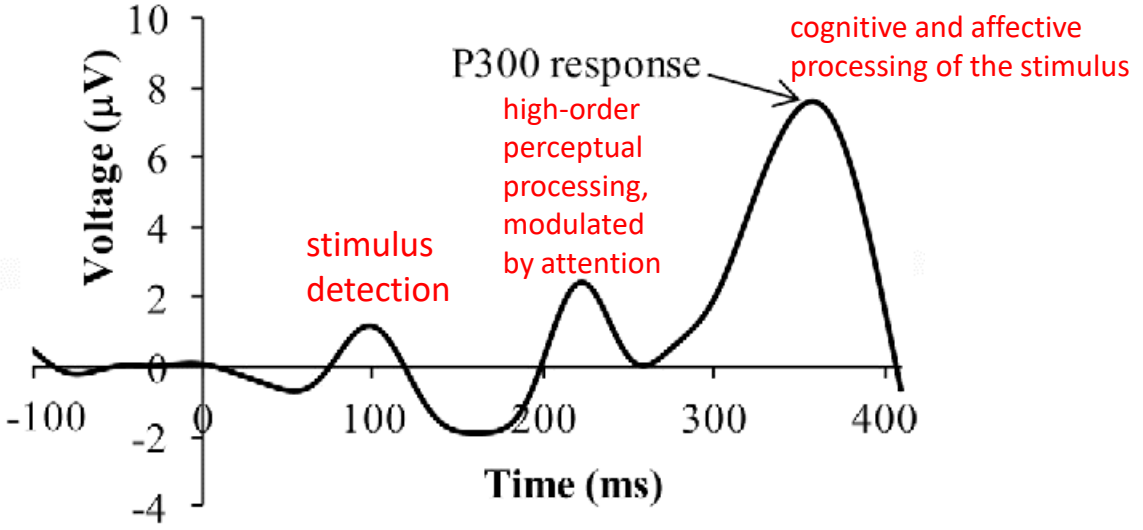
C posterior level

Fig. 2. NGFr immunoreactivity of the NSP neurons (arrows) at selected levels. (A) Anterior (septo-chiasmatic) level (subject no. 27). (B) Intermediate (tubero-infundibular) level (subject no. 19). (C) Posterior (premammillary-mammillary) level (subject no. 19). Scale bars = 1 mm.



(D) NGFr immunoreactivity counterstained with Giemsa stain at the intermediate level (subject no. 10). Arrows mark NGFr-positive fibers originating in NSP. Note that NSP also projects towards the amygdala (open arrow). (E) Enlarged picture from D. More than 90% of the NSP neurons display immunoreactivity for p75 NGFr. (F) Enlarged picture from E. Subputaminal p75 NGFr-positive axons ascending along the lateral margin of the putamen. Scale bars: (A, C, D, E)=1 mm, (B, F)=0.03 mm.





The **P300 wave** (P3) is a positive deflection in the human event-related potential (ERP)

It is most commonly elicited in an **oddball paradigm** when a subject detects an occasional "target" (novel) stimulus in a regular train of standard stimuli.

Neurons within the basal nucleus are known to respond to novel stimuli triggering the release of ACh within the cerebral cortex, which enhances responsiveness (at psychological level this corresponds to attention) to further excitatory inputs.

These effects are mediated mainly by the **muscarinic M1** receptors.

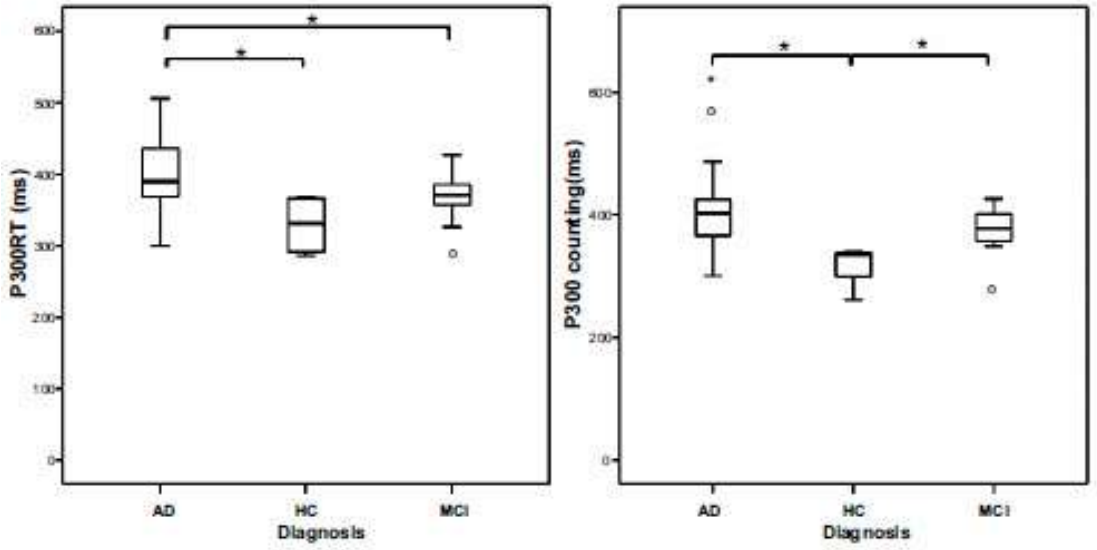
Current Alzheimer Research, 2018, *15*, 1244-1260

RESEARCH ARTICLE

Event-related Potentials Improve the Efficiency of Cerebrospinal Fluid Biomarkers for Differential Diagnosis of Alzheimer's Disease

Mirjana Babić Leko[a], Magdalena Krbot Skorić[b], Nataša Klepac[c], Fran Borovečki[c,d], Lea Langer Horvat[a], Željka Vogrinc[e], Zdenko Sonicki[f], Patrick R. Hof[g] and Goran Šimić[a,*]

97 subjects



The subjects who participated in the auditory oddball paradigm had to complete two different tasks. In the first task (paradigm RT), they had to press a button as the response to target auditory tones. In the second task (paradigm counting), subjects had to count all target auditory tones among non-target and interfering tones.

Sensitivity, specificity and cut-off values of ERPs, RT and CSF biomarkers.

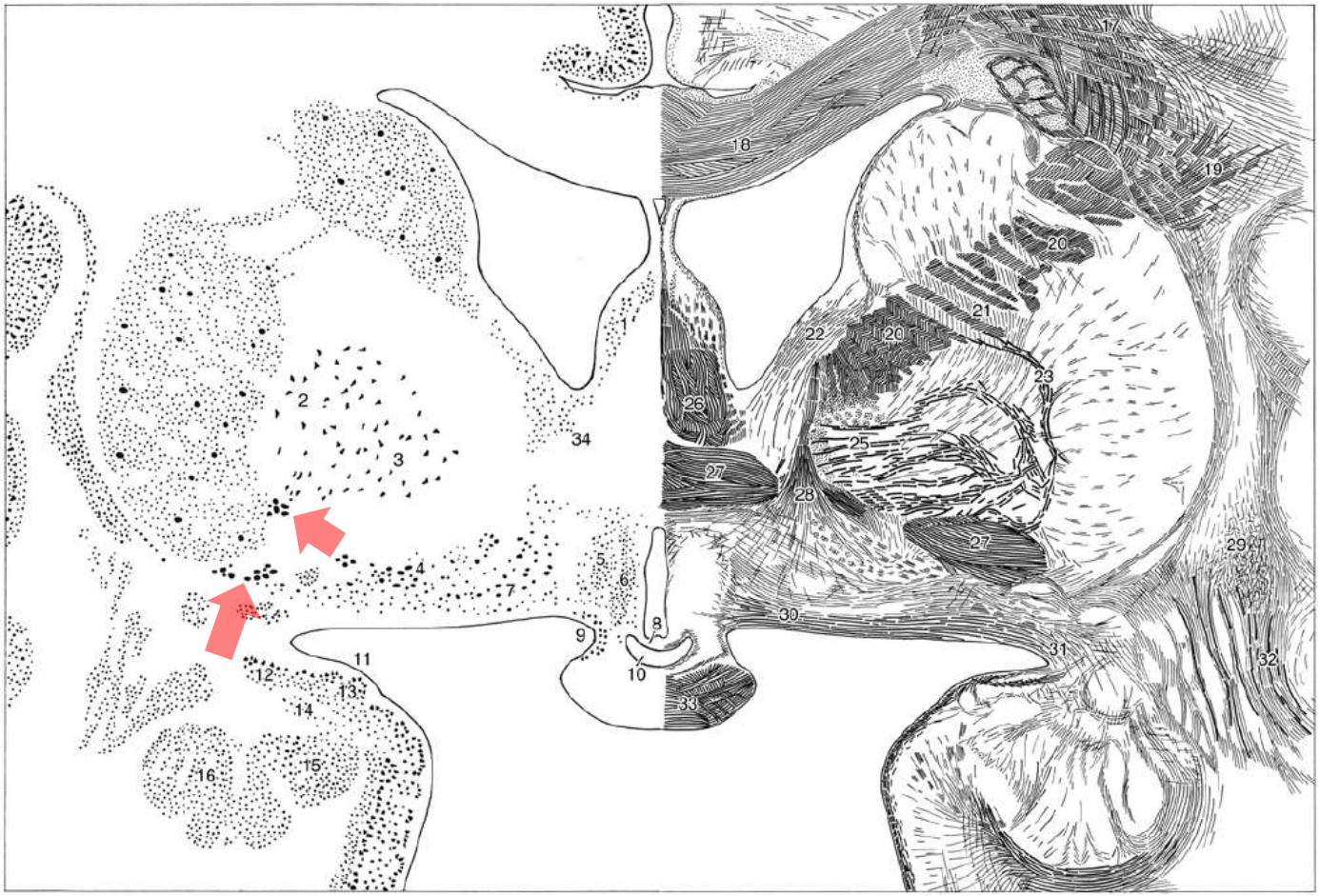
	Sensitivity (%)	Specificity (%)	Cut-off	AUC, p
RT	89.3	50	397.5 ms	0.589, p=0.569
N200 RT	63.3	100	249 ms	0.847, p=0.030*
P300 RT	72	100	368.5 ms	0.865, p=0.021*
N200 counting	63.2	100	245 ms	0.842, p=0.035*
P300 counting	90.9	100	341.5 ms	0.932, p=0.007*
$A\beta_{1-42}$	73.7	60	669 pg/ml	0.658, p=0.022*
Total tau	66	80	309.5 pg/ml	0.757, p<0.001*
p-tau_{181}	80.6	73.7	46.83 pg/ml	0.819, p<0.001*
p-tau_{199}	58.8	78.9	3.06 pg/ml	0.701, p=0.004*
p-tau_{231}	76.7	77.8	0.734 U/ml	0.791, p<0.001*
VILIP-1	58.9	80	116.26 pg/ml	0.713, p=0.002*

$A\beta_{1-42}$, amyloid β_{1-42}; AUC, area under curve; p-tau_{181}, tau protein phosphorylated at threonine 181; p-tau_{231}, tau protein phosphorylated at threonine 231; p-tau_{199}, tau protein phosphorylated at serine 199; RT, reaction time. *$p < 0.05$.

R. Nieuwenhuys J. Voogd
C. van Huijzen

The Human Central Nervous System

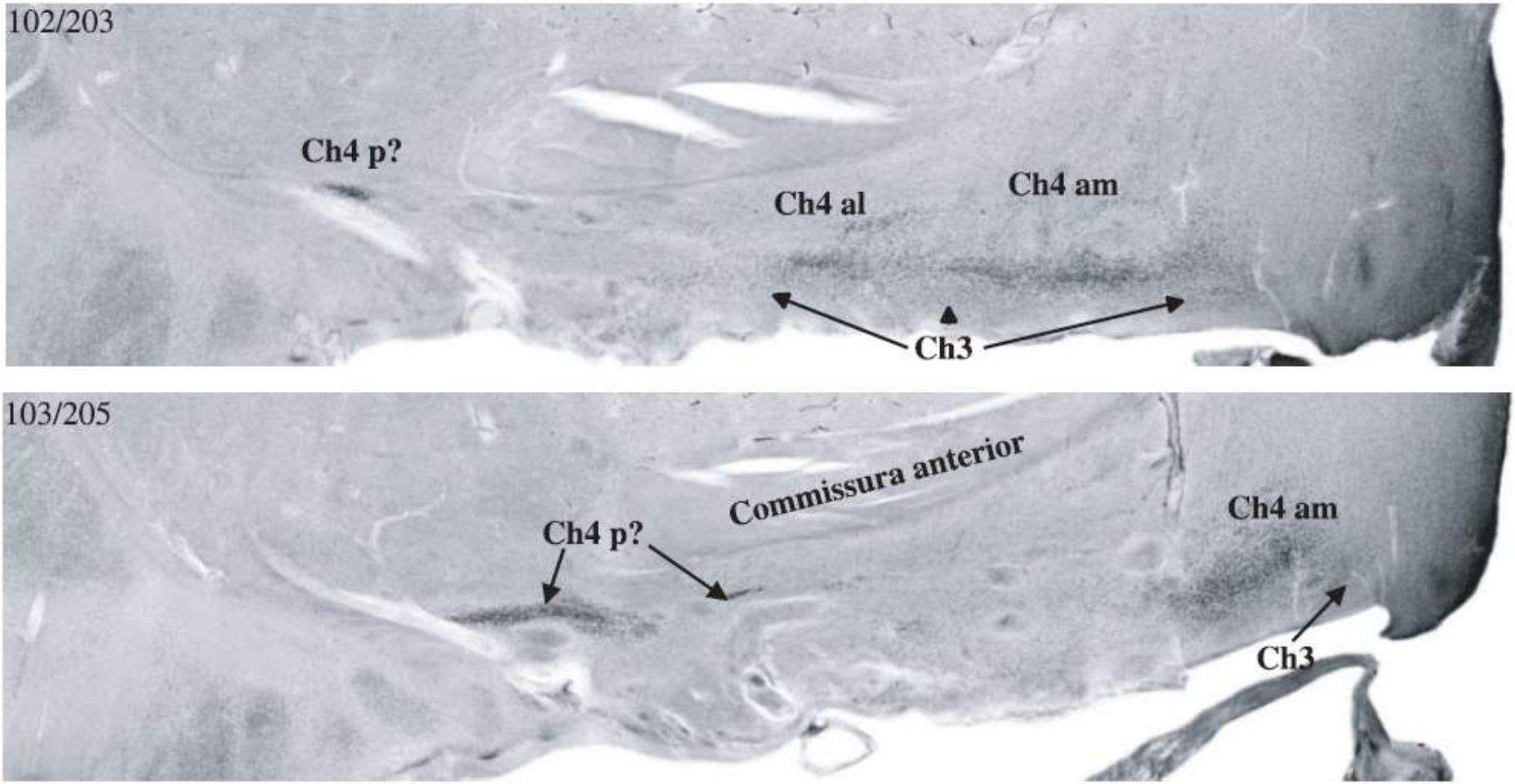
Fourth Edition
Printed in Germany

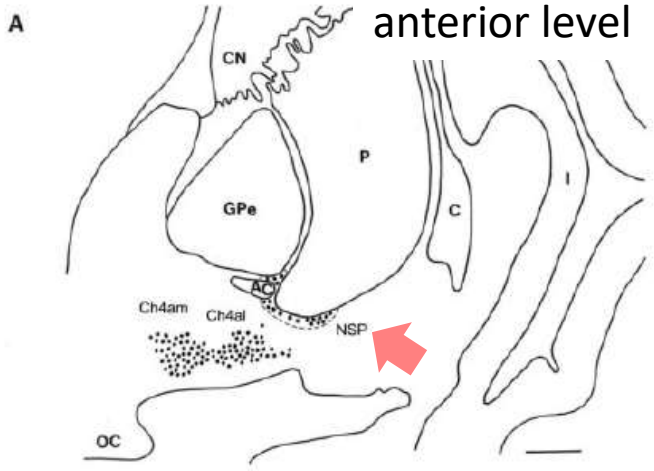


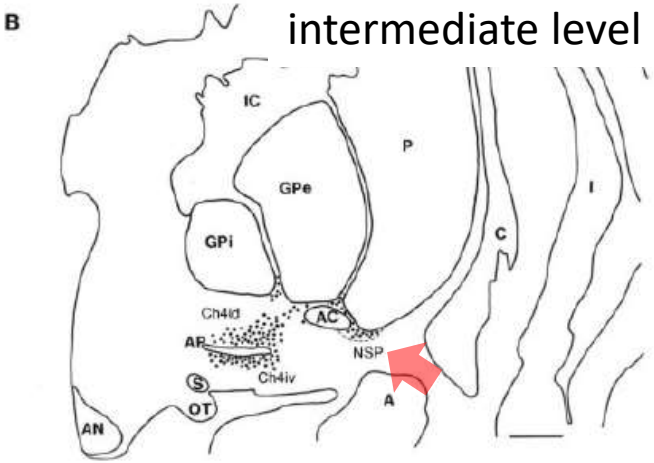
1 Septal nuclei
2 Globus pallidus, external segment
3 Globus pallidus, internal segment
4 Innominate substance
5 Lateral preoptic nucleus
6 Medial preoptic nucleus
7 Nucleus of the diagonal band
8 Lamina terminalis
9 Supraoptic nucleus
10 Optic recess
11 Semilunar gyrus
12 Anterior nucleus of the amygdaloid body
13 Cortical nucleus of the amygdaloid body
14 Accessory basal nucleus of the amygdaloid body
15 Basal nucleus of the amygdaloid body
16 Lateral nucleus of the amygdaloid body
17 Radiation of the corpus callosum
18 Trunk of the corpus callosum
19 Corona radiata
20 Internal capsule, anterior limb
21 Caudatopallidal fibres
22 Anterior thalamic peduncle
23 Lateral medullary lamina
24 Medial medullary lamina
25 Lenticular fascicle
26 Column of the fornix
27 Anterior commissure
28 Stria terminalis
29 Occipitofrontal fascicle
30 Diagonal band
31 Lateral olfactory stria
32 Uncinate fascicle
33 Optic chiasm
34 Bed nucleus of the stria terminalis

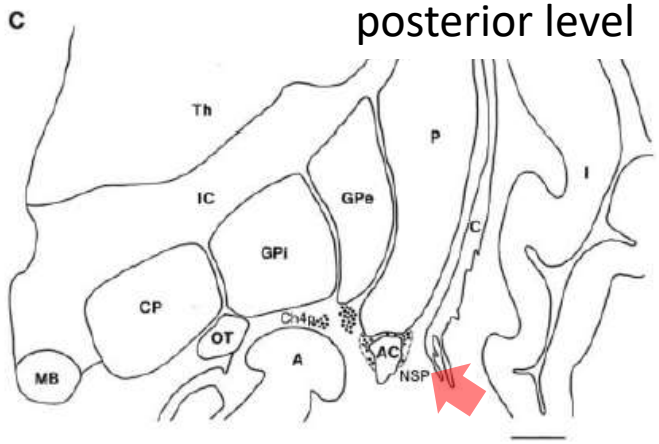
Fig. 6.40. Section through the anterior commissure and the optic chiasm (5/2×)

Brain (2005), **128,** 2626–2644









Brain (2006), **129** E42

LETTER TO THE EDITOR

Nucleus subputaminalis: neglected part of the basal nucleus of Meynert

Marina Boban, Ivica Kostovic and Goran Simic

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doi:10.1093/brain/awl025

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In conclusion, we recommend that the designation 'Ch4 p?' in the article by *et al.* (2005) should be replaced with the 'NSP' (NSP of Ayala).

Fig. 1 (**A–C**) Schematic representation of the subputaminal nucleus (NSP). (**A**) Anterior (septal-chiasmatic) level. (**B**) Intermediate (tubero-infundibular) level. (**C**) Posterior (premammillary) level. Scale bars = 5 mm. CN = caudate nucleus; P = putamen; C = claustrum; I = insular cortex; Gpe = globus pallidus, external segment; IC = internal capsule, AC = anterior commisure; NSP = nucleus subputaminalis; Ch4am = anteromedial division of the cholinergic cell group 4; Ch4al = anterolateral division of the cholinergic cell group 4; OC= optic chiasm; Gpi = globus pallidus, internal segment; Ch4id = intermediodorsal division of the cholinergic cell group 4; Ch4iv = intermedioventral division of the cholinergic cell group 4; AP = ansa peduncularis; S = supraoptic nucleus; OT = tractus opticus; AN = anterior nucleus of hypothalamus; A = amygdala; Ch4p = posterior division of the cholinergic cell group 4; Th = thalamus; CP = cerebral peduncle; MB = mamillary body.

The relatively **small magnocellular group of cholinergic neurons** located within the **rostrolateral extension of the basal forebrain** was named and described as the **nucleus subputaminalis (NSP)** in the human brain by Giuseppe Ayala in 1915 (Ayala G., *Brain*, 1915).

Upon detailed analysis of the NSP in 33 normal subjects, we found the human NSP **projects through the external capsule towards the inferior frontal gyrus** and cingulum (it projects to amygdala too), which strongly suggests it is **connected with the cortical speech area** and is involved in generation of **P300 event-related potential** (Šimić G. et al., *Neuroscience*, 1999).

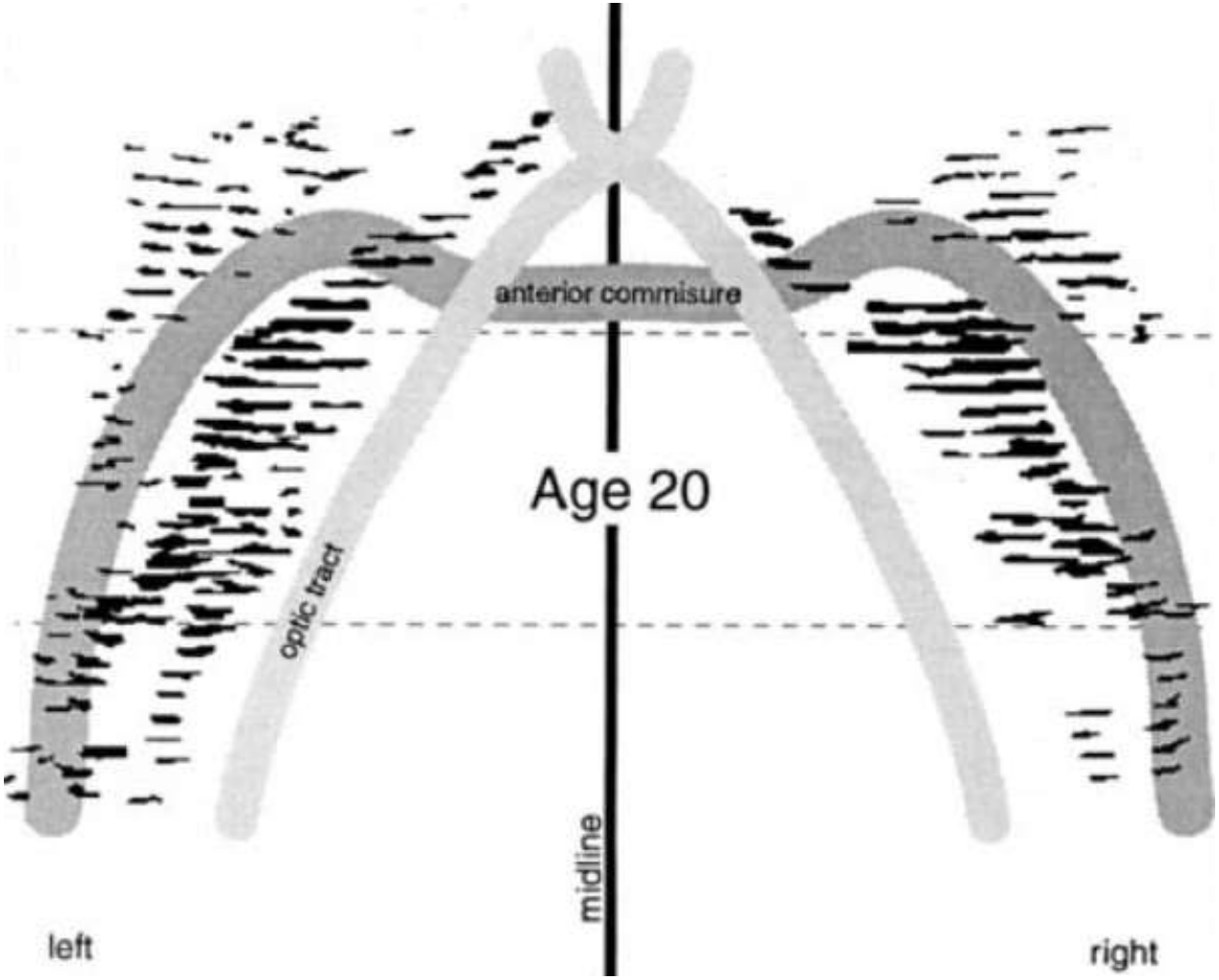
Ad. 3.

The **larger size of the NSP on the left side** (an observation that still needs a quantitative confirmation), the **most protracted development among all magnocellular aggregations within the basal forebrain** ("albino group", Kračun and Rösner, 1986) and the fact that **anterointermediate and rostral parts of NSP are usually negligible or missing in monkeys** (Rhaganti M.A., Šimić G., et al., 2011) indicates that these neurons are human specific.

SYNAPSE 15:1–16 (1993)

Quantitation and Three-Dimensional Reconstruction of Ch4 Nucleus in the Human Basal Forebrain

GLENDA M. HALLIDAY, KAREN CULLEN, AND MURRAY J. CAIRNS
Department of Pathology, University of Sydney, Sydney, Australia 2006



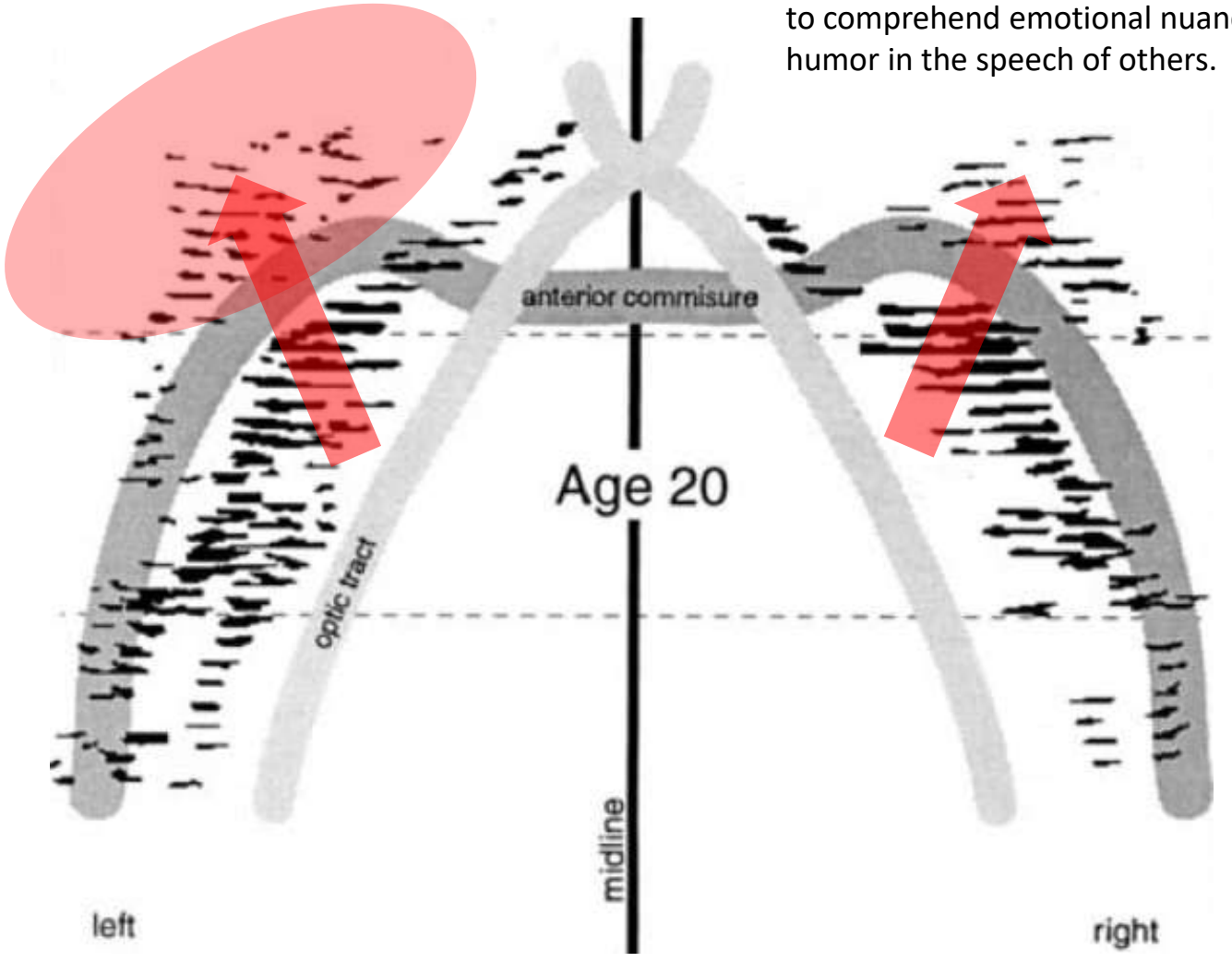
anterior level

intermediate level

posterior level

Most carnivores have a moderately developed NB with a better expression of its medial division, while rodents have only medial, sub- and peripallidal equivalents of the NB.

The corresponding speech production region in the right (non-dominant) hemisphere has also roles in linguistic abilities: patients with right hemisphere disease may have **dysprosody -** sound flat in their intonation due to absence of rhythm, accent, melody, vocal quality, etc. and may fail to comprehend emotional nuances, irony, sarcasm, and humor in the speech of others.



anterior level

intermediate level

posterior level

Neuroscience 184 (2011) 1–15

COMPARATIVE ANALYSIS OF THE NUCLEUS BASALIS OF MEYNERT AMONG PRIMATES

M. A. RAGHANTI,[a,b*] G. SIMIC,[c] S. WATSON,[a] C. D. STIMPSON,[d] P. R. HOF[e] AND C. C. SHERWOOD[d]

23 individual brains from 12 anthropoid species
ChAT-ihc

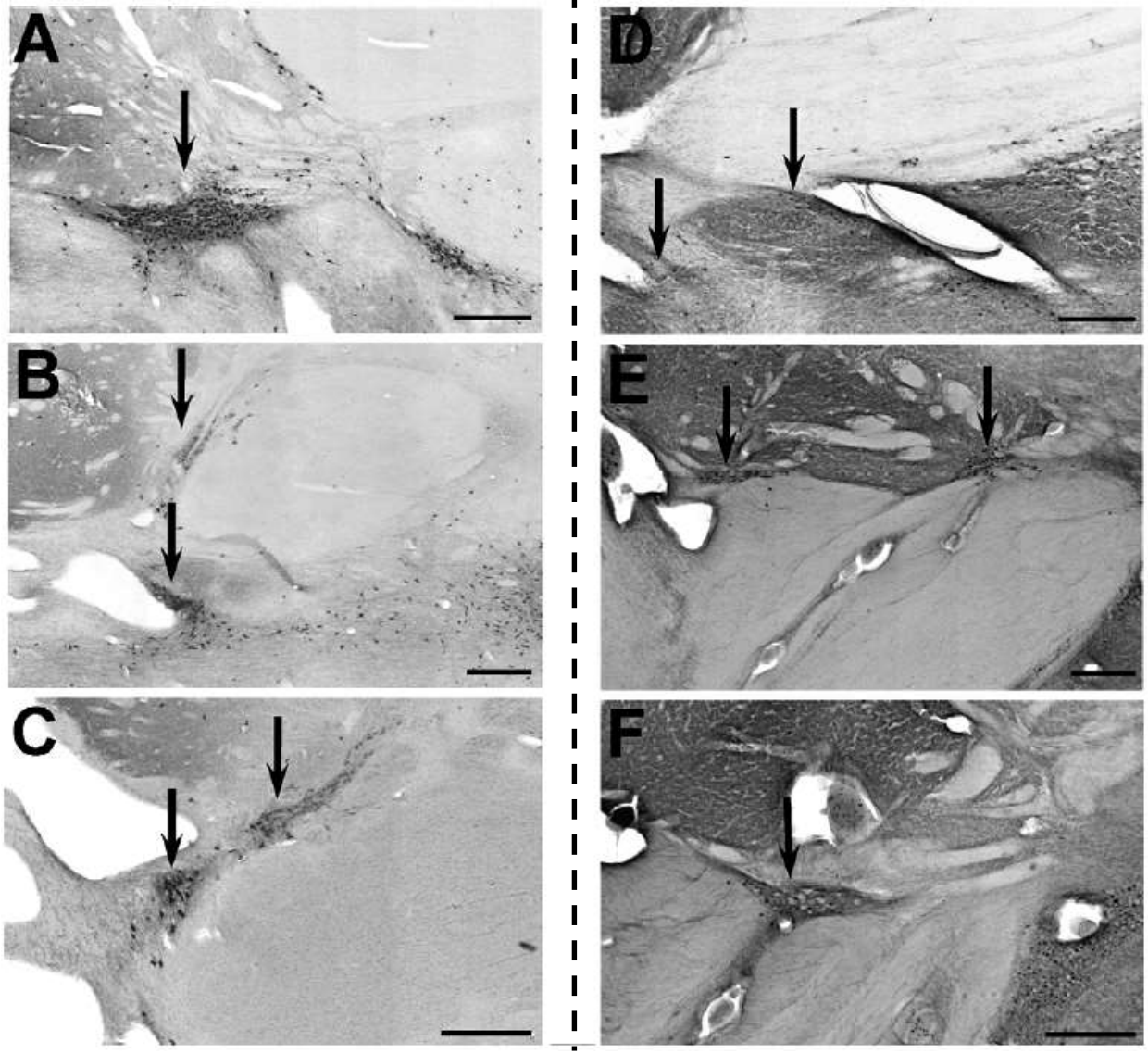
HUMAN NSP

CHIMPANZEE NSP

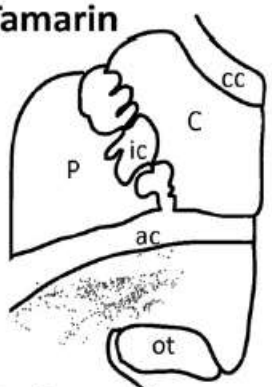
anterior level

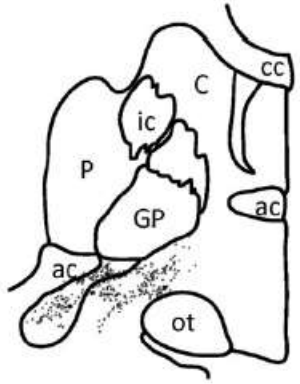
intermediate level

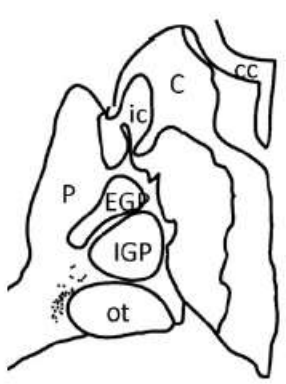
posterior level



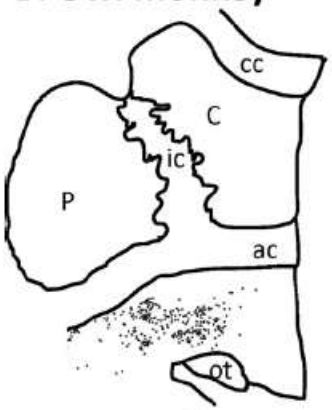
A. Tamarin

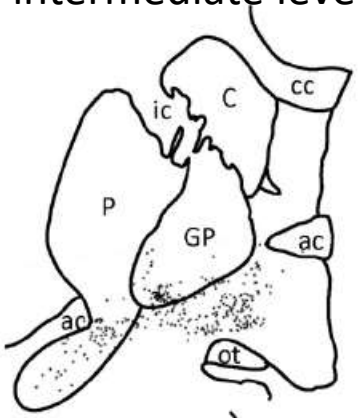


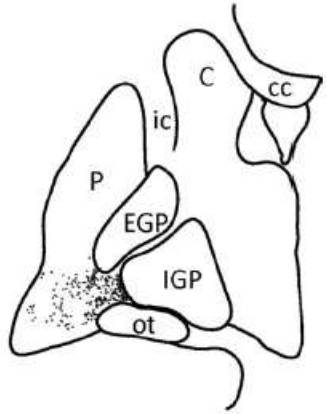




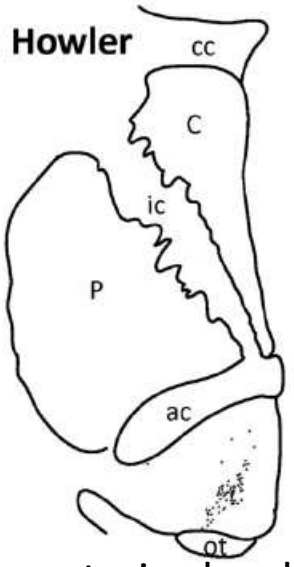
B. Owl monkey

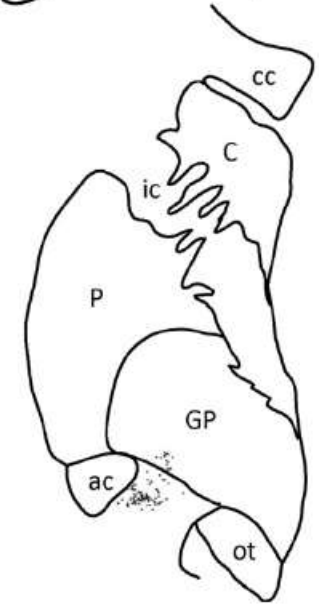


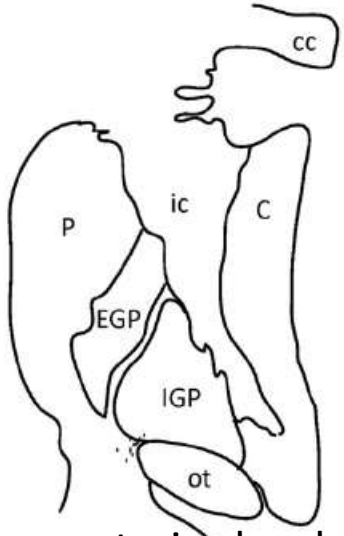




C. Howler





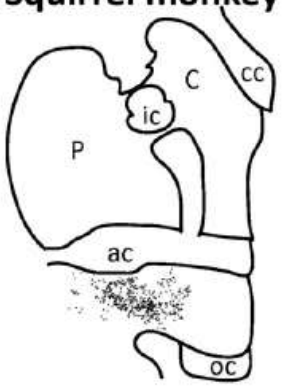


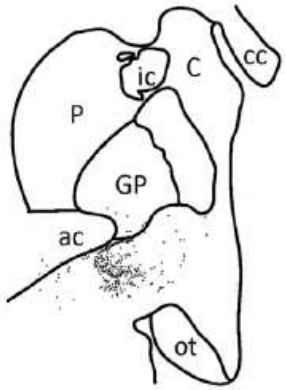
intermediate level

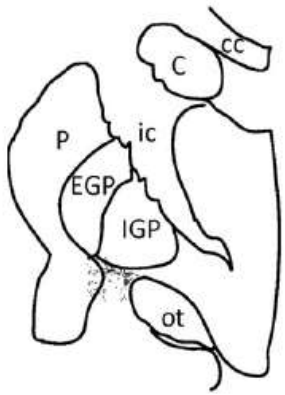
anterior level

posterior level

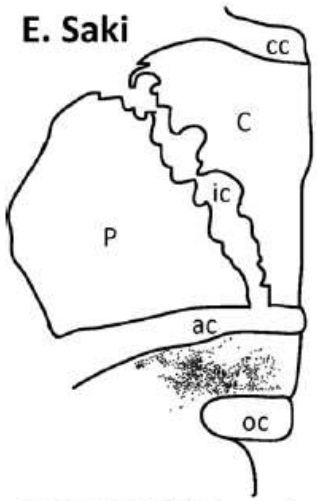
D. Squirrel monkey

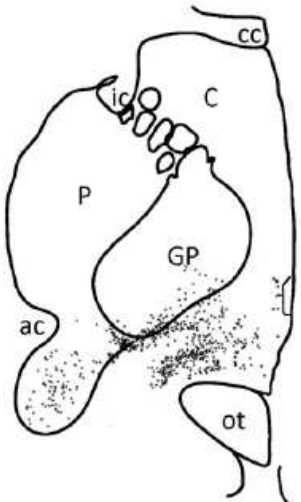


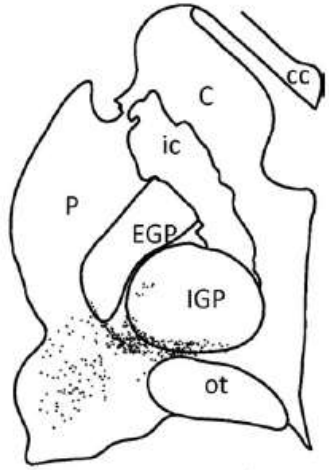




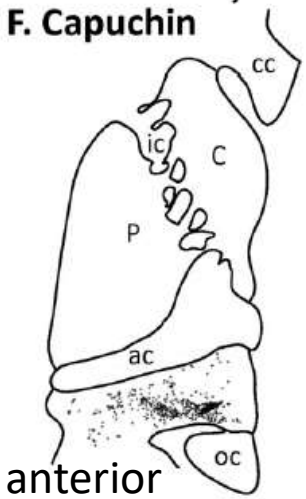
E. Saki

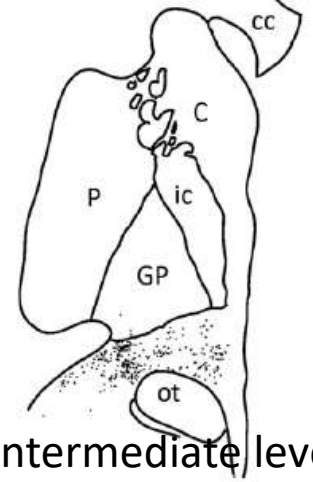


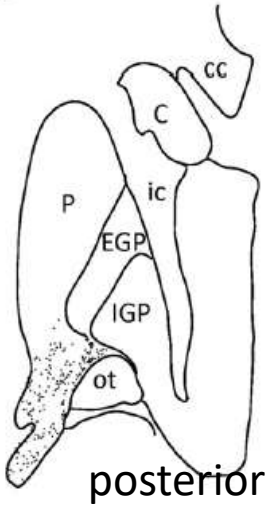




F. Capuchin





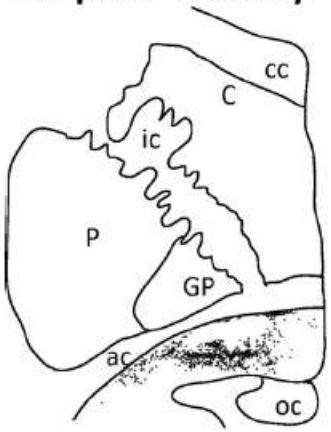


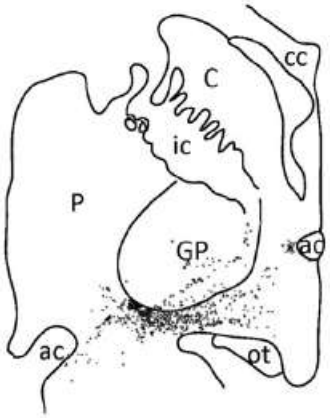
anterior

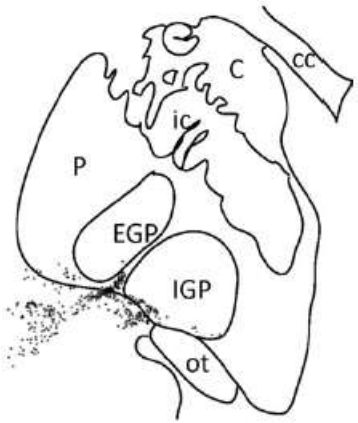
intermediate level

posterior

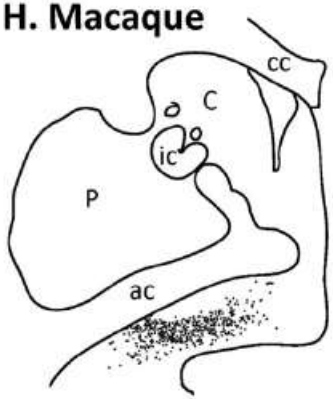
G. Spider monkey

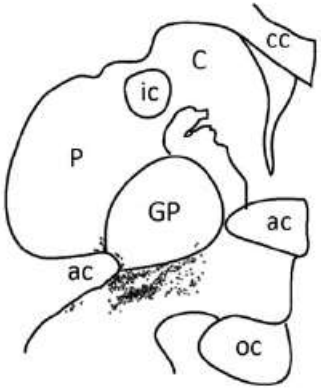


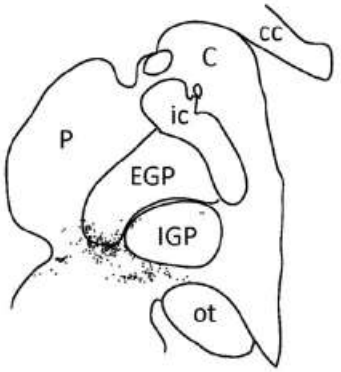




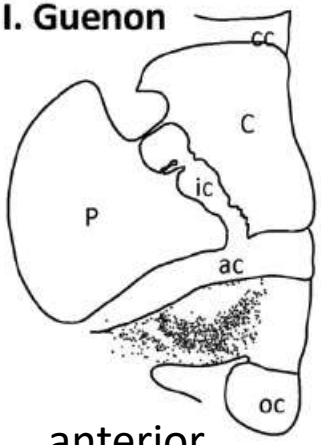
H. Macaque

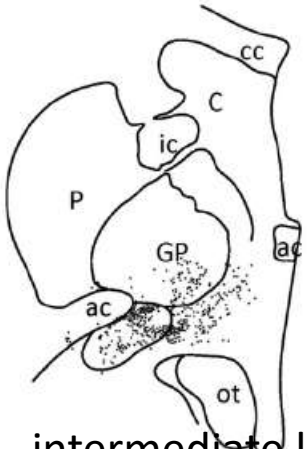


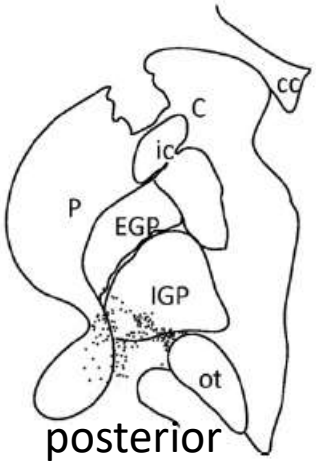




I. Guenon





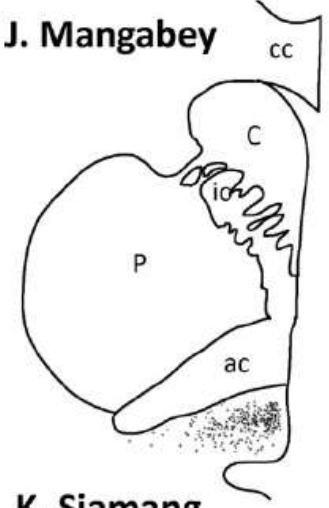


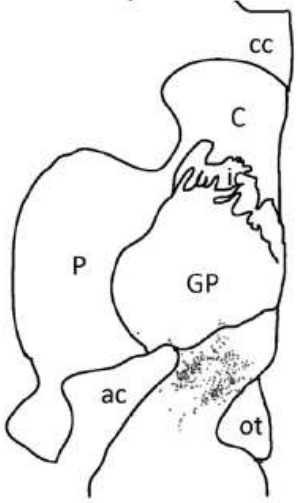
anterior

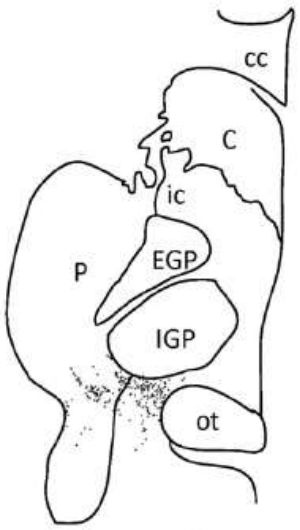
intermediate level

posterior

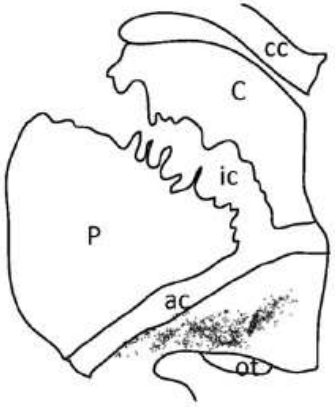
J. Mangabey

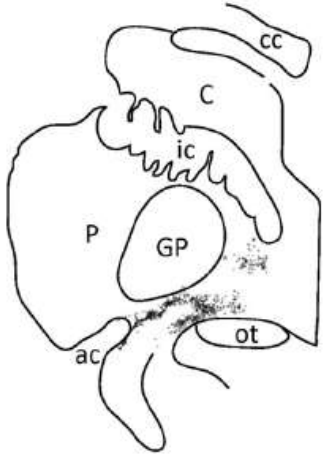


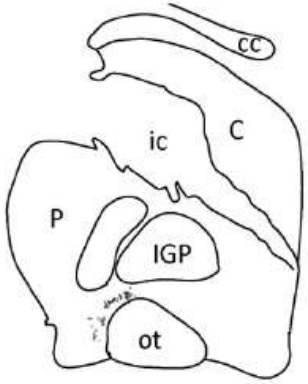




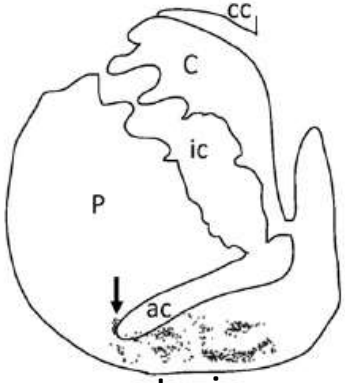
K. Siamang

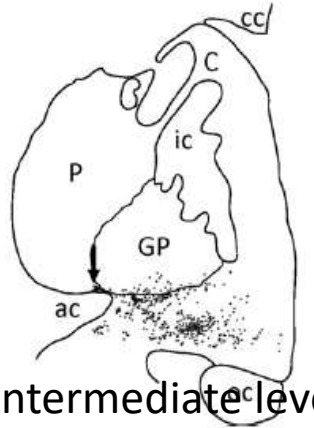


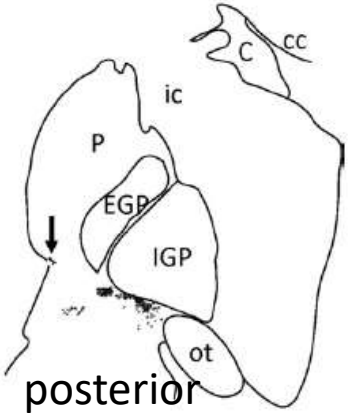




L. Chimpanzee



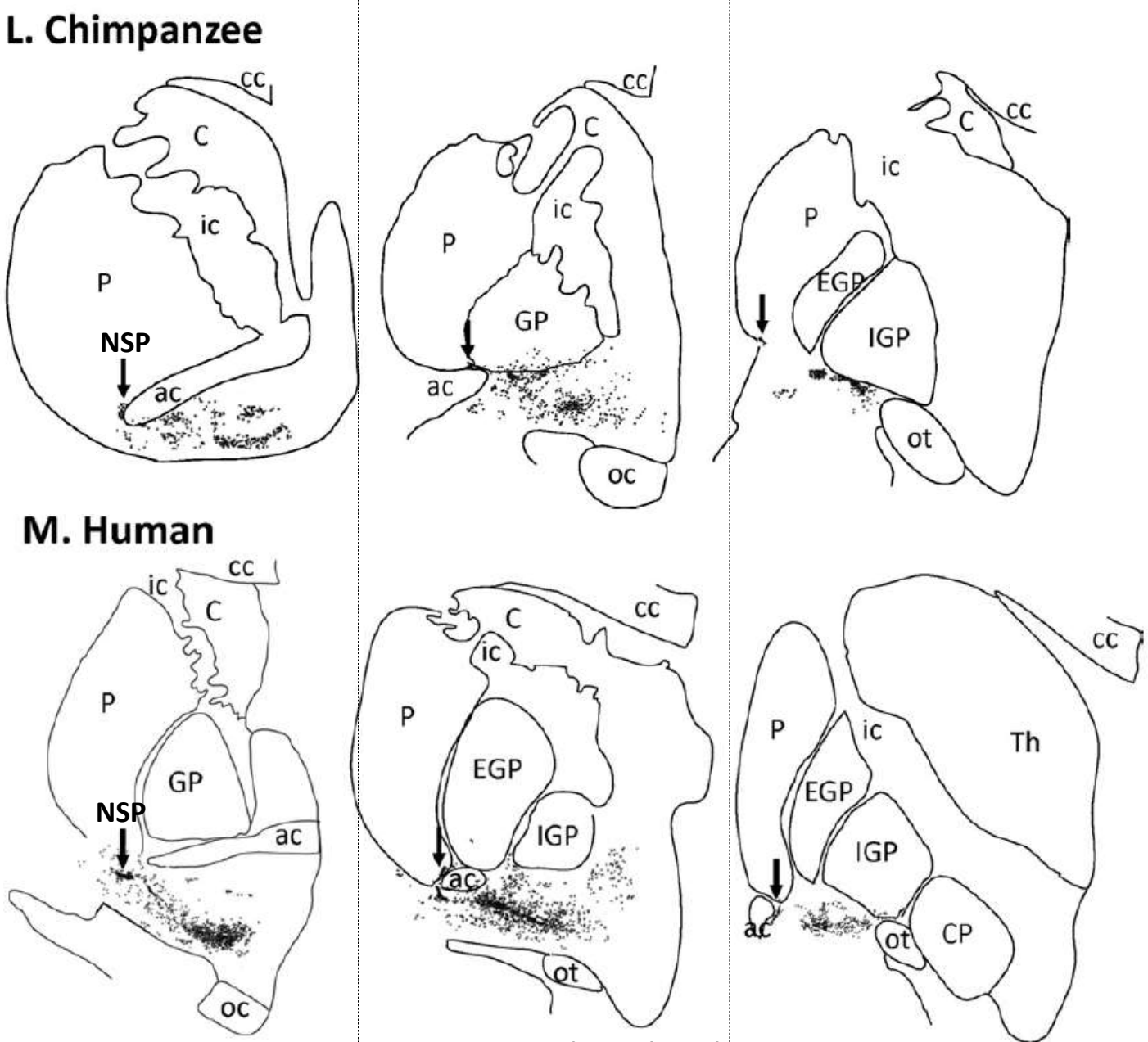




anterior

intermediate level

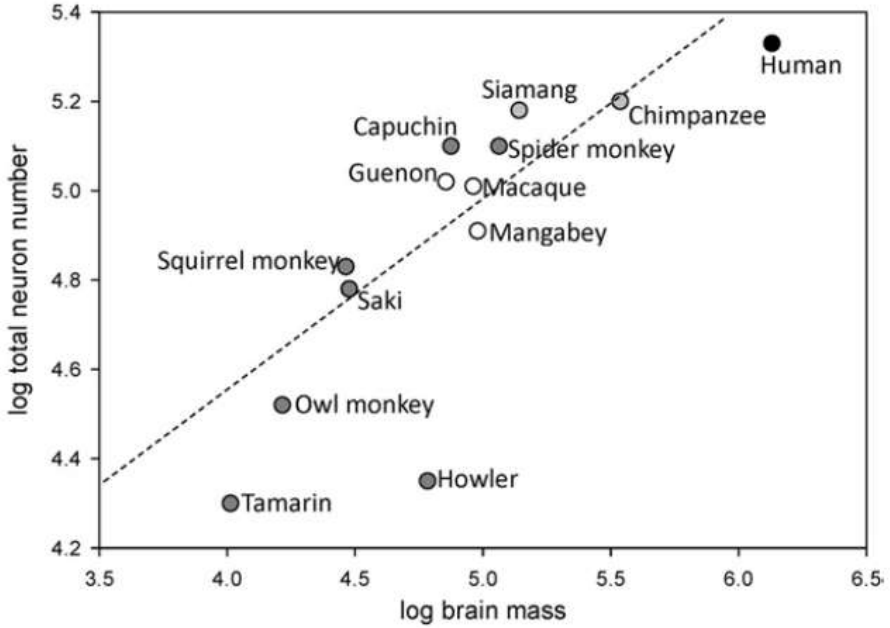
posterior


L. Chimpanzee
cc
C
ic
P
NSP
ac
GP
oc
EGP
IGP
ot
M. Human
Th
CP
anterior
intermediate level
posterior

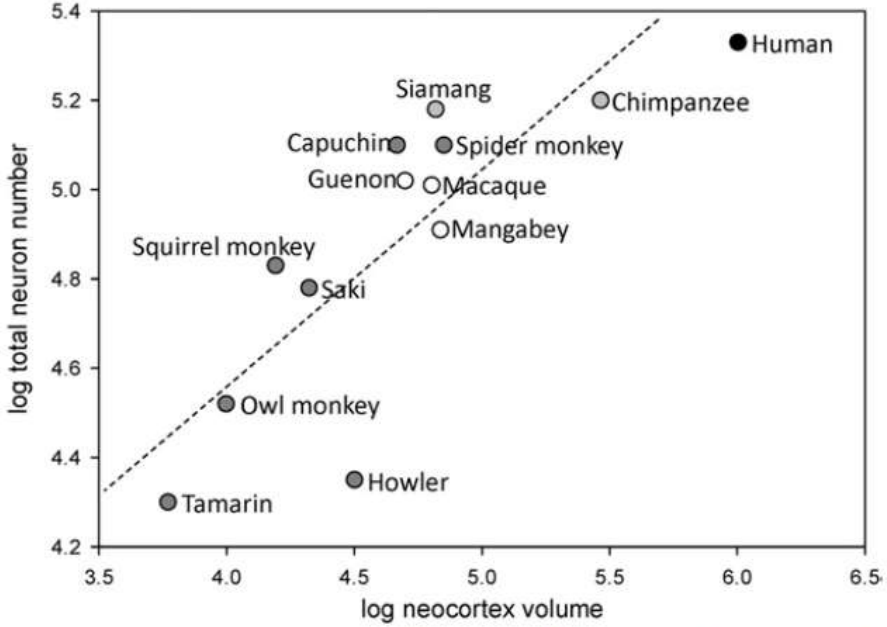
Neuroscience 184 (2011) 1–15

COMPARATIVE ANALYSIS OF THE NUCLEUS BASALIS OF MEYNERT AMONG PRIMATES

M. A. RAGHANTI,[a,b*] G. SIMIC,[c] S. WATSON,[a] C. D. STIMPSON,[d] P. R. HOF[e] AND C. C. SHERWOOD[d]



Total neuron number within the nbM regressed on brain mass. Data points for New World monkeys are dark grey; Old World monkey data points are white; lesser and great ape data points are light grey.



Total neuron number within the nbM regressed on neocortical volume. Data points for New World monkeys are dark grey; Old World monkey data points are white; lesser and great ape data points are light grey.

We concluded that many **monkeys have a prominent NB complex, but lack a developed NSP**.

Only some anthropoid monkeys have all subdivisions of the NB complex.

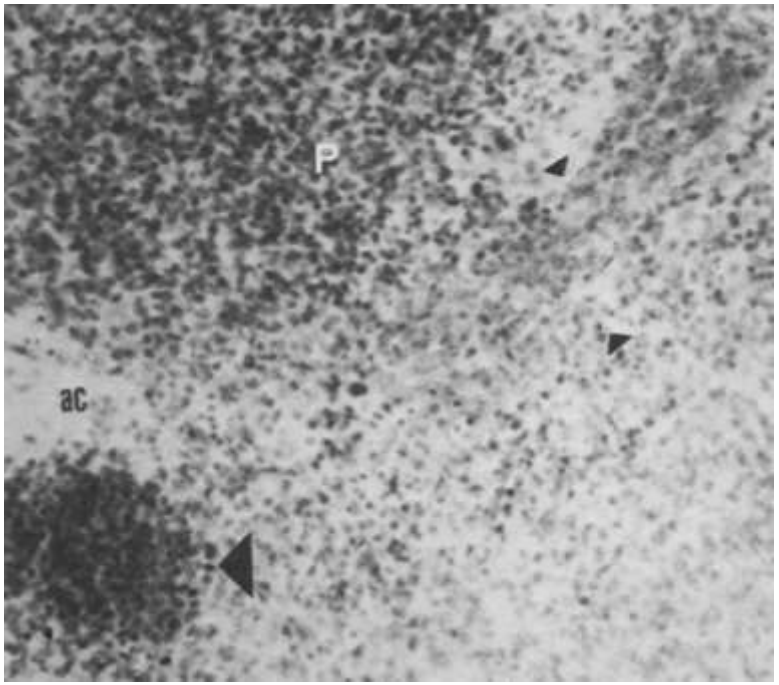
Only chimpanzees have a very small number of NSP neurons.

Int. J. Devl. Neuroscience, Vol. 4, No. 2, pp. 143–149, 1986.
Printed in Great Britain.

0736–5748/86 $03.00+0.00
Pergamon Press Ltd.

EARLY CYTOARCHITECTONIC DEVELOPMENT OF THE ANLAGE OF THE BASAL NUCLEUS OF MEYNERT IN THE HUMAN FETUS

IVICA KRAČUN*† and HARALD RÖSNER‡



Human, 15 w.g. "albino cell group„ i.e. the future NSP (in between small arrowheads) indicates the **most protracted development among all magnocellular aggregations within the basal forebrain**

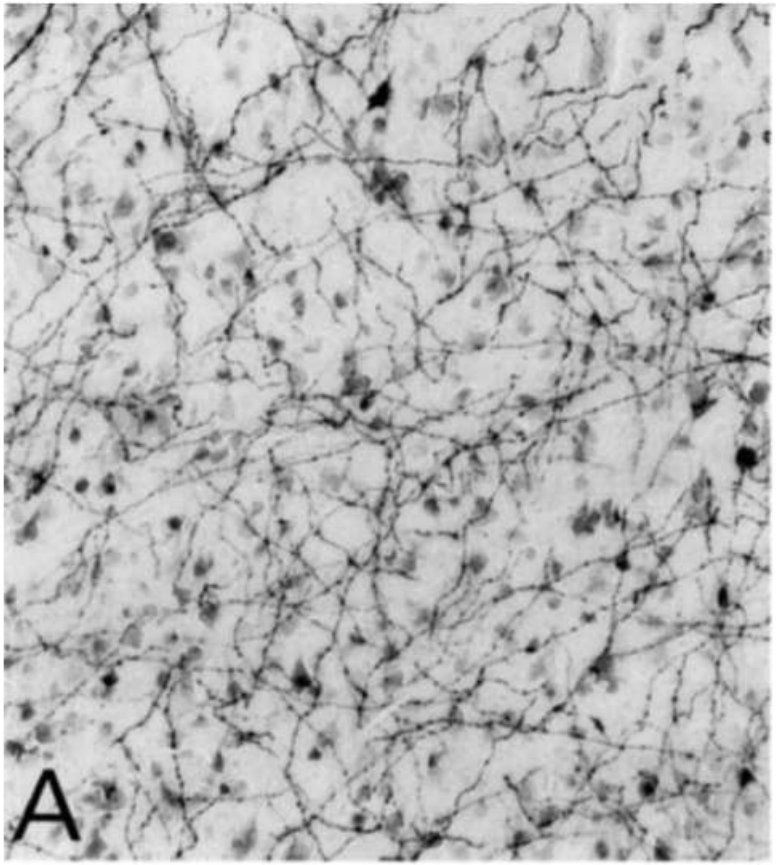
THE JOURNAL OF COMPARATIVE NEUROLOGY 275:216–240 (1988)

Nucleus Basalis (Ch4) and Cortical Cholinergic Innervation in the Human Brain: Observations Based on the Distribution of Acetylcholinesterase and Choline Acetyltransferase

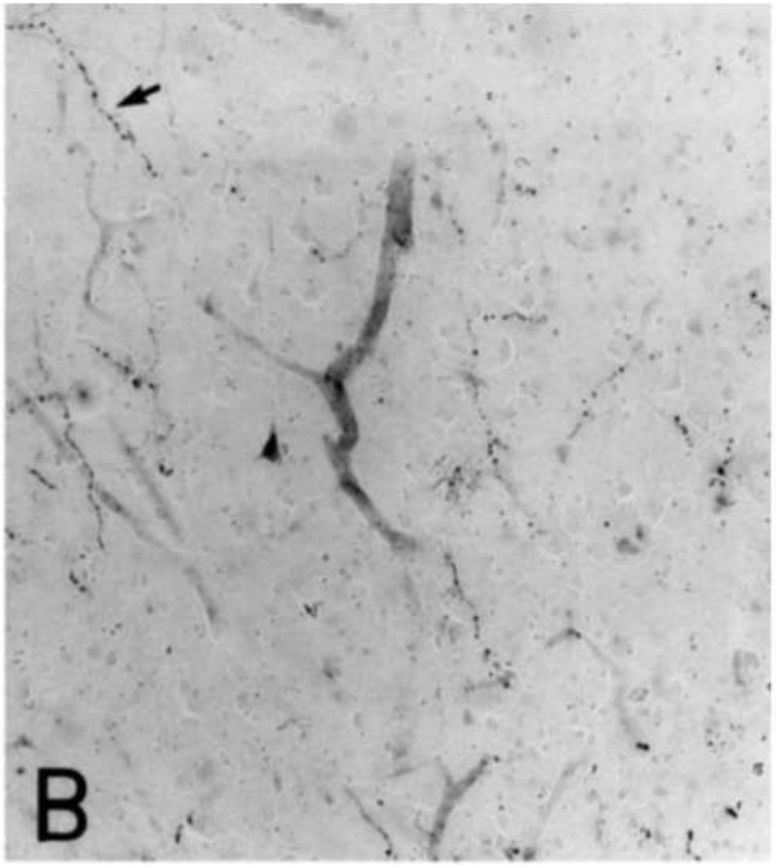
M-MARSEL MESULAM AND CHANGIZ GEULA

AChE ihc

temporopolar cx, CON



temporopolar cx, Alzheimer's disease



The relatively **small magnocellular group of cholinergic neurons** located within the **rostrolateral extension of the basal forebrain** was named and described as the **nucleus subputaminalis (NSP)** in the human brain by Giuseppe Ayala in 1915 (Ayala G., *Brain*, 1915).

Upon detailed analysis of the NSP in 33 normal subjects, we found the human NSP **projects through the external capsule towards the inferior frontal gyrus** and cingulum (it projects to amygdala too), which strongly suggests it is **connected with the cortical speech area** and is involved in generation of **P300 event-related potential** (Šimić G. et al., *Neuroscience*, 1999).

The **larger size of the NSP on the left side** (an observation that still needs a quantitative confirmation), the **most protracted development among all magnocellular aggregations within the basal forebrain** ("albino group", Kračun and Rösner, 1986) and the fact that **anterointermediate and rostral parts of NSP are usually negligible or missing in monkeys** (Rhaganti M.A., Šimić G., et al., 2011) indicates that these neurons are human specific.

Ad. 4.

Recent postmortem analysis of NSP of **cases presenting with primary progressive aphasia (PPA) revealed marked loss of cholinergic neurons in NSP regardless of underlying pathology**, providing further evidence for the importance of NSP in language (Hamodat H. et al., *Can. J. Neurol. Sci.*, 2019). Possible role of NSP in other neurological (variants of FTLD), neurodegenerative (AD) and psychiatric disorders (SCH) should be carefully investigated in future studies.

Slowly Progressive Aphasia Without Generalized Dementia

M.-Marsel Mesulam, MD

Ann Neurol 11:592–598, 1982

Clinical Details on Six Patients with Progressive Aphasia

Patient No. and Sex	Age at Onset (yr)	Years of Follow-up	Initial Condition	Language at Advanced Stage of Aphasia		
				Running Speech	Auditory Repetition	Auditory Comprehension
1, F	69	5	Anomic aphasia	Logopenia, long word-finding pauses, circumlocution, rare paraphasias	Moderately impaired	Preserved
2, M	57	11	Anomic aphasia	Logopenia, long word-finding pauses, circumlocutions, rare paraphasias	Normal	Moderately impaired
3, F	48	8	Anomic aphasia	Logopenia, long word-finding pauses, no paraphasias, dysarthria	Severely impaired	Probably intact
4, F	17	10	Pure word deafness	Normal	Parallels auditory comprehension	Severely impaired
5, M	54	9	Anomic aphasia	Normal quantity, circumlocutions, some paraphasias	Moderately impaired	Probably intact
6, M	61	8	Anomic aphasia	Logopenia, long word-finding pauses, circumlocutions, rare paraphasias	Mildly impaired	Mildly impaired

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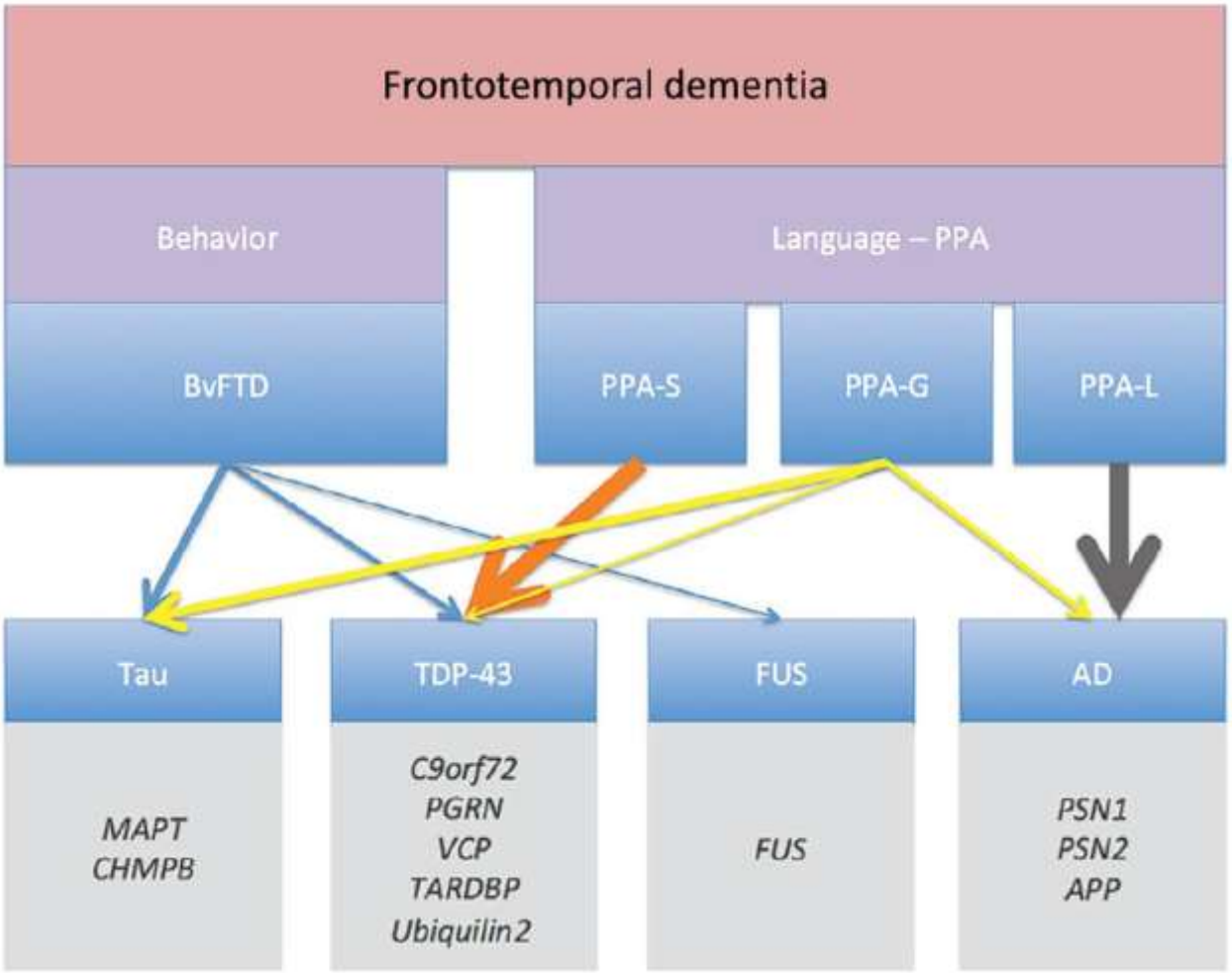
Frontotemporal dementia

EMMA M. DEVENNEY[1†], REBEKAH M. AHMED[2†], AND JOHN R. HODGES[1*]



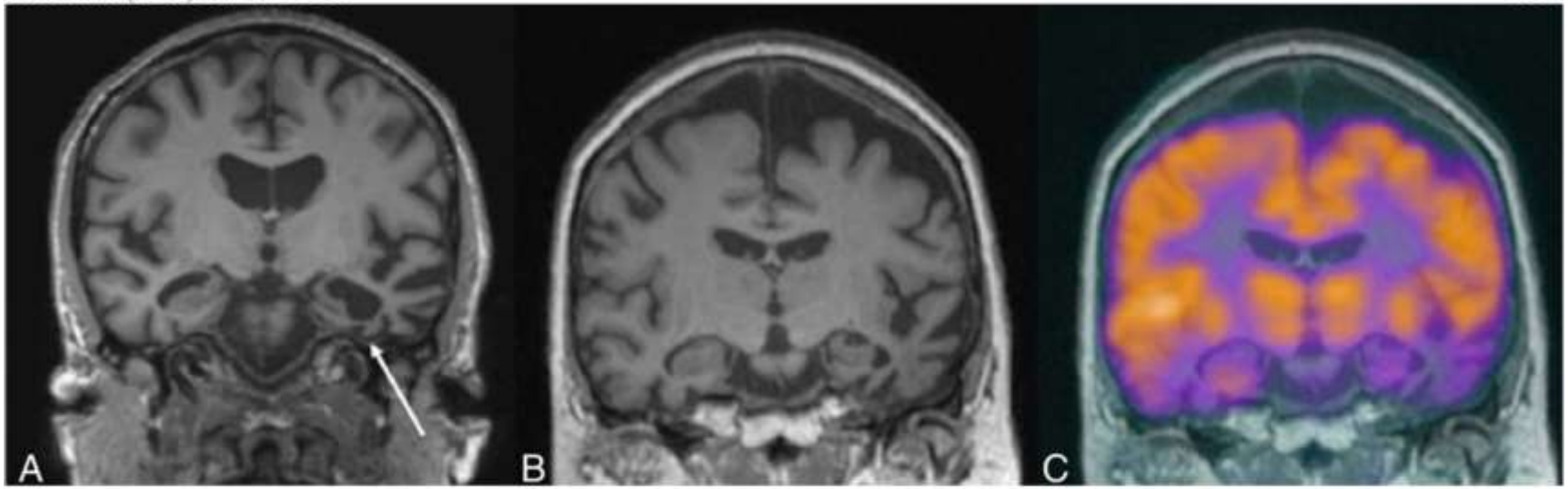
Clinical and pathological subtypes of FTD.
Weighted lines represent the approximate frequency of pathology for each variant.

Clinical and MRI features of language variants of FTD

Feature	"knife-edge" atrophy of the anterior temporal lobe **SD (svPPA)**	Atrophy of BA44/BA45 (P3b) **PNFA (nfPPA)**	Atrophy of angular g., middle temp. g. inf. parietal lobule, post. part. of sup. temp. g. **LPA (lvPPA)**
Agrammatism	–	+++/– *	–
Motor speech disorder	–	+++/– *	–
Anomia	+++	+	+++
Single word comprehension	+++	–	–
Comprehension complex or sequential instructions	–	++	+++
Single word-repetition	–	++	–
Sentence repetition	–	++	+++
Surface dyslexia	+++	–	–

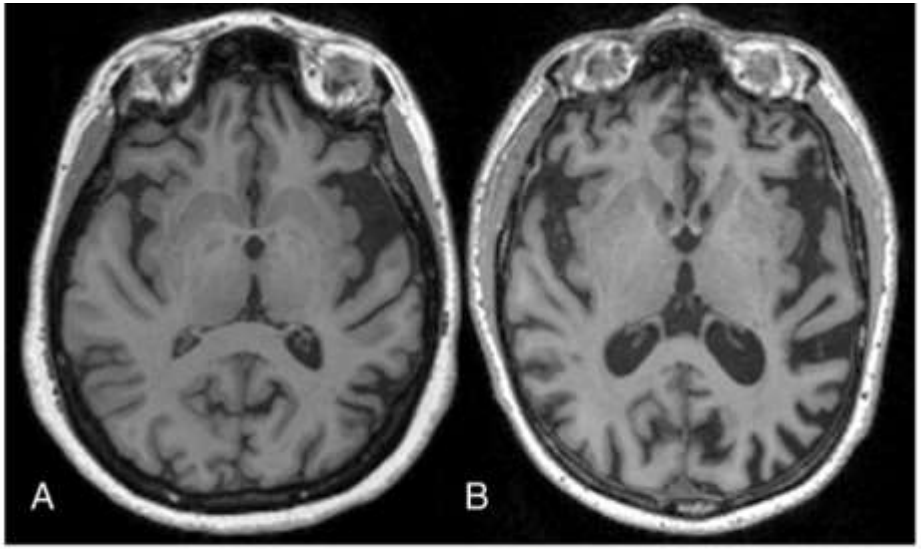
*Either agrammatism or motor speech disorder must be included.

svPPA



Coronal T1-weighted images (**a**, **b**) and fused FDG PET MRI image (**c**) in a patient with sematic variant PPA (semantic dementia). **a**, **b** Marked asymmetrical volume loss is found in the left temporal lobe affecting all temporal gyri and particularly the fusiform gyrus (*arrow*). **c** The FDG PET MRI demonstrates glucose hypometabolism not only in the left but also in the right temporal lobe, which shows much less marked atrophy

nfPPA



lvPPA

Axial T1-weighted MRI images in two different types of language led FLTD: non-fluent/agrammatic PPA (**a**) and logopenic variant PPA (**b**). Both cases show a markedly asymmetrical atrophy affecting predominantly the left hemisphere. In non-fluent/agrammatic PPA, the volume loss is centred around the left perisylvian region with resulting enlargement of the left Sylvian fissure (**a**). In the logopenic variant PPA, there is much more marked involvement of the left angular gyrus and posterior temporal lobe as well as occipital lobe (**b**)

Cholinergic Neurons in Nucleus Subputaminalis in Primary Progressive Aphasia

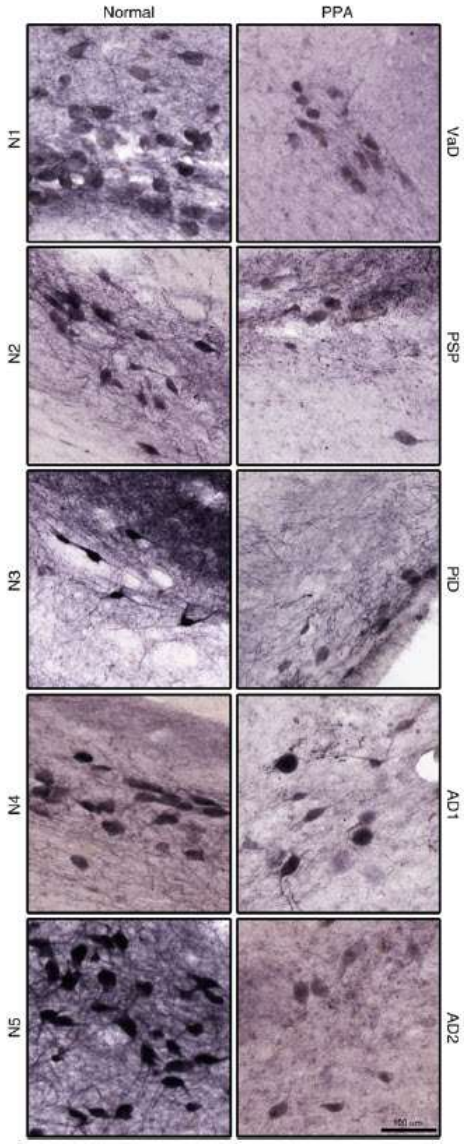
Hayam Hamodat, John D. Fisk, Sultan Darvesh

Case demographics

Diagnosis	Sex	Age (year)	PMI (h)[a]	TIF[b] (days)	Brain Weight (g)	Cause of Death	Diagnosis
Primary Progressive Aphasia							
VaD	F	86	20	1.97	1230	Pneumonia	Vascular dementia
PSP	M	93	<24	4.81	1391	Unknown	Progressive supranuclear palsy
PiD	M	74	10	3.02	1100	Heart failure	Pick's disease
AD1	M	71	20	1.97	1340	Pneumonia	Alzheimer's disease
AD2	M	70	<24	205	1150	Pneumonia	Alzheimer's disease
Normal (N 1-5) Controls							
N 1	F	80	9	2.27	1300	Peritoneal carcinomatosis	Normal
N 2	F	82	3.5	0.79	1140	Renal failure	Normal
N 3	F	71	24	2	1250	Hepatic surgery complications	Normal
N 4	M	61	20	7	1420	Myocardial Infarction	Normal
N 5	M	53	24	2.17	1620	Heart failure	Normal

[a]PMI, post-mortem interval.
[b]TIF, time in fix.

	NSP				
PPA/ Normal	Total Neuronal Counts		Average Neuronal Count/Section		% Reduction for PPA
	PPA	N	PPA	N	
VaD/N1	319	927	53	155	65.6
PSP/N2	243	478	49	96	49.3
PiD/N3	343	647	57	108	47.0
AD1/N4	172	582	29	97	70.4
AD2/N5	128	1429	16	179	91.0
Group Mean (SD)	-	-	41 (18)	127 (38)	64.7



Conclusion: Regardless of underlying pathology, all cases presenting with PPA showed a marked loss of cholinergic neurons in the NSP, providing further evidence for the importance of this nucleus in language function.

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Thank you for your attention!
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