Nucleus basalis of Meynert

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Articles to check 1
ANATOMY 1
CONNECTIVITY 5
MR IMAGING 7
Anatomical borders 7
Subnuclei of basal forebrain 8
HISTOLOGY 9
FUNCTION 9
COGNTIVE FUNCTION 10
Function: memory 10
Function: attention 10
Function: modulation of the behavioural state 11
CLINICAL SIGNIFICANCE 11
ROLE IN COGNITIVE DYSFUNCTION IN PD 13
Hanyu 13
Choi 14
Teipel 14
DBS OF NBM 14
TRIALS 15

Nucleus basalis of Meynert - group of neurons in substantia innominata of basal forebrain which has wide projections to neocortex and is rich in acetylcholine and choline acetyltransferase.

ARTICLES TO CHECK

Sasaki M, Ehara S, Tamakawa Y, et al **MR anatomy of the substantia innominata and findings in Alzheimer disease: a preliminary study.** *AJNR Am J Neuroradiol* 1995;16:2001–2007

Oikawa, H., Sasaki, M., Ehara, S., Abe, T., 2004. Substantia innominata: MR findings in Parkinson's disease. Neuroradiology 46, 817–821.

Teipel et al., 2005 - localization of the cholinergic nuclei in MRI standard space based on postmortem data :

Teipel SJ, Flatz WH, Heinsen H, Bokde AL, Schoenberg SO, Stockel S, Dietrich O, Reiser MF, Moller HJ, Hampel H (2005): Measurement of basal forebrain atrophy in Alzheimer's disease using MRI. Brain 128(Part 11):2626–2644.

Teipel SJ, Stahl R, Dietrich O, Schoenberg SO, Perneczky R, Bokde AL, Reiser MF, Moller HJ, Hampel H (2007b): Multivariate network analysis of fiber tract integrity in Alzheimer's disease. Neuroimage 34:985–995.

morphometric studies based on postmortem data:
Grinberg LT, Heinsen H (2007): Computer-assisted 3D reconstruction of the human basal forebrain complex. Dementia Neuropsychol 2:140–146.

Halliday GM, Cullen K, Cairns MJ (1993): Quantitation and threedimensional reconstruction of Ch4 nucleus in the human basal forebrain. Synapse 15:1–16.

ANATOMY

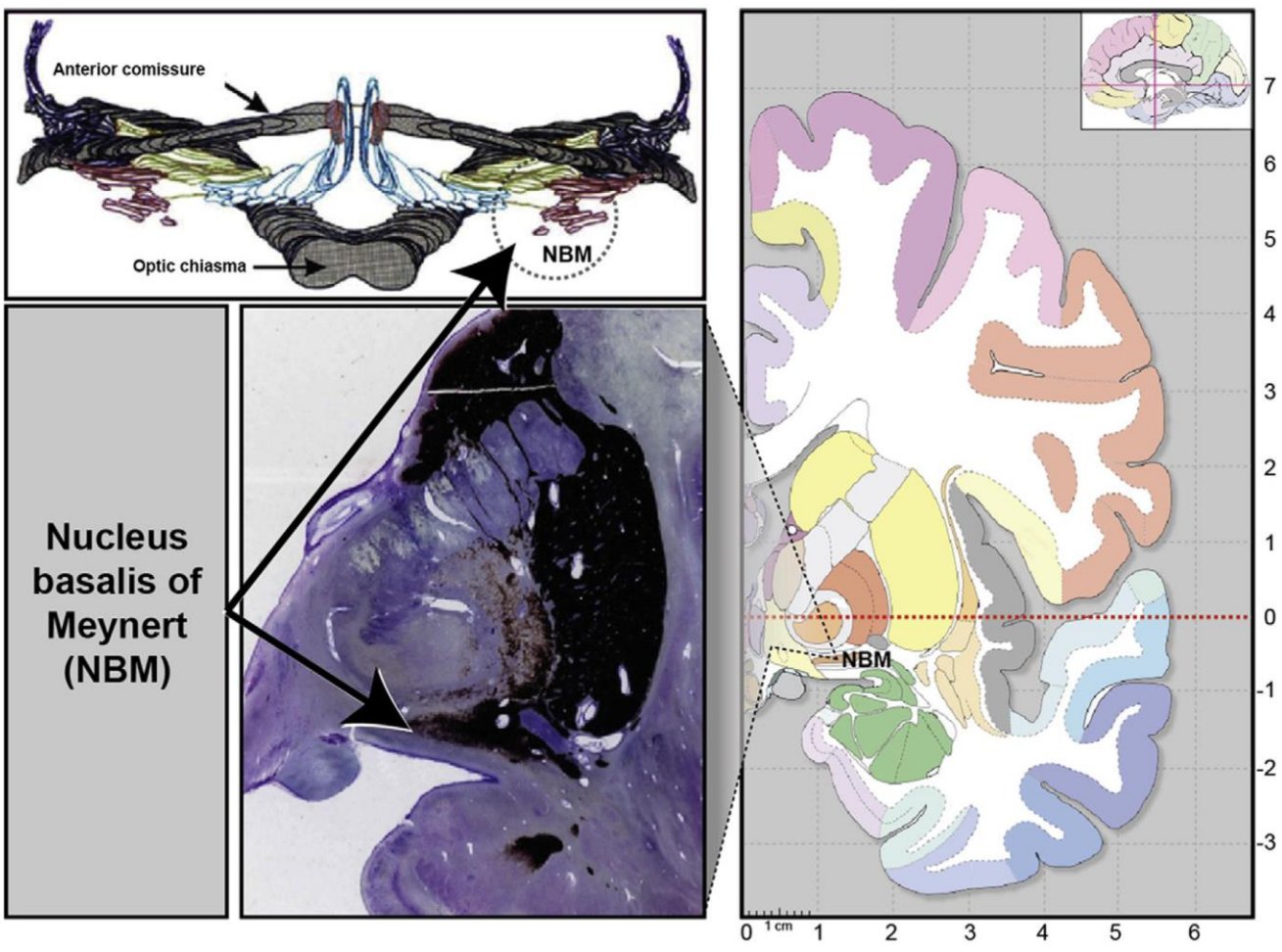
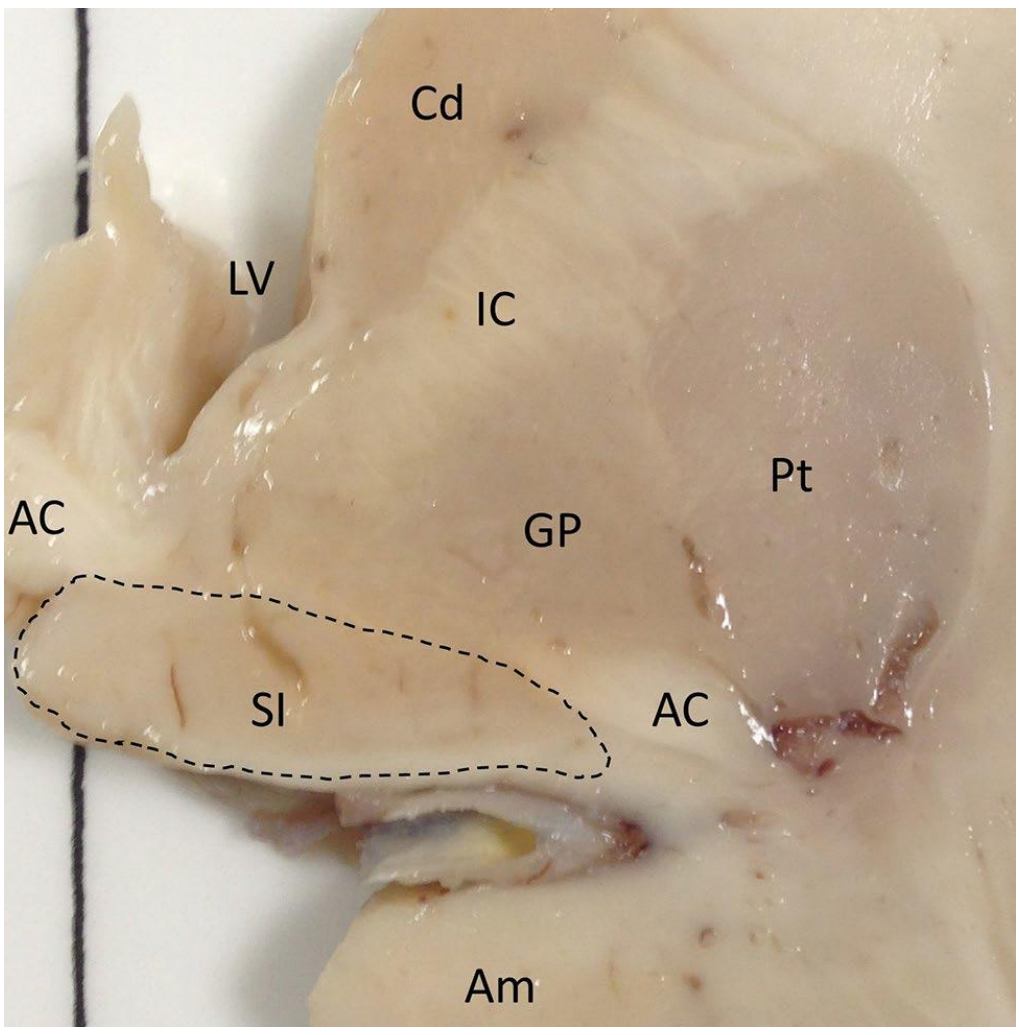


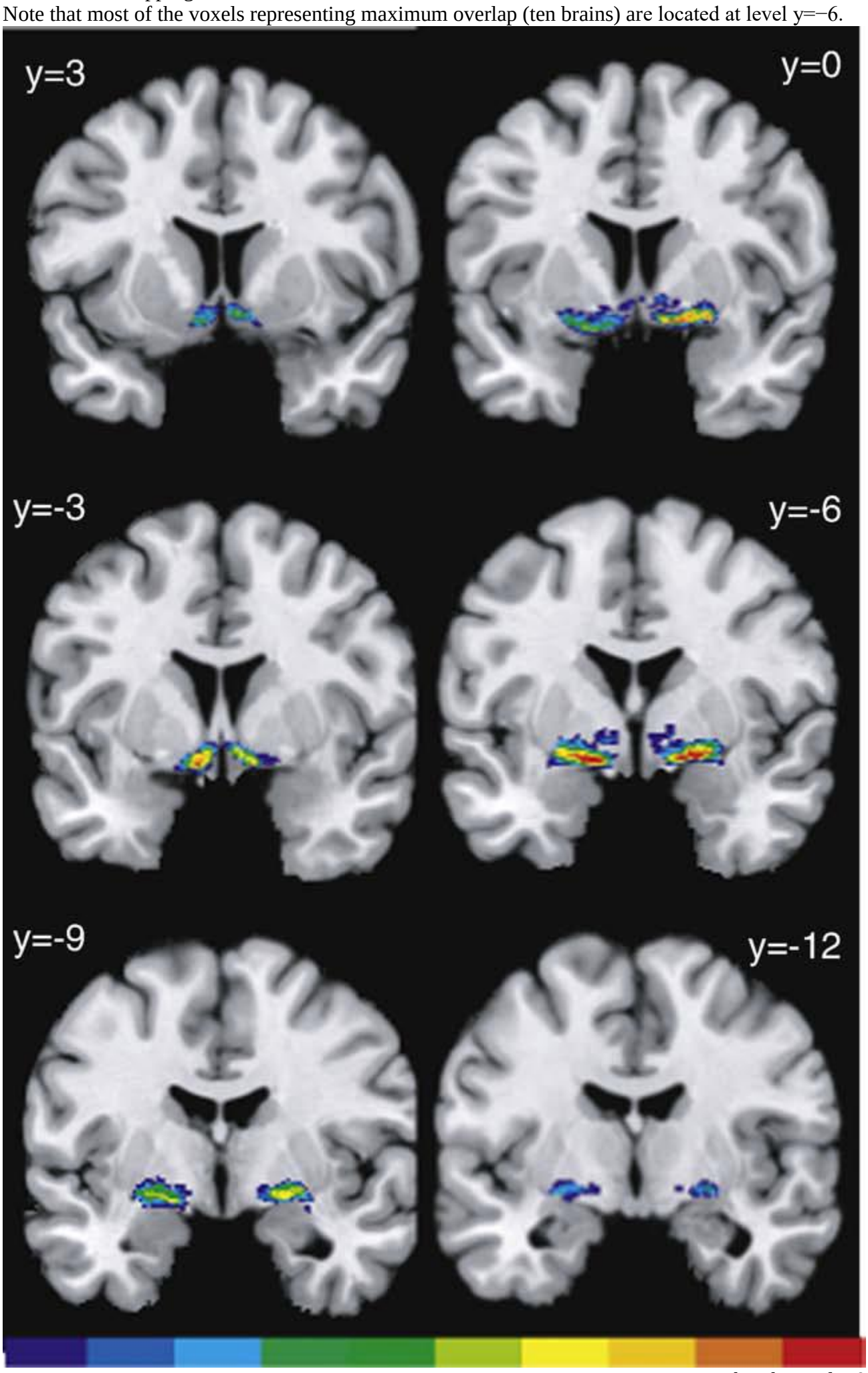
Figure 1. Histological and graphic presentation of the nucleus basalis Meynert. (Used with permission from Mai J, Voß T, Paxinos G: Atlas of the Human Brain. 3rd ed. San Diego: Elsevier Academic Press; 2008.)

Basal forebrain (AC anterior commissure, Am amygdala, Cd caudate, GP globus pallidus, IC internal capsule, LV lateral ventricle, Pt putamen, SI substantia innominata):



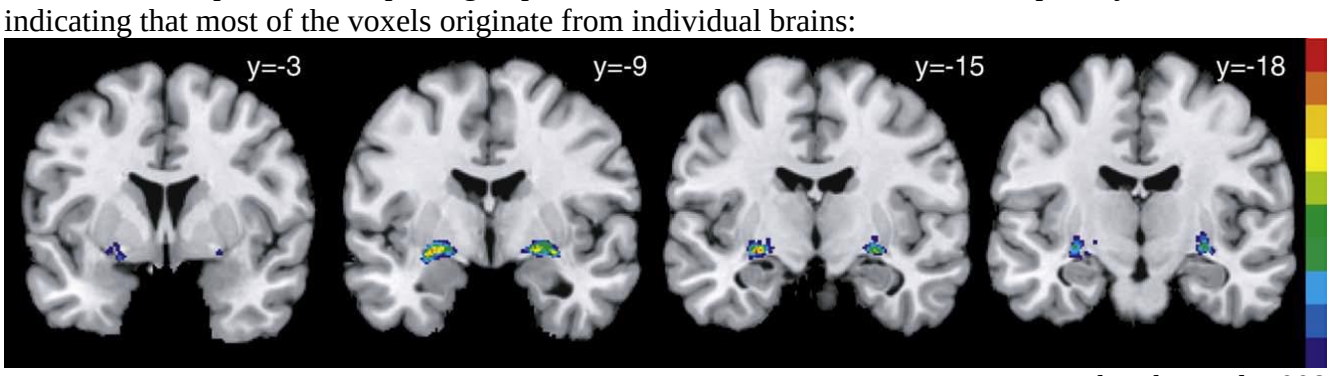
Liu et al. 2015

Study of 10 brains. Probabilistic map of the Ch4 cell groups at six rostro-caudal levels (y coordinates indicate distances from the anterior commissure in mm in the rostrocaudal directions).
The frequency with which the actual anatomical structure is overlapped in the sample of ten brains is color coded. The scale at the bottom of this figure indicates the degree of overlap in each voxel. The blue areas show that only one brain is represented with its actual structure, red color shows that all ten brains are overlapping.
Note that most of the voxels representing maximum overlap (ten brains) are located at level y=−6.



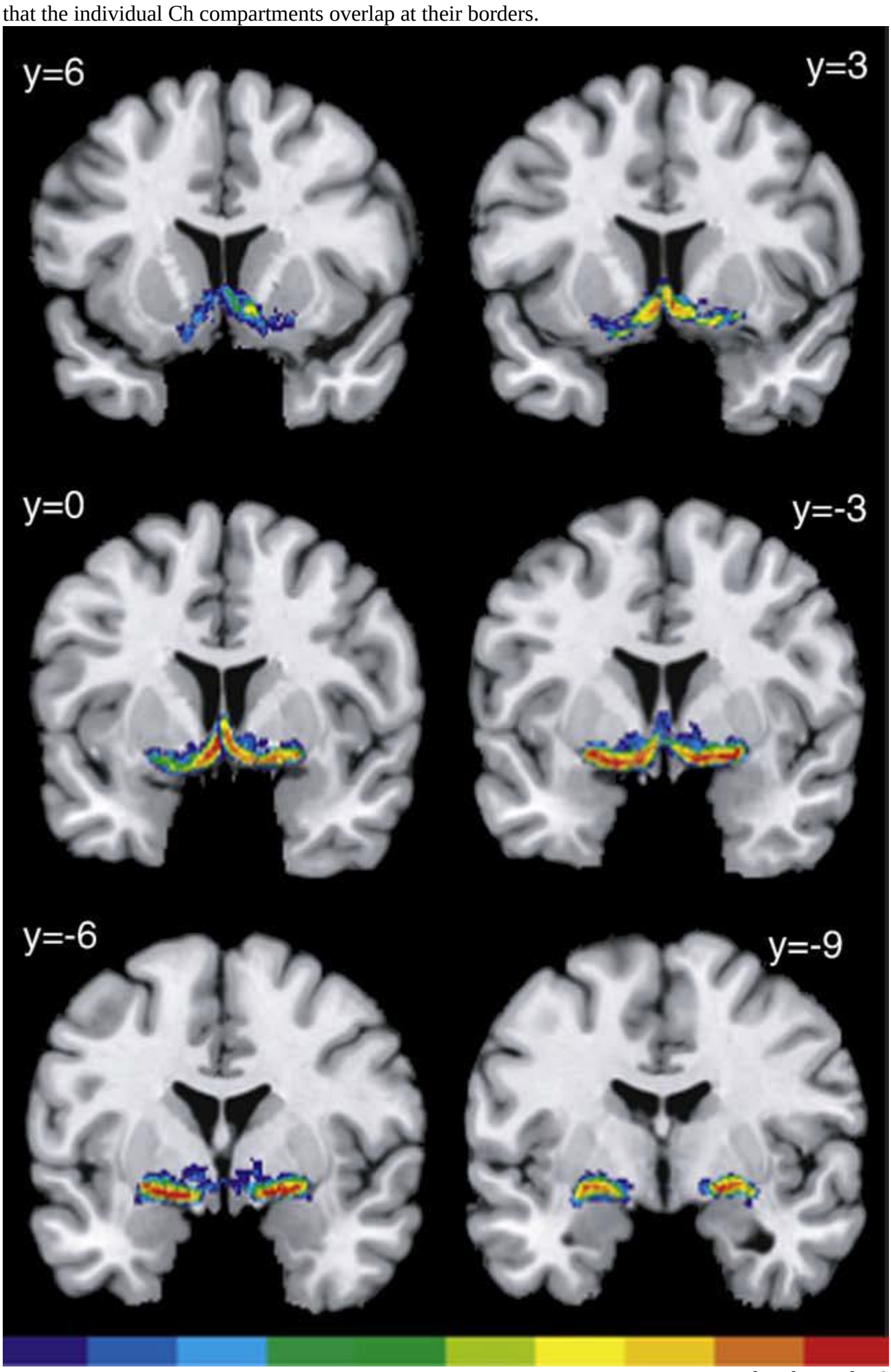
Zaborsky et al. 2008

Probabilistic maps of the Ch4p cell groups at four rostro-caudal levels. Note the paucity of red voxels, indicating that most of the voxels originate from individual brains:



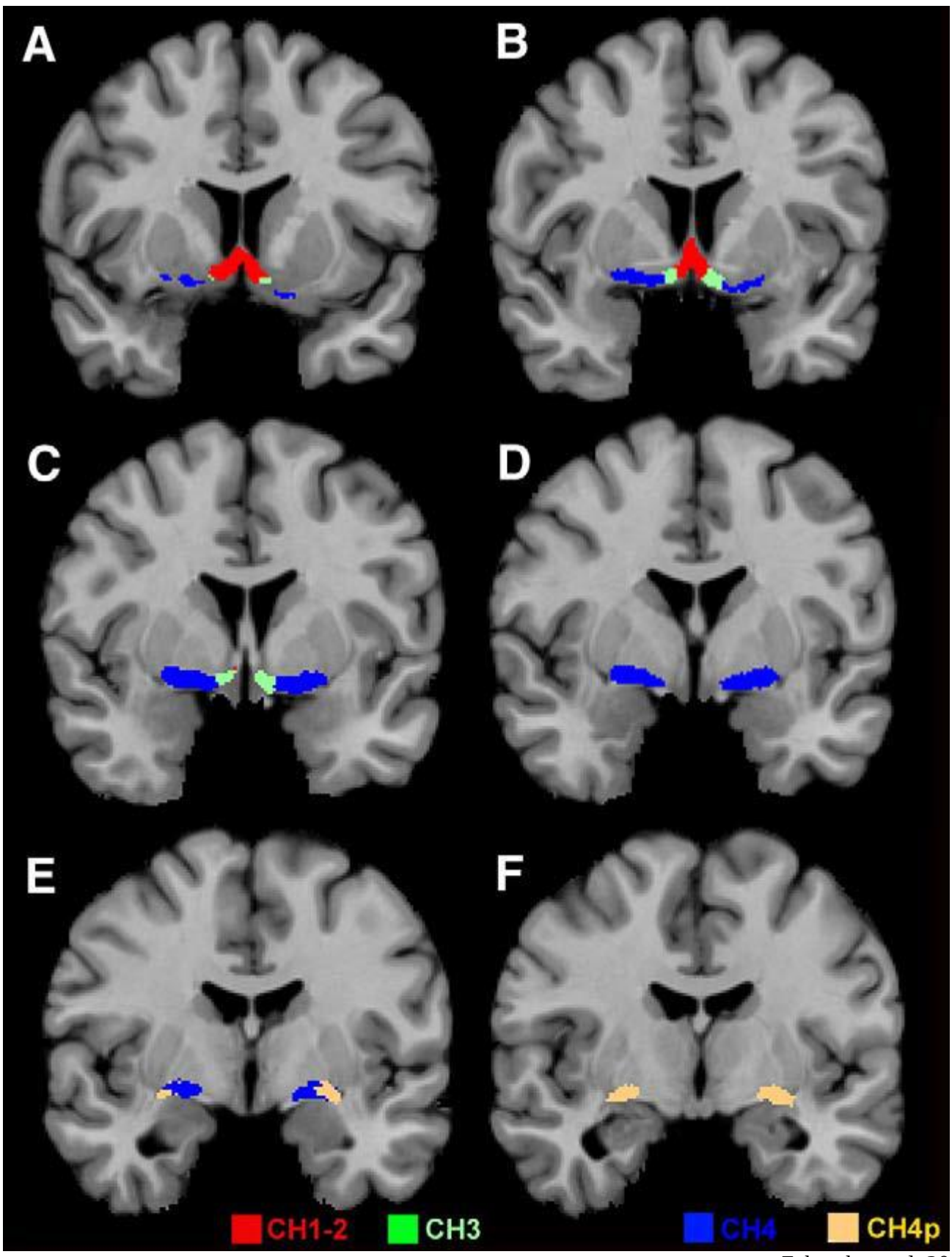
Zaborsky et al. 2008

Probabilistic maps showing all Ch groups without divisions into different compartments. Note that these maps show many more red voxels than previous maps of individual compartments due to the fact that the individual Ch compartments overlap at their borders.



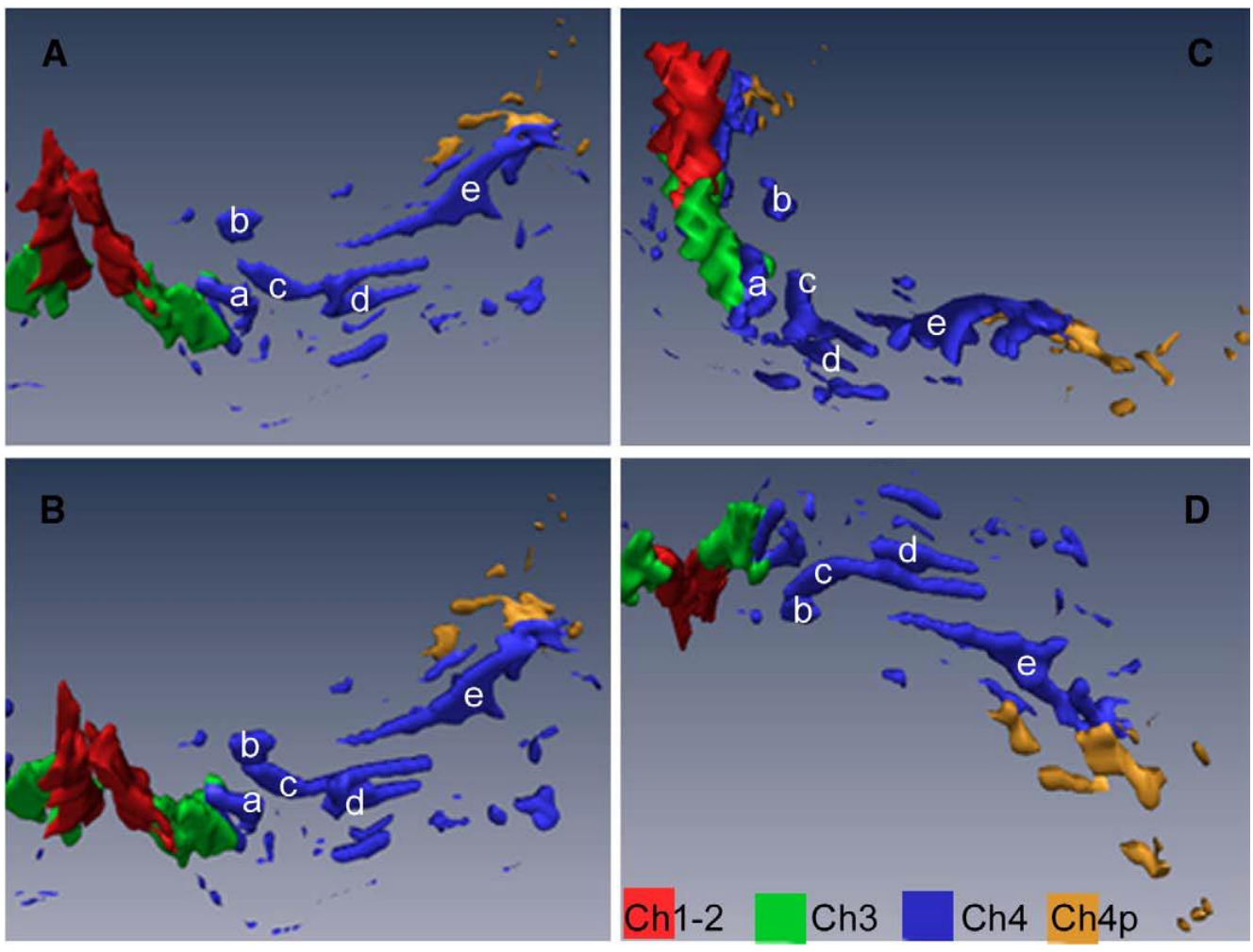
Zaborsky et al. 2008

Maximum probability maps (MPMs) of all Ch groups (A, rostral; F, caudal). In the MPM each voxel is assigned to the cytoarchitectonic compartment that showed the greatest overlap among the ten examined brains (i.e. each voxel was assigned to the cytoarchitectonic area that showed the greatest overlap - "winner take all" - among the ten examined post-mortem brains; as a result, MPMs show a nonoverlapping representation of the Ch compartments).
Note the colors represent individual Ch compartments (Ch1–2: red; Ch3: green; Ch4: blue and Ch4p: beige) and not the degree of overlap as in Figs above. The left hemisphere is right.



Zaborsky et al. 2008

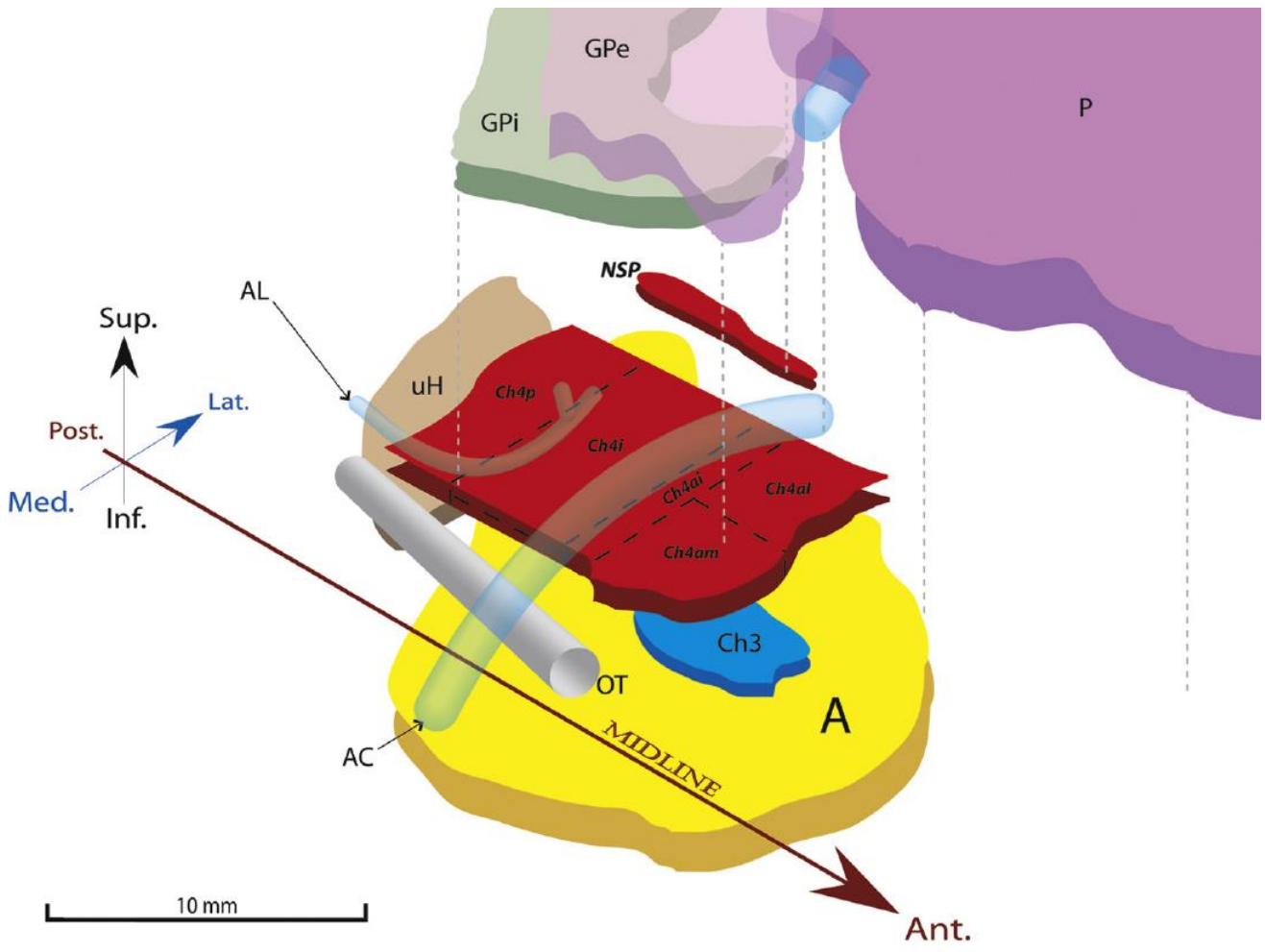
3D reconstruction of the Ch1–4 cell groups of the right hemisphere of one person.
(A and B) Coronal view with two different angles inclined towards the viewer. (C) Lateral view. (D) Ventral view, i.e. aspect from below.
The Ch4 (blue) compartment consists of various size and shaped bands or clusters that are in part parallel and in part are associated each other. For better orientation, some of the larger clusters are arbitrarily termed with letters a–e.
If other structures were added to this rendering it becomes obvious that the various cell aggregates of the Ch4 compartment penetrate the nucleus accumbens, ventral pallidum, and the bed nucleus of the stria terminalis to some extent.



Zaborsky et al. 2008

Gratwicke et al. / Neuroscience and Biobehavioral Reviews 37 (2013):
NBM is a flat, nearly horizontal structure extending from the olfactory tubercle anteriorly to the level of the uncal hippocampus at its most caudal extent, spanning a distance of 13–14 mm in the sagittal plane. It reaches its greatest cross-sectional diameter under the anterior commissure in a region known as the substantia innominata, with a medio-lateral width of 16–18 mm (Mesulam and Geula,1988). In its anterior portion the nucleus is limited inferiorly by the horizontal limb of the nucleus of the diagonal band of Broca, superomedially by the ventral globus pallidus, and superolaterally by the lateral extension of the anterior commissure (Figs. 1 and 2). In its posterior portion it abuts the ansa lenticularis superiorly, the puta-men laterally, the posterior tip of the amygdala inferiorly, and the optic tract medially (Fig. 2) (Mesulam and Geula, 1988; Rossor et al., 1982).

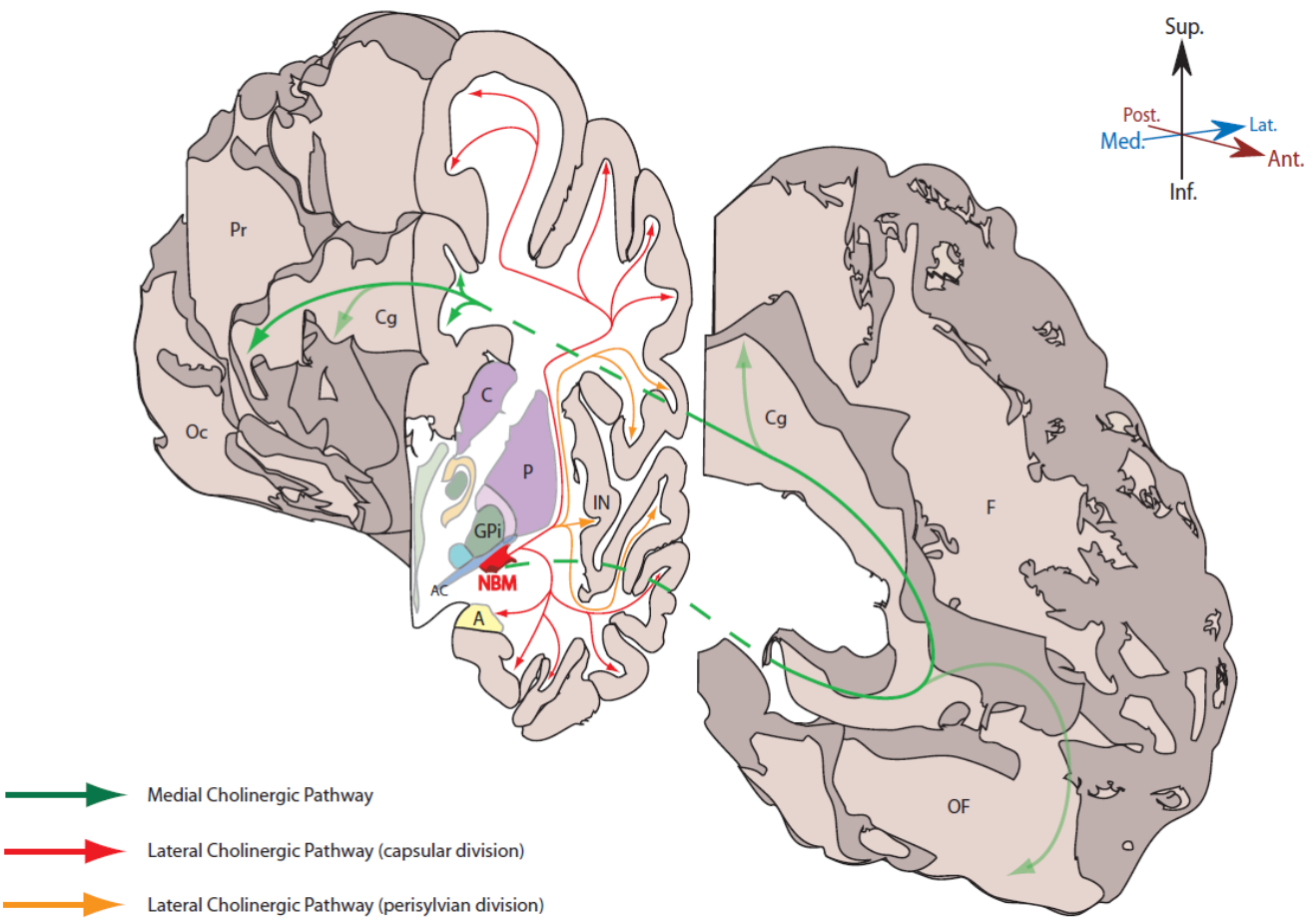
Gratwicke et al. / Neuroscience and Biobehavioral Reviews 37 (2013):
Representation of the major anatomical structures and fibre tracts related to the nucleus basalis of Meynert (Ch4, in red) in the human basal forebrain region. Overlying structures have been lifted upward to expose the NBM, as indicated by dashed grey lines. The major subsectors of the NBM are shown within the nucleus; their approximate anatomical boundaries are indicated by dashed black lines. The diagram is based on anatomical observations in the human brain by Mesulam and Geula (1988) and Rossor et al. (1982). A = amygdala; AC = anterior commissure (lateral aspect); AL = ansa lenticularis; Ch3 = horizontal limb nucleus of the diagonal band of Broca (cholinergic cell group 3 of the basal forebrain); GPi = globus pallidus internus; GPe = globus pallidus externus; OT = optic tract; P = putamen; uH = uncal hippocampus. Subsectors of NBM as described in the main text, NSP = nucleus subputaminalis.



CONNECTIVITY

Gratwicke et al. / Neuroscience and Biobehavioral Reviews 37 (2013):

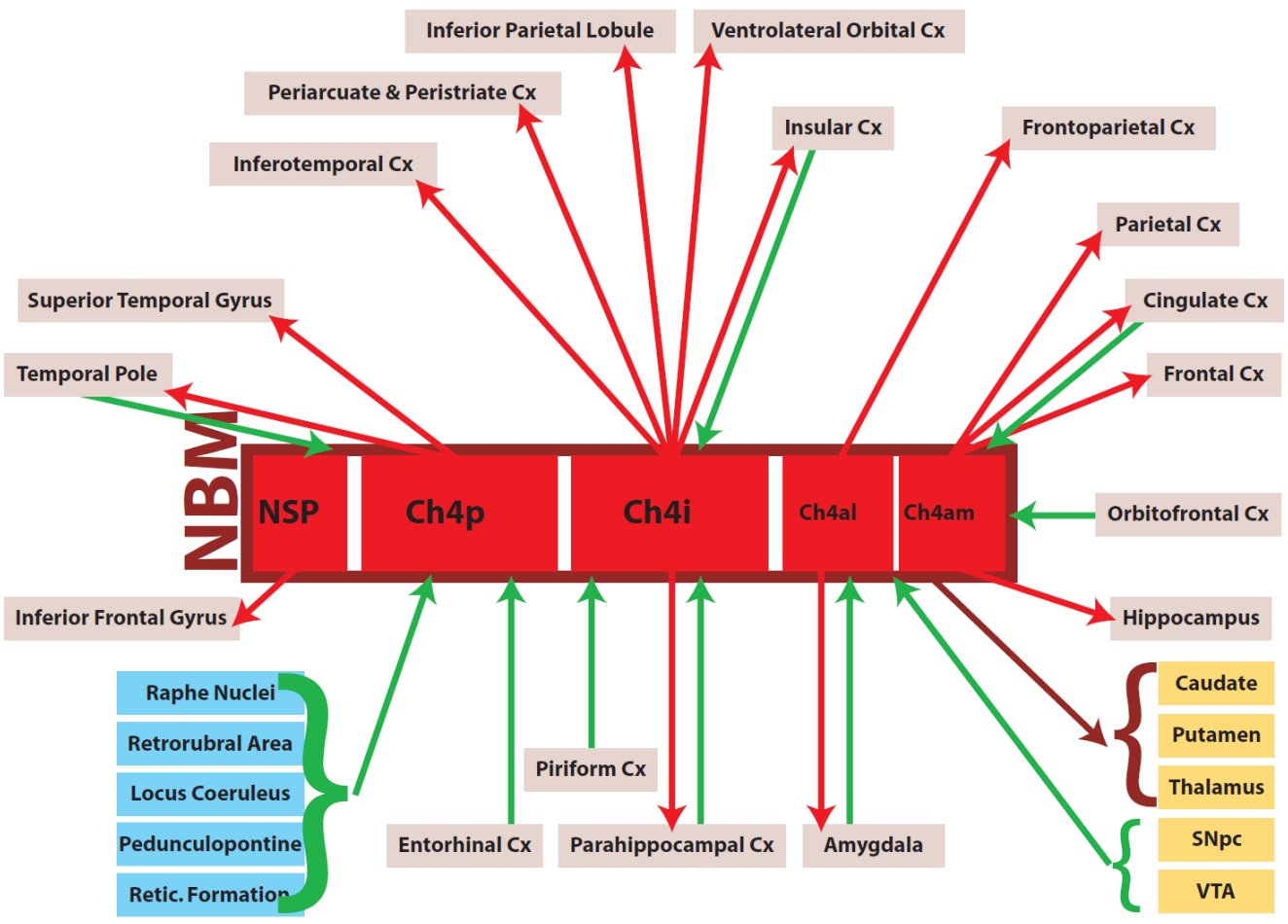
Anatomical diagram of the left hemisphere demonstrating location of the nucleus basalis of Meynert and its major projecting cholinergic pathways in the human brain. The medial surface of the left hemisphere is closest to the viewer. A coronal section is presented at approximately 6 mm posterior to the midpoint of the anterior commissure. The diagram is based on anatomical observations in the human brain by Selden et al. (1998) and human diffusion tensor imaging studies by Hong and Jang(2010). A = amygdala; AC = anterior commissure (lateral aspect); C = caudate; Cg = Cingulate gyrus; F = frontal lobe (medial surface); GPi = globus pallidus (internus); IN = insular cortex; NBM = nucleus basalis of Meynert; Oc = occipital lobe (medial surface); OF = orbitofrontal cortex; P = putamen; Pr = parietal lobe (medial surface).



The efferent connectivity between individual subsec-tors of NBM and cortical areas displays a topographic specificityaccording to both retrograde tracer experiments in the primate andneuropathological studies in human AD patients (Fig. 3): Ch4amprovides the major cholinergic projection to frontal, parietal andcingulate cortices situated along the medial wall of the hemisphere.Lesser projections are directed to the hypothalamus, hippocampalformation, ventral somatosensory cortex, amygdala, ventrolateralorbital, middle insular, periarcuate, peristriate, parahippocampalregions and the inferior parietal lobule. The Ch4al subsector is theprincipal source of cholinergic projections to frontoparietal oper-cular regions and the amygdala. Additional projections are directedto the olfactory bulb, medial frontal pole, dorsomedial motor cor-tex, ventrolateral orbital cortex, insular, inferotemporal area andparahippocampal regions. The Ch4id and Ch4iv subsectors havesimilar projection patterns: they give prominent projections toventrolateral orbital, insular, periarcuate, peristriate, inferotempo-ral, and parahippocampal areas as well as to the inferior parietallobule. Minor projections occur to the medial frontal pole, dorso-medial motor cortex, frontoparietal opercular areas, the amygdala,anterior auditory cortex, and the temporal pole. Lastly the Ch4psubsector has a more restricted major projection to the superiortemporal gyrus and the temporal pole. Its lesser projections areconfined to adjacent inferotemporal and posterior insular regions(Jones et al., 1976; Mesulam and Geula, 1988; Mesulam et al., 1983).Efferent cholinergic fibres from the human NSP course in the exter-nal capsule towards the inferior frontal gyrus, which lead Simicet al. to propose that it projects to the cortical speech area in man(Simi´c et al., 1999).The complex topographical arrangement of Ch4 efferent con-nectivity also contains considerable overlap between individualsubsectors according to primate tracing studies. Some corticalareas, such as the ventrolateral orbital, insular, parahippocam-pal and peristriate cortices, receive projections of comparable sizefrom many different Ch4 subsectors (Mesulam et al., 1983). Thismay allow for some redundancy in the system, which could pre-vent these cortical areas from substantial cholinergic denervationshould one Ch4 subsector be preferentially affected by disease. Onthe other hand, other cortical regions such as medial frontoparietal,superior temporal and temporopolar regions receive Ch4 projec-tions from a much more restricted number of subsectors, and couldtherefore be much more vulnerable to cholinergic denervation fol-lowing limited NBM cell loss in those areas. This is supported byobservations in human post-mortem brain tissue which show thatthere is secondary degeneration in the nucleus basalis followingtemporal lobe lesions, but not after frontal or parietal lobe lesions(Kodama, 1929).

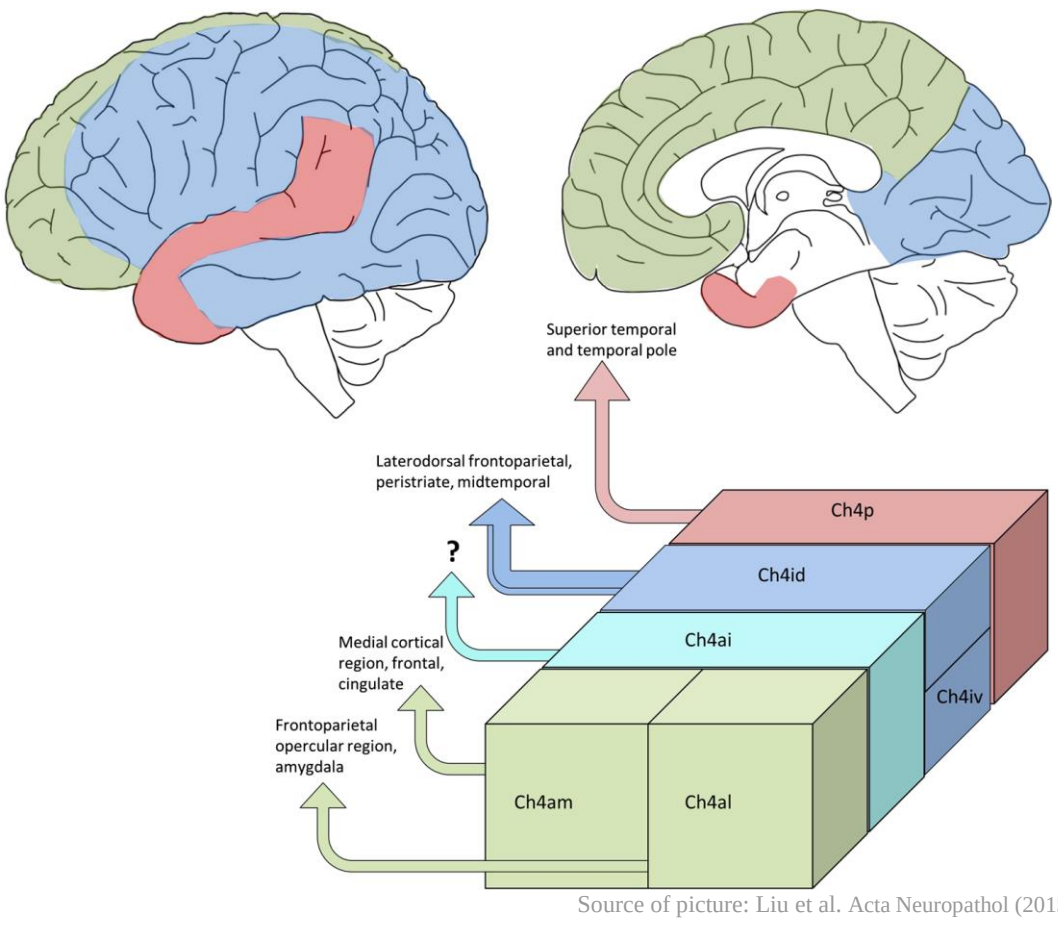
The major proposed connections of the human NBM with cortical and subcortical structures (see text for details). Major afferent projections (bright green arrows) are inputs to NBM as a whole: catecholaminergic projections from VTA, SNpc, retrorubral field, raphe nuclei and locus coeruleus; serotonergic projections from dorsal raphenuclei and VTA; cholinergic projections from pedunculopontine nucleus. Major efferent projections (bright red arrows) are shown according to their principle NBM subsectorof origin. Most NBM subsectors have additional minor projections which overlap with the cortical target fields of other subsectors, creating redundancy in the

topographicalarrangement of projections (these are not shown but are detailed in the text). The major efferent projections to the caudate/putamen and thalamus are from NBM as a whole (dark red arrow). All efferent projections are cholinergic. The diagram is based on axonal tracing experiments in primates (Mesulam et al., 1983; Russchen et al., 1985), immunohistochemical studies in rodents (Jones and Cuello, 1989) and pathological observations in human tissue (Mesulam and Geula, 1988). Cx = abbreviation for 'cortex';NBM = nucleus basalis of Meynert (subsectors of NBM as described in main text); retic. formation = brainstem reticular formation; SNpc = substantia nigra pars compacta;VTA = ventral tegmental area.:



Immunohistochemical mapping in post-mortem brain tissue from healthy human subjects shows that efferent cholinergic projections from the NBM leave the nucleus in two highly discrete organized fibre bundles which form the medial and lateral cholinergic pathways (Fig. 1) (Selden et al., 1998). The cholinergic axons in these bundles are mostly unmyelinated (Wainer and Mesulam,1990). Both the human post-mortem studies and MRI diffusion tensor tractography in healthy volunteers demonstrate that the medial pathway leaves the NBM anteriorly and joins the white matter ofthe gyrus rectus. It curves round the rostrum of the corpus callosum to enter the cingulum, travels posteriorly to the splenium andenters the retrosplenial white matter to merge with fibres of the lateral pathway in the occipital lobe (Hong and Jang, 2010; Seldenet al., 1998). Individual axons radiate from this pathway to supply the medial orbitofrontal, subcallosal, cingulate, pericingulate and retrosplenial cortices. The lateral pathway subdivides into a capsular division, travelling within the external capsule, and a perisylvian division, travelling within the claustrum (Selden et al., 1998). Onleaving the lateral aspect of NBM the capsular division gives off a bundle of fibres ventrally which travel in the white matter ofthe uncinate fasciculus to supply the amygdala and temporal lobe cortices. The rest of the capsular division ascends in the externalcapsule adjacent to the putamen and its individual fibres radiateout to supply the dorsal frontoparietal cortex, middle and infe-rior temporal gyri, inferotemporal cortex and the parahippocampalgyrus. The perisylvian division courses within the claustrum intothe white matter of the inferior frontal and superior temporal gyri. From here its fibres radiate out to supply the frontoparietal opercu-lar cortices, superior temporal gyrus and the insula. The medial andlateral cholinergic pathways merge anteriorly in the white matter of the orbitofrontal gyri. These cortical projections from the NBMalso have a weak contralateral component (Mesulam et al., 1983).These cholinergic projection fibres form a dense plexus in all regions of the human neocortex, displaying numerous end-terminal swellings which likely represent synaptic specializationsas they are often in intimate contact with cortical cholinoceptive neurons (Mesulam and Geula, 1988). There are differencesin the regional densities of NBM cortical innervations: limbic andparalimbic areas (particularly hippocampal, amygdala and piriformregions) receive substantially higher levels of cholinergic inputthan adjacent neocortical association areas. Apart from the cor-tex and amygdala both primate and human pathological studiesshow that the NBM also sends substantial efferent projections to anumber of diencephalic structures, including the caudate nucleus, putamen, thalamus (Fig. 3) and habenular nucleus (via the striamedullaris)(Jones et al., 1976; Mesulam and Geula, 1988; Mesulamet al., 1992).Overall, the heterogeneous neural input to NBM from predomi-nantly limbic structures combined with its dominant cholinergicoutput to the entire neocortex places it in a unique positionin the brain where it can influence all aspects of complex behaviour according to the prevailing emotional or motivationalstate (Mesulam, 1987).

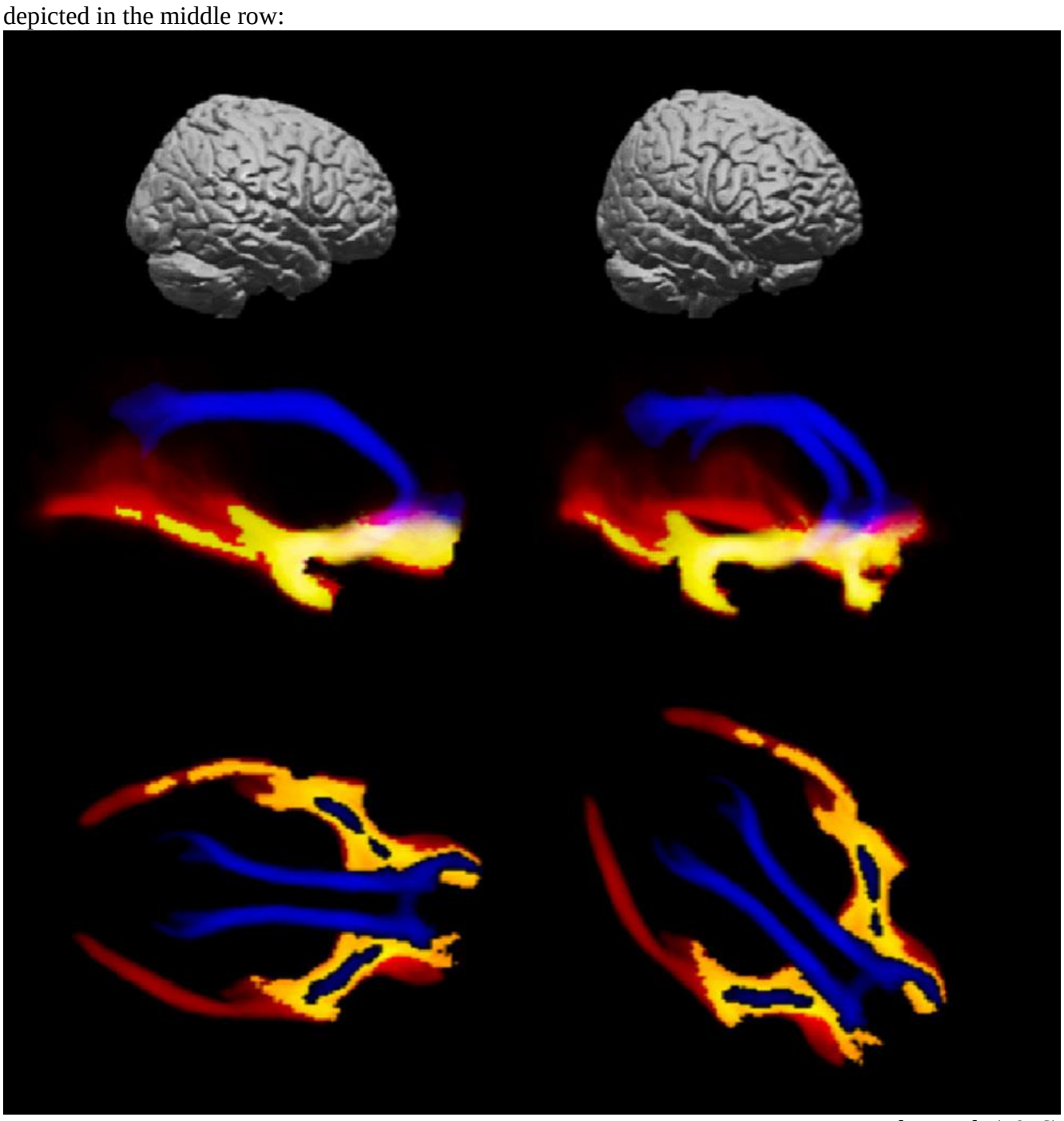
Projected innervation map of the various Ch4 regions (Ch4a, green; Ch4i, blue; Ch4p, red) in the human brain on the lateral surface (top left) and at the mid-sagittal plane (top right). Cortical projection from the Ch4ai (turquoise) is currently unknown in the human brain:



Source of picture: Liu et al. Acta Neuropathol (2015) 129:527–540

3D view of the nucleus basalis of Meynert (NbM) cortical pathway reconstructions thresholded at 5 % with colours depicting the contribution of the projections from the medial and lateral seed ROI separately. Blue: contribution of projections from the medial seed ROI (medial NBM). Red: contribution of projections from the lateral seed ROI (lateral NBM). Yellow: overlap between the projections from the medial and lateral seed ROIs. Top row: 3D brain depicting the viewing angle of the middle row (not to scale). Middle row: lateral view of the 3D reconstruction at an angle of 90, 45

and 20 degrees from the frontal view. Bottom row: craniocaudal view of the 3D reconstruction depicted in the middle row:



van Dalen et al. (2016)

MR IMAGING

- thin-section T2-weighted MR
- same signal intensity as that of the gray matter
- inferior to globus pallidus.
- in substantia innominata of anterior perforated substance
- substantia innominata has no clear anatomical borders at its anterior, posterior, and lateral extent

Probabilistic maps of compartments of the basal forebrain magnocellular system are now available as an open source reference for correlation with fMRI, PET, and structural MRI data of the living human brain (Zaborsky 2008)

Volume: normalized SI volume in normal subjects 1.68 ± 0.11 (Choi et al. 2012)
The volume of the basal forebrain complex in the human brain varies from 58 to 154 mm3 [Grinberg and Heinsen, 2007; Halliday et al., 1993].

Coronal (through the anterior commissure):

- narrow band between the margin of subcommissural part of the globus pallidus and surface of the substantia innominata
- rostrocaudal thickness of NBM - measured at the narrowest portion of the substantia innominata on the plane through the anterior commissure - about 2 mm.
- immediately inferior to anterior commissure and superior and lateral to anterior portion of hypothalamus.

ANATOMICAL BORDERS

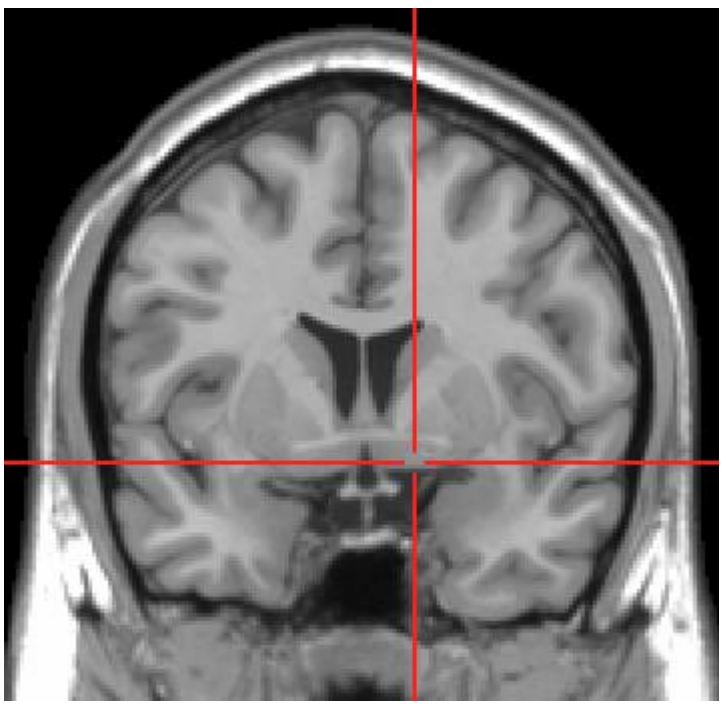
superior - anterior commissure*, margin of subcommissural part of the globus pallidus
*at the superior part of the posterior end of the anterior third of the substantia innominata

inferior - surface of the substantia innominata (13 mm ventral from the superior edge of the anterior commissure at the midline?).

anterior, posterior - 6 mm anterior and 12 mm posterior from the middle of the anterior commissure.
Our protocol for study: 4 mm anterior (2 AC widths) to AC; posterior – anterior border of mammillary body.
NBM is extending from the olfactory tubercle anteriorly to the level of the uncal hippocampus at its most caudal extent, spanning a distance of 13–14 mm in the sagittal plane. NBM reaches its greatest cross-sectional diameter under the anterior commissure in a region known as the substantia innominata, with a medio-lateral width of 16–18 mm. In its anterior portion the nucleus is limited inferiorly by the horizontal limb of the nucleus of the diagonal band of Broca, superomedially by the ventral globus pallidus, and superolaterally by the lateral extension of the anterior commissure (Figs. 1 and 2). In its posterior portion it abuts the ansa lenticularis superiorly, the putamen laterally, the posterior tip of the amygdala inferiorly, and the optic tract medially. (Mesulam and Geula, 1988).
The large neurons in the Ch4 compartment extend as far rostrally as cell aggregates underneath the nucleus accumbens.

medial - anterior portion of hypothalamus (25 mm lateral from the midline).
lateral – lateral edge of GPe.

For NBM segmentation we are using the following anatomical borders:
superior - inferior margin of subcommissural part of the globus pallidus
inferior – pial (basal) surface of the brain.
anterior – two sagittal widths of anterior commissure anterior from the center of anterior commissure
posterior – anterior border of mammillary bodies
medial – medial border of the globus pallidus
lateral – lateral edge of globus pallidus but sometimes it extends as far as putamen



Neuroimaging studies reporting significant effect in the substantia innominata-diagonal band with specific coordinates in the Talairach space

Author	Region as defined by the authors	X	Y	Z	Comment
Paus et al. (1997)	Substantia innominata	24	6	−15	Significant negative co-variations of rCBF with time on-task, PET
		23	6	−15	CBF co-variations with CBF in the left thalamus, PET
Morris et al. (1997)	Basal forebrain	12	−10	−8	rCBF, in an aversive classical conditioning the BF region co-varied with the right pulvnar, PET
Braun et al. (1997)	Basal forebrain (AH-POA)	−2	−8	−4	rCBF: SWS vs pre-sleep W, PET
		4	−6	−8	rCBF: REM vs SWS, PET
		4	2	4	rCBF: SWS vs post-sleep W, PET
Maquet et al. (1997)	Basal forebrain	2	2	−4	Decreased rCBF during SWS, PET
Morris et al. (1998)	Basal forebrain	−10	−10	−2	rCBF, Discriminatory aversive auditory conditioning, PET,
	Basal forebrain	8	−2	−12	
Fujii et al. (2002)	N. diagonal band of Broca	−3	5	−6	rCBF, Episodic memory retrieval, PET
De Rosa et al. (2004)	Medial septum/diagonal band	8	7	−7	Proactive interference in a discriminatory associative learning paradigm, fMRI
	Ventral striatum	14	−2	−2	

AH-POA = anterior hypothalamic-preoptic area.
BF = basal forebrain.
CBF = cerebral blood flow.
rCBF = regional cerebral blood flow.
REM = rapid eye movement sleep.
SWS = slow wave sleep.
W = wake.

Zaborszky 2008

the reference space of the **Montreal Neurological Institute (MNI)** single subject brain:

Collins, D.L., Neelin, P., Peters, T.M., Evans, A.C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J. Comput. Assist. Tomogr. 18, 192–205.

Holmes, C.J., Hoge, R., Collins, L., Woods, R., Toga, A.W., Evans, A.C., 1998. Enhancement of MR images using registration for signal averaging. J. Comput. Assist. Tomogr. 22, 324–333.

SUBNUCLEI OF BASAL FOREBRAIN

- Ch4al region has the strongest connections to wide-spread cortical areas in the human brain [Mesulam and Geula, 1988; Selden et al., 1998].
- Teipel (2011) study suggests a sequence of atrophy from Ch4al to Ch4am and Ch2/3;

Anatomy of the basal forebrain complex.
3D-reconstruction of the basal forebrain complex (BFC–view from anterior) from the brain of a 29-year-old man who had died of pulmonary arrest [Grinberg and Heinsen, 2007]. The BFC is located within the substantia innominata that is delimited by the caudal rim of the ventral striatum, the ventral pallidum, the ventral parts of the internal capsule and the regions medial to the outlines of the anterior commissure. The BCF can be subdivided into four cell groups arranged in an arch-like path mainly beneath the anterior commissure:

Ch1 - medial septal nucleus

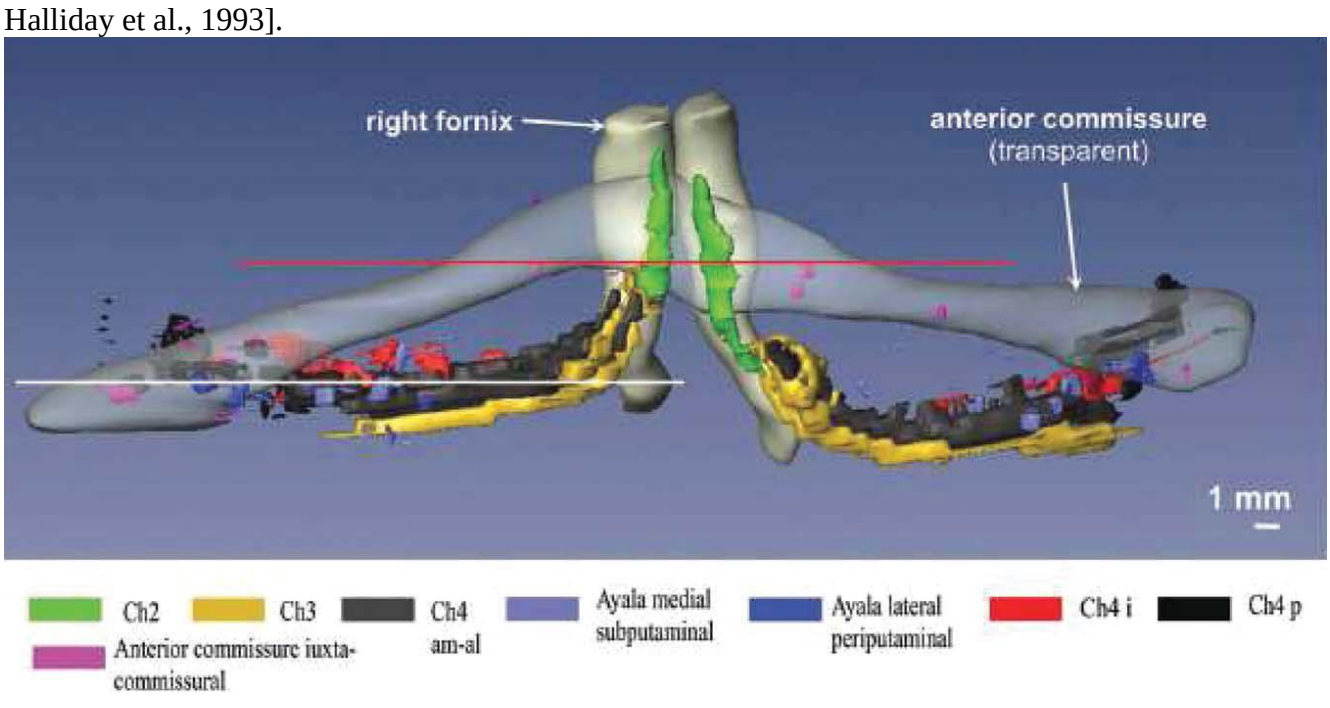
Ch2 - nucleus of vertical limb of the diagonal band of Broca.
Ch1–2 are called magnocellular cell groups within the septum.

Ch3 - nucleus of horizontal limb of the diagonal band of Broca;

Ch4 also called as the nucleus basalis of Meynert [Mesulam et al., 1983] or sublenticular part of the basal forebrain [Zaborsky 2008].

The nucleus subputaminalis, also called Ayala's nucleus, has only been described in the human brain so far [Heinsen et al., 2006; Simic et al., 1999].

The volume of the BFC in the human brain varies from 58 to 154 mm3 [Grinberg and Heinsen, 2007; Halliday et al., 1993].



Talairach-Tournoux x/y/z coordinates

Subnucleus	Right	Left
Ch2/3		-5/6/-8
Ch4am	12/4/-10	
Ch4al (lateral subst. innominata)	22 / 3-4 /-7 to -10	-17/5/-7
Ch4p (posterior subst. innominata)	24 / -11 / -8	
Ch4i (medial subst. innominata)	4 / -2 / -7	

x, the medial to lateral distance relative to midline (positive = right hemisphere);
y, the anterior to posterior distance relative to the AC (positive = anterior);
z, superior to inferior distance relative to the AC-PC line (positive = superior).

Table 3
Centers of gravity of cytoarchitectonic areas in the anatomical MNI space[a]

Cytoarchitectonic area	X[b]	Y[b]	Z[b]
Ch1–2L[c]	−1.8	3.7	−2.0
Ch1–2R[c]	3.0	4.3	−2.5
Ch3L	−6.0	2.0	−6.7
Ch3R	7.5	2.1	−6.9
Ch4L	−17.2	−2.3	−7.1
Ch4R	18.2	−1.5	−6.3
Ch4pL	−23.9	−8.6	−4.8
Ch4pR	24.0	−9.3	−4.5

[a] See definition in Materials and methods.
[b] In mm.
[c] L,R left, right side.

Table 4
Mean volumes of the basal forebrain structures in mm^3 with standard deviations ($N=10$) using individual correction for shrinkage[a]

Structure	Left hemisphere	Right hemisphere
Ch1_2	45.02±29.90	51.09±26.75
Ch3	23.21±16.15	22.75±13.88
Ch4	85.03±36.26	89.73±36.65
Ch4p	30.36±16.84	27.51±16.72
CH_all	183.62±49.22	191.08±55.22

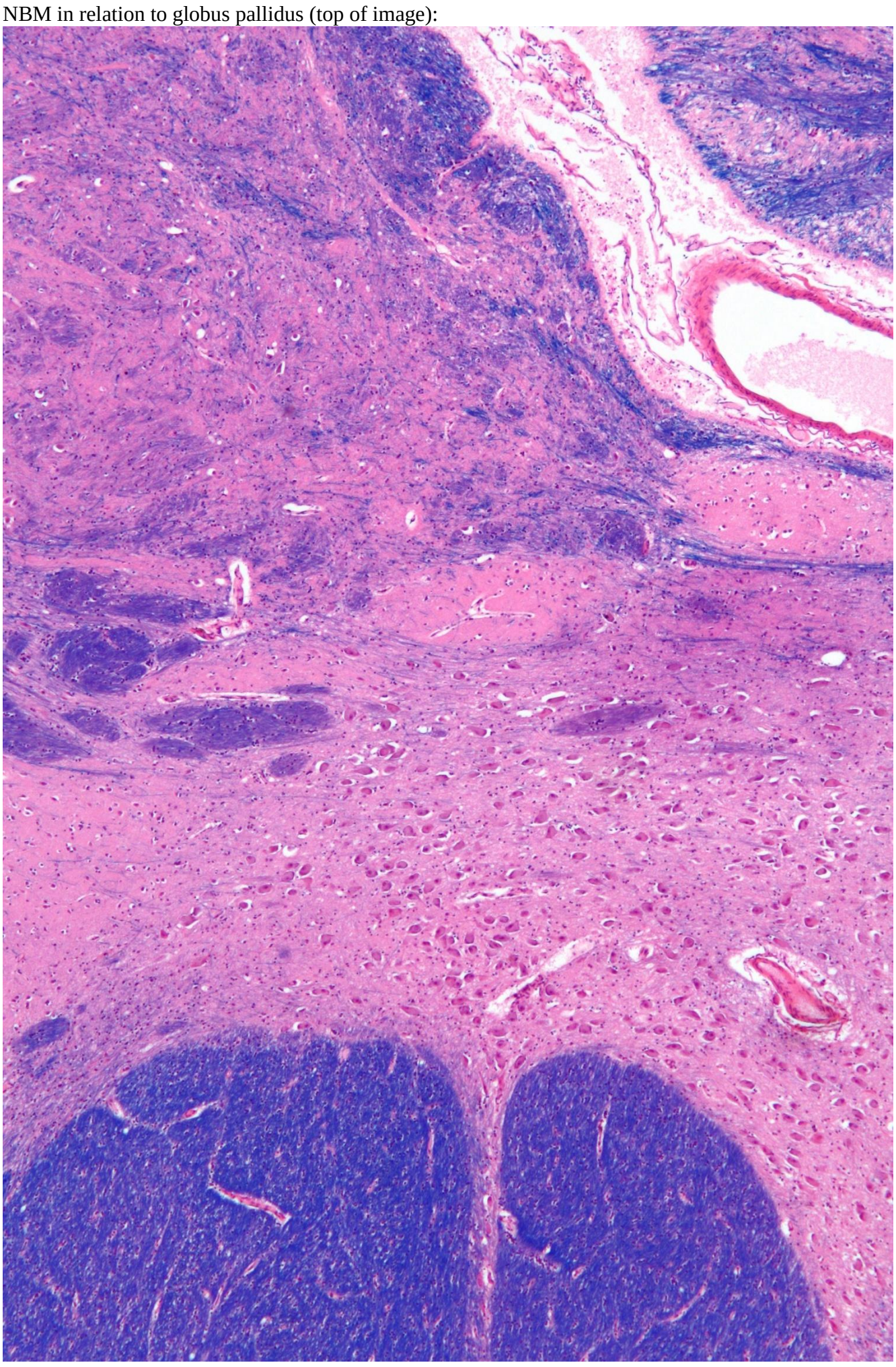
Neither interhemispheric or gender differences were significant ($p>0.05$).

Zaborzsky 2008

HISTOLOGY

Several postmortem studies have found that total number of nucleus basalis Meynert neurons in the nineth decade was 20–30% below that in newborns [Lowes-Hummel et al., 1989; Mann et al., 1984; McGeer et al., 1984].

NBM in relation to globus pallidus (top of image):

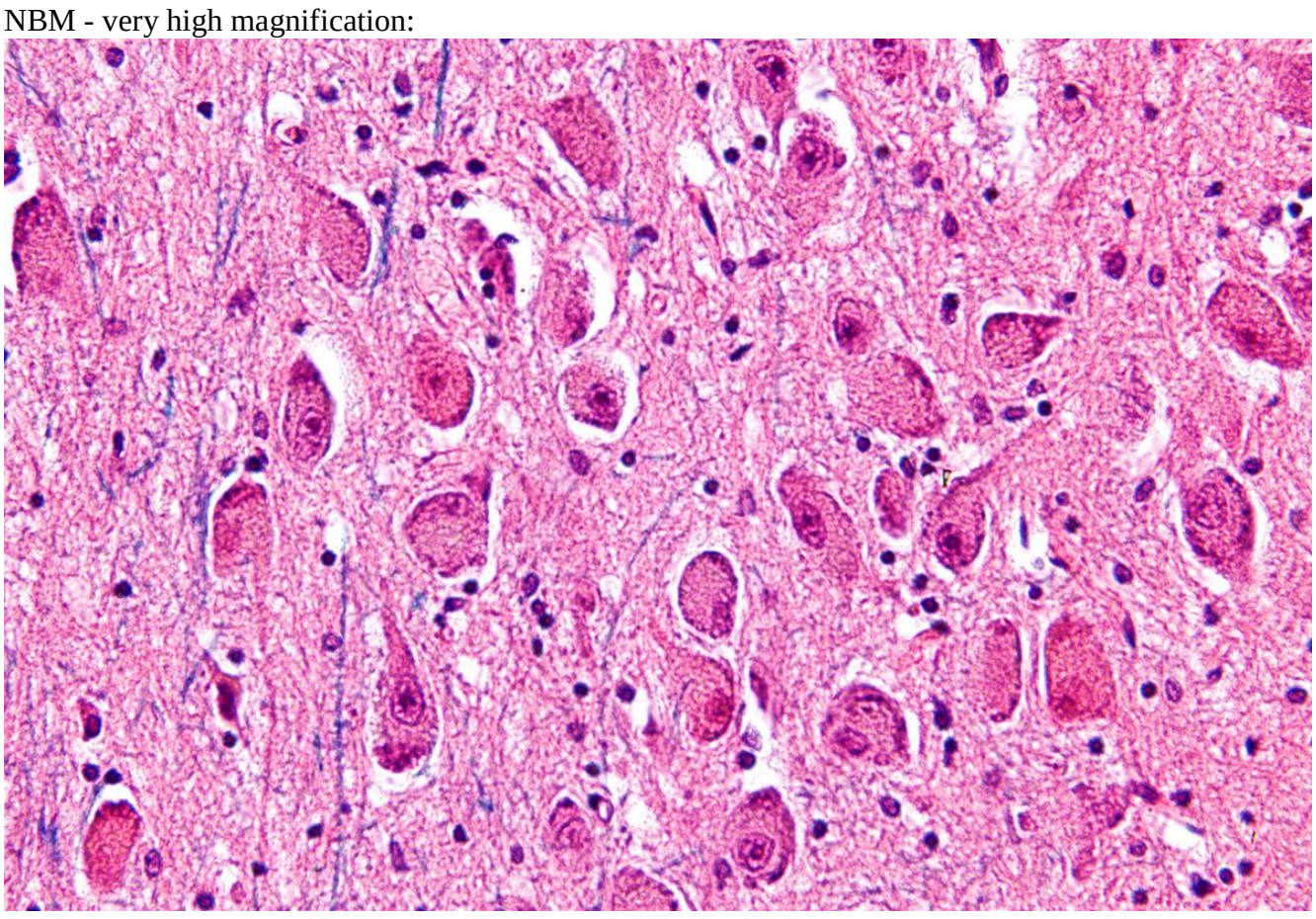


FUNCTION

These cholinergic neurons have a number of important functions in particular with respect to modulating the ratio of reality and virtual reality components of visual perception.[1] Experimental evidence has shown that normal visual perception has two components.[1] The first (A) is a bottom-up component in which the input to the higher visual cortex (where conscious perception takes place)

comes from the retina via the lateral geniculate body and V1. This carries information about what is actually outside. The second (B) is a top-down component in which the input to the higher visual cortex comes from other areas of the cortex. This carries information about what the brain computes is most probably outside. In normal vision, what is seen at the center of attention is carried by A, and material at the periphery of attention is carried mainly by B. When a new potentially important stimulus is received, the Nucleus Basalis is activated. The axons it sends to the visual cortex provide collaterals to pyramidal cells in layer IV (the input layer for retinal fibres) where they activate excitatory nicotinic receptors and thus potentiate retinal activation of V1.[2] The cholinergic axons then proceed to layers 1-11 (the input layer for cortico-cortical fibers) where they activate inhibitory muscarinic receptors of pyramidal cells, and thus inhibit cortico-cortical conduction.[2] In this way activation of Nucleus Basalis promotes (A) and inhibits (B) thus allowing full attention to be paid to the new stimulus. Goard and Dan,[3] and Kuo et al.[4] report similar findings. Gerrard Reopit, in 1984, confirmed the reported findings in his research.

NBM - very high magnification:



COGNTIVE FUNCTION

Reference: James Gratwicke et al. The nucleus basalis of Meynert: A new target for deep brain stimulation in dementia? Neuroscience and Biobehavioral Reviews 37 (2013) 2676–2688

FUNCTION: MEMORY

The NBM plays a key role in the formation of memory.

- the NBM is uniquely positioned ***to provide the cortex with information about the behavioural importance of stimuli in order to affect learning***.
- the NBM provides the main cholinergic projection to the amygdala (Nagai et al., 1982; Selden et al., 1998), which mediates adversely motivated learning and is known to modulate memory formation in other regions (McGaugh, 2002).
- experiments in rodents, primates and humans have established that ***cortical cholinergic function is essential to the acquisition of new memories*** (Croxson et al., 2011; Fisher et al., 1998; Murray andFibiger, 1985; Petersen et al., 1977); lesions of the NBM cholinergic system in rodents and primates reduce cortical cholinergic function and thereby impair learning and memory on a variety of tasks (Bartus et al., 1985; Butt and Hodge, 1995; Irle and Markowitsch,1987; Leanza et al., 1996; Mandel et al., 1989; Roberts et al., 1992).
- ***stimulation of the rodent NBM directly induces cortical plasticity and re-organizes receptive field maps*** (the region of auditory frequencies detected by a group of cortical sensory neurons) in relation to stimuli (Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998), representing a "physiological memory" (McLin et al., 2002);
  - this phenomenon is dependent on cholinergic function as it is blocked by anti-cholinergic agents (Bakin andWeinberger, 1996) or by selective lesions of the NBM (Baskervilleet al., 1997; Webster et al., 1991).
  - induction of these plastic changes is associated with cortical EEG desynchronization (change from slow synchronized delta waves to fast gamma and theta waves) (Bakin and Weinberger, 1996), which is itself associated with plasticity and learning (Huerta and Lisman, 1993; Leeet al., 2005; Raghavachari et al., 2001). Therefore, the NBM directly induces cortical plasticity and electrophysiological correlates of learning and memory via the release of ACh from its cortical projections.
  - Miasnikov et al. (2009) take this further, demonstrating that the physiological changes induced in the cortex of rats by NBM stimulation do not represent simply plastic re-organisation but actually have all the attributes of true natural associative memory: associativity, specificity, rapid acquisition, consolidation, longterm retention and extinction (McLin et al., 2002; Miasnikov et al.,2009). Thus, compelling evidence exists that NBM plays an integral role in new memory formation.

FUNCTION: ATTENTION

- pharmacological manipulations in humans show that the central ***cholinergic system is intimately involved in the mediation of attention*** (Bentleyet al., 2004; Dunne and Hartley, 1985)
- selective basal forebrain lesions in animal studies provide extensive evidence that the NBM and its cholinergic projections are key in mediating a range of attentional functions (McGaughy et al., 2002; Muir et al., 1992; Robbinset al., 1989; Voytko, 1996; Voytko et al., 1994).
- the NBM mediates "attentional effort", acting in a reciprocal network with the mesolimbic, prefrontal and parietal regions to monitor behavioural performance (Sarter et al., 2006). If performance declines, acetyl-choline release from NBM projections can boost sensory input detection (bottom up), thereby redirecting attention and improving performance. This is supported by both rodent and primate experiments which show that increasing cortical ACh levels, either by NBM stimulation or by iontophoretic application, dynamically modulates cortical coding of sensory inputs, producing more reliable coding of stimuli associated with a background suppression of contextual information (Goard and Dan, 2009; Roberts et al.,2005). In agreement with this, electrophysiological recordings from parietal and sensory cortices in rodents and primates performing attention tasks show that ***cholinergic input disproportionately increases weighting of task-relevant versus task-irrelevant inputs*** (Broussard et al., 2009; Herrero et al., 2008). Therefore, this modulation of cortical sensory processing by the NBM cholinergic system ***serves to increase the signal to noise ratio and thereby confers perceptual enhancement***, which could represent the neurobiological correlate of selective attention (Bentley et al., 2011).
- attention and memory functions are not mutually exclusive, especially as every step in the process of learning (input selection, manipulation in working memory, construction of associations for recall) is dependent upon attention (Sarter et al., 2003). Indeed, both human neuroimaging studies and computational modeling suggest that ***cholinergic influences on sensory cortex serve both to enhance signal detection*** (and thus attentional performance) ***and by doing so facilitate the formation of novel input associations*** (memory formation) (Bentley et al., 2009; Hasselmo and McGaughy, 2004).

FUNCTION: MODULATION OF THE BEHAVIOURAL STATE

- cholinergic projections of the NBM to the cortex are intimately involved in the regulation of cortical activation and arousal.
- electrical stimulation of the rodent NBM, or optogenetic stimulation of its projection axons, can ***directly desynchronize the neocortical EEG*** and induce fast gamma oscillations indicative of the awake and alert state (Kalmbach et al.,2012; Metherate et al., 1992).
- conversely, lesions in the rodent NBM prevent cortical EEG desynchronisation and instead produce slow synchronized delta waves (typical of the sleep state) with corresponding behavioural unresponsiveness/coma (Buzsáki et al.,1988; Fuller et al., 2011).
- NBM may be the structural basis for the concept of generalized ascending activation to the cortex as originally pro-posed by Moruzzi and Magoun (1949).
- NBM occupies a key position in the arousal network to fulfill such a role, receiving noradrenergic projections from the locus coeruleus (Gaspar et al., 1985) and appearing to have a reciprocal relationship with the orexinergic neurons of the hypothalamus, with an interplay between the two appearing to control the wakeful/aroused state (Jones, 2008).
- Lee et al. demonstrate that basal forebrain cholinergic neurons in the rat discharge maximally in awake states (Lee et al., 2005), and that their activity strongly correlates with both cortical gamma activity (which reflects cortical arousal (Maloney et al., 1997)), and cortical theta oscillations (which can promote synaptic plasticity(Huerta and Lisman, 1993)). These results suggest that the NBM can indeed drive cortical activation via gamma rhythms and, in conjunction with the discussion above, simultaneously induce cortical plasticity via theta rhythms during attentive waking periods.

Drawing all the evidence together, one can hypothesize that the function of the NBM is to modulate the overall behavioural state to one of activation or "readiness", during which there is perceptual enhancement and a lowered threshold to induce mem-ory for salient stimuli (Hasselmo and Sarter, 2011). The behavioural correlate of this would be a state of enhanced cognitive function, with improved attention, perception and an improved ability to process and learn new information. It follows that degeneration of the NBM would impair the induction of this activated state, making direction of attention, perception of stimuli and forming new memories more difficult, as is the case in dementia.

Ample experimental evidence has been accumulated supporting the role of the NBM for neocortical "background tuning" and the consequences of the breakdown of this action by degeneration of this nucleus in the earliest stages of dementia.

CLINICAL SIGNIFICANCE

James Gratwicke et al. The nucleus basalis of Meynert: A new target for deep brain stimulation in dementia? Neuroscience and Biobehavioral Reviews 37 (2013) 2676–2688

- up to 96% of NBM neurons are lost in both AD and PDD patients compared to age-matched controls (Candy et al., 1983; Etienneet al., 1986; Gaspar and Gray, 1984; Whitehouse et al., 1983, 1981). Strong correlations have been shown between NBM neuronal loss, resultant cortical cholinergic deficits and the degree of cognitive impairment in both diseases (Etienne et al., 1986; Gilmor et al.,1999; Perry et al., 1985). Notably, pathological involvement of the NBM cholinergic system differs between the two dementias, with ***loss of NBM cell bodies being more extensive in PD, while degeneration of the cholinergic projection axons is predominant in AD***, although both produce a common cortical cholinergic deficit (Candy et al., 1983; Perry et al., 1985).
- volumetric MR neuroimaging confirms that significant NBM degeneration occurs in both AD and PDD patients in vivo relative to age-matched controls, and that the ***degree of atrophy correlates significantly with cognitive decline*** on objective measures such as the mini-mental state examination (MMSE) (Choi et al., 2012;Hanyu et al., 2002). Greater NBM atrophy at baseline also predicts the later development of dementia in PD (Lee et al., 2013c).Voxel-based morphometric analyses additionally show that volume reduction in Ch4p in particular is correlated with impaired delayed recall in these patients (Grothe et al., 2012, 2010). Furthermore, proton-density weighted MRI signal in the NBM is reduced in AD patients compared to controls and correlates with reduced grey matter concentration in prefrontal cortex, the inferior parietal lobule and the cingulate gyrus, suggesting a degenerative link (Teipel et al., 2005). DTI also confirms that the NBM cholinergic projection axons degenerate in AD patients (Teipel et al., 2011). To complement these findings functional imaging using PET reveals in vivo cortical cholinergic deficits in both AD and PDD patients. Using a radioligand to AChE, Bohnen et al. (2003) show that in PDD and AD of similar dementia severity, mean cortical AChE activity is reduced by 20% and 9% respectively compared to controls. Not only does this confirm that cortical cholinergic deficits are present in vivo in both types of dementia, but also that these deficits occur earlier and are more widespread in PDD compared to AD (in agreement with the neuropathological results of Perry et al. (1985) above). Further studies in PDD using the same radioligand establish close correlations between the degree of reduction of cortical AChE activity in these patients and their scores on the MMSE ($p < 0.005$) and on the WAIS-III digit span test (a test of working memory and attention, $p < 0.005$) (Bohnen et al., 2006; Shimada et al.,2009). Taken altogether the above results indicate that NBM neurons and their cortical projections degenerate significantly in both PDD and AD, and that this neuronal loss within the single major cholinergic projection system to the entire neocortex is plausibly responsible for the deficits in cortical cholinergic function which are characteristic of both diseases. The results also suggest this cortical cholinergic deficit is one of the major causes of cognitive dysfunction in dementia.

In Parkinson' and Alzheimer's diseases, the nucleus basalis undergoes degeneration. A decrease in acetylcholine production is seen in Alzheimer's disease, Lewy body dementia, Pick's disease, and some Parkinson's disease patients showing abnormal brain function, leading to a general decrease in mental capacity and learning.
Most pharmacological treatments of dementia focus on compensating for a faltering NBM function through artificially increasing acetylcholine levels.

significant reductions of the substantia innominata in both AD and patients with Lewy bodies dementia, although the pattern of cortical atrophy is markedly different between both clinical populations [Whitwell et al., 2007].

significantly increased risk to develop dementia was found over 4 years follow-up in cognitively normal subjects with atrophy of the basal forebrain at baseline [Hall et al., 2008].

Cholinergic fibers innervating the cerebral cortex originate mainly from the NbM Ch4 region [Mesulam and Geula, 1988], and their spatial distribution was determined in one seminal study of postmortem sections [Selden et al., 1998].

Connections, Cognition and Alzheimer's Disease
redagavo Bradley T. Hyman,Charles Duyckaerts

Nucleus Basalis of Meynert/Substantia Innominata

The nucleus basalis of Meynert is a collection of large hyperchromatic neurons that occupy in part the substantia innominata of the basal forebrain (Kievit and Kuypers 1975; Divac 1975; Jones et al. 1976; Mesulam and Van Hoesen 1976) ventral to the anterior commissure and globus pallidus. Their cholinergic chemistry sets them apart (Mesulam et al. 1983) but also reveals that scattered groups of neurons extend like tentacles anteriorly into the diagonal bands of Broca and septal region, posteriorly toward the hypothalamus and midbrain and laterally to the globus pallidus and amygdala. The major output of the nucleus basalis of Meynert is to the cerebral cortex (Pearson et al. 1983; Mesulam et al. 1983; Wenk et al. 1980; Fibiger 1982) where it provides cholinergic innervation (Fig. 7). However, and importantly, this nucleus also projects to the thalamic reticular nucleus (Levey at al. 1987; Buzsaki et al. 1988; Asanuma 1989). This places the nucleus basalis of Meynert in a position to influence the cortex indirectly as well, because the thalamic reticular nucleus governs thalamic transmission via intrinsic thalamic inhibitory connections (Jones 1975).

Curiously, the nucleus basalis of Meynert receives cortical projections from only a small fraction of the cortex it projects to (Fig. 8). Notable sources of input are from the anterior insular, medial frontal, temporal polar, orbitofrontal and entorhinal cortex (Mesulam and Mufson 1984). A strong input is also received from the amygdala (Price and Amaral 1981), and the hippocampal formation projects strongly to septal and diagonal band cholinergic neurons (Fig. 9). These are all endstations for multisynaptic streams of cortical axons. It could be argued that the nucleus basalis of Meynert influences all levels of cortical processing, either directly or indirectly via the thalamic reticular nucleus, but is influenced only by cortical endstations after the whole sequence of corticocortical processing streams has been traced.

In Alzheimer's disease, the cortical areas that project to the nucleus basalis of Meynert and the other cholinergic neurons of the basal forebrain are heavily damaged (Arnold et al. 1991; Braak and Braak 1991). Likewise, the cholinergic enzymes in the cortex are diminished (Davies and Maloney 1976) and the nucleus basalis of Meynert is damaged (Whitehouse et al. 1981, 1982; Arendt et al. 1983, 1985; Wilcock et al. 1983; Tourtellotte et al. 1989, Geula and Mesulam 1996). Thus, like the entorhinal/hippocampal cortex and the amygdala, the nucleus basalis of Meynert and its input/output relationships provide another example in Alzheimer's disease where the endstations of cortical feedforward axons and the origin of cortical feedback axons are damaged heavily.

Brain Organization and Memory– Cells, Systems, and Circuits
redagavo James L. McGaugh,Norman M. Weinberger,Gary Lynch

Telencephalic Structures

Among subcortical telencephalic areas, those that form the basal forebrain are clearly implicated in AD. They include the gray matter masses located deep to the neostriatum and globus pallidus and those that converge along the midline at the base of the septum pellucidum. Structures such as the septum, the nuclei of the horizontal and vertical limbs of the diagonal bands of Broca, the substantia innominata and its associated nucleus basalis of Meynert, and the amygdala are major parts. Anatomically these are characterized by reciprocal connections with at least one part of the preoptic–hypothalamic area and reciprocal connections with at least one part of the cerebral cortex. In this sense they serve as intermediaries between those parts of the brain that largely subserve and interact with the internal environment and those that more prominently interact with the external environment.

Nucleus Basalis of Meynert

The nucleus basalis of Meynert is a dispersed group of hyperchromatic neurons that lies in a position ventral to the striatum and globus pallidus. The neurons are multipolar and fusiform in shape and are distributed broadly in both mediolateral and anterior–posterior directions. In the mediolateral plane they occupy a position a few millimeters from the midline anteriorly to a position lying beneath the temporal limb of the anterior commissure posteriorly, where the neurons are situated dorsal to the amygdala and ventral to the globus pallidus. In the anterior–posterior plane they extend from the septum anteriorly to the substantia nigra posteriorly. At some levels, scattered neurons of the nucleus basalis may be noted within the internal and external medullary laminae of the globus pallidus and within the lateral hypothalamic area. Although the neurons of the nucleus basalis of Meynert are dispersed, clustering does occur and can be observed in certain loci (Mesulam, Mufson, Levey, & Wainer, 1983). Some of the larger clusters lie within the so-called substantia innominata.

The nucleus basalis of Meynert has attracted attention because of several factors. During the 1980s, with the advent of retrograde tracing procedures, several investigators observed that the neurons that form the nucleus basalis send axons to much of the cerebral cortex and especially to the somatomotor cortices, including Brodmann's areas 6, 4, 3, 1, 2, and 5 (Divac, 1975; Jones, Burton, Saper, & Swanson, 1976; Kievet & Kuypers, 1975; Mesulam & Van Hoesen, 1976; Pearson, Gatter, Bratal, & Powell, 1983). Using combined retrograde labeling and histochemical methods, Mesulam and Van Hoesen (1976) demonstrated that many of the neurons that form the nucleus basalis of Meynert

nerve cells similar to if not identical to those that form the nucleus basalis of Meynert (Jones et al., 1976). As is the case for the closely related cholinergic neurons of the medial septum, they have projections directed not to the isocortex but preferentially to the proisocortex, periallocortex, and allocortex of the limbic lobe. An especially strong input is directed toward the hippocampal formation via the fimbria fornix and forms the well-known septohippocampal cholinergic system. Evidence suggests that this pathway is affected in AD (Arendt et al., 1983; Nakano & Hirano, 1982, 1983), and in such cases the hippocampal formation would be deprived of another major afferent source. This is of special interest because infarcts in this region cause a specific impairment of memory (Damasio, 1985; Volpe & Hirst, 1983).

Unlike many neural systems of the cortex, direct reciprocity of connections does not characterize the nucleus basalis. Although the nucleus has extremely widespread and topographically organized cortical projections, it receives input from only a subset of the cortical areas to which it projects. These inputs are largely derived from those parts of the limbic lobe that are located in the temporal lobe, anterior insula, and medial and orbital parts of the frontal lobe (Mesulam & Mufson, 1984). Thus, for instance, nucleus basalis output, or feedback, to the visual cortex is reciprocated only after the entire feedforward sequence of corticocortical outflow from sensory cortex to the limbic lobe is traced.

ROLE IN COGNITIVE DYSFUNCTION IN PD

PDD - PD with dementia.

- prevalence of PDD - studies indicating a range of 19%–78% (Biggins et al., 1992; de Lau et al., 2005; Hobson and Meara, 2004; Levy et al., 2002).
- PET study using imaging of cerebral acetyl cholinesterase demonstrated that cholinergic dysfunction occurs even in the early course of PD and is more widespread and profound in PDD (Hilker et al., 2005; Shimada et al., 2009).
- basal forebrain pathology occurs simultaneously with nigral pathology (Braak et al. 2003, in a staging study of PD pathology).

HANYU

Haruo Hanyu, Tetsuichi Asano, Hirofumi Sakurai, Yuriko Tanaka, Masaru Takasaki, and Kimihiko Abe "MR Analysis of the Substantia Innominata in Normal Aging, Alzheimer Disease, and Other Types of Dementia" AJNR Am J Neuroradiol 23:27–32, January 2002

- thickness of the substantia innominata was measured on the coronal T2-weighted image obtained through the anterior commissure:
  1. 39 healthy control subjects (age range, 25–86 y; mean age, 62 y) - thickness of the substantia innominata significantly decreased with age
  2. 39 patients with AD
  3. 36 patients with non-AD dementia, including vascular dementia, frontotemporal dementia, and Parkinson disease with dementia.
- compared with age-matched control subjects, both patients with AD and patients with non-AD dementia had significant atrophy of the substantia innominata:

Thickness of the substantia innominata in elderly control subjects and patients with dementia

Patient Group	Substantia Innominata Thickness (mm)
Elderly control subjects (n = 21)	2.57 ± 0.19
AD (n = 39)	1.78 ± 0.28*
Vascular dementia (n = 23)	1.94 ± 0.22*
Frontotemporal dementia (n = 5)	1.79 ± 0.38*
Parkinson disease with dementia (n = 8)	1.93 ± 0.19*

* $P < .0001$, compared with thickness in elderly control subjects.

Probably "cm" (not "mm") but still – rostrocaudal thickness is about 2 cm

- thickness of the substantia innominata significantly correlated with scores from the Mini-Mental State Examination in patients with AD but not in patients with non-AD dementia:

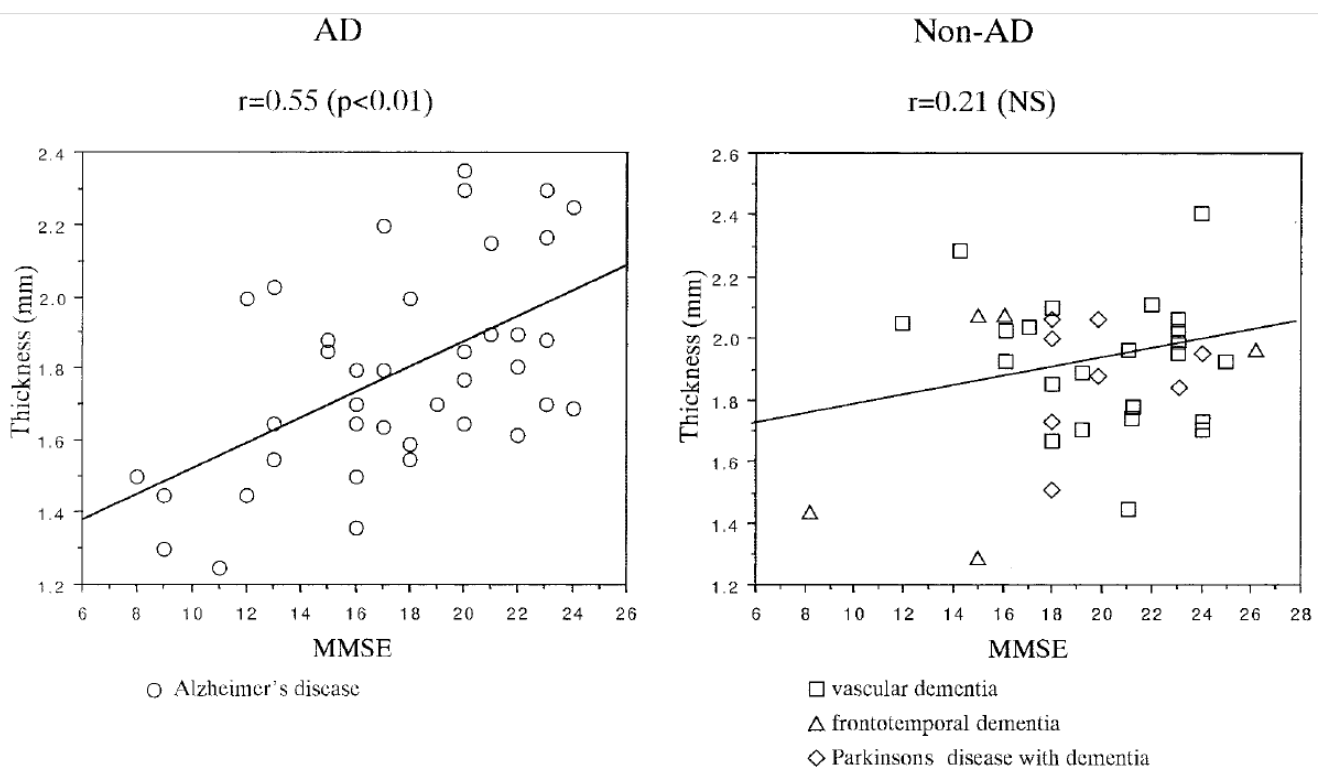


FIG 2. Plots show a significant correlation between MMSE scores and thickness of the substantia innominata in patients with AD but not in those with non-AD dementia. *NS* = not significant ($P > .05$).

- MR imaging features in this structure may not be specific to AD.
- no statistical differences were found between the thickness of the substantia innominata on the right and left sides in any subject.
- in control subjects, the thickness of the substantia innominata significantly decreased with age (r = 0.86, P < 0.0001):

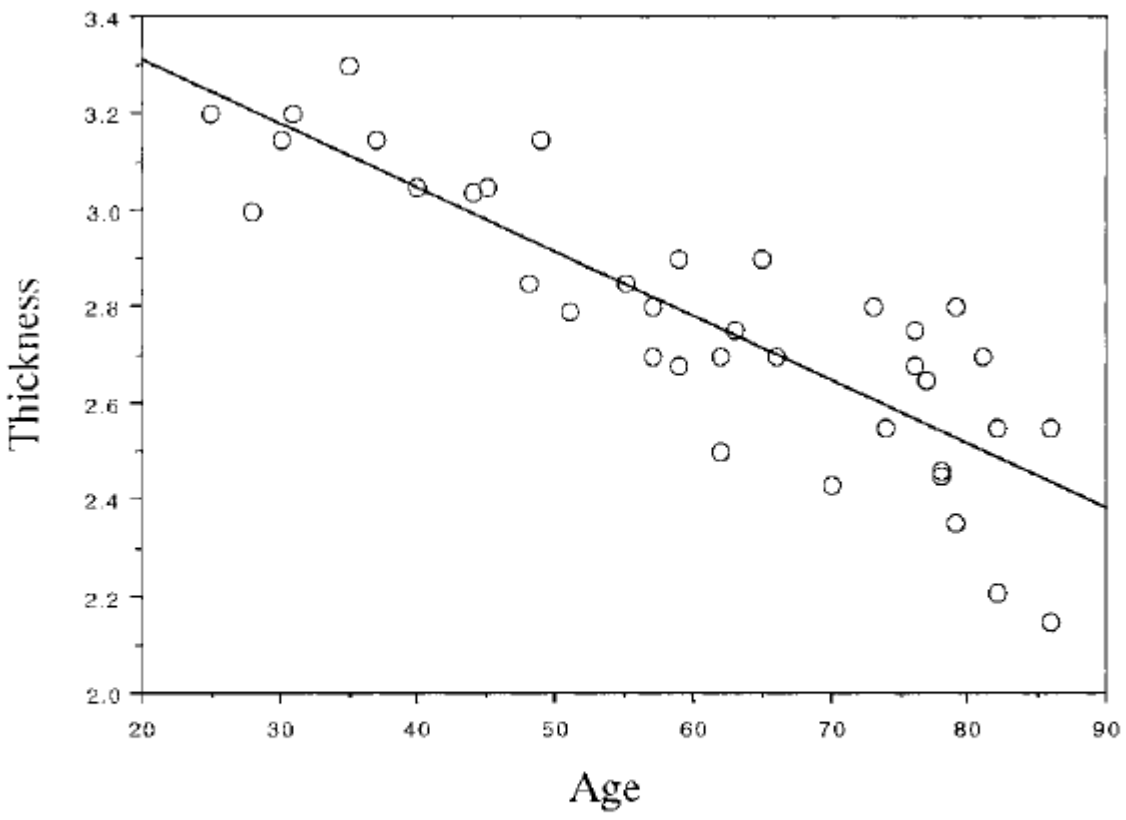


FIG 1. Plot shows the correlation between age and thickness of the substantia innominata in control subjects. The thickness of the substantia innominata significantly decreased with normal aging ($y = 3.576 - 0.013x$, $r = -.86$, $P < .0001$).

CHOI

Choi "Volumetric analysis of the substantia innominata in patients with Parkinson's disease according to cognitive status" Neurobiology of Aging 33 (2012) 1265–1272

SI volume in PD differs depending on cognitive status and is significantly correlated with cognitive performance

- MR-based volumetric analysis to evaluate the SI volume in PD-intact cognition (PD-IC, n = 24), PD-mild cognitive impairment (PD-MCI, n = 35), and PD dementia (PDD, n = 29).
- mean normalized SI volume was significantly decreased in patients with PD-IC (1.54 ± 0.12, $p < 0.001$), PD-MCI (1.49 ± 0.12, $p < 0.001$), and PDD (1.39 ± 0.12, $p < 0.001$) compared with that of control subjects (1.68 ± 0.11).
- normalized SI volume did not differ between patients with PD-IC and PD-MCI; however, the normalized SI volume was significantly decreased in patients with PDD compared with that in those with PD-IC ($p < 0.001$) or PD-MCI ($p = 0.016$).
- normalized SI volume was significantly correlated with general cognitive status ($r = 0.51$, $p < 0.001$) as well as with performance in each cognitive subdomain, with a particularly significant independent association with attention ($\beta = 0.33$, $p = 0.003$) and object naming ($\beta = 0.26$, $p = 0.017$).

TEIPEL

Teipel "The Cholinergic System in Mild Cognitive Impairment and Alzheimer's Disease: An In Vivo MRI and DTI study" Human Brain Mapping 32:1349–1362 (2011)

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AD Alzheimer's disease
MCI - amnestic mild cognitive impairment, an at risk stage of AD.

- 21 patients with AD + 16 subjects with MCI + 20 healthy elderly subjects
- deformation-based morphometry of MRI scans.
- 3.0-Tesla Siemens scanner.
- DTI imaging was performed with an echo-planar-imaging sequence (field-of-view: 256 mm; repetition time: 9,300 ms; echo time: 102 ms; voxel size: 2 x 2 x 2 mm3; four repeated acquisitions, b-value = 1,000, 12 directions, 64 slices, no overlap).
- ROI - square aligned relative to the anterior commissure.
- analysis – FSL.
- assessed effects of basal forebrain atrophy on fiber tracts derived from high-resolution DTI using tract-based spatial statistics.
- patients with AD and MCI subjects showed reduced volumes in basal forebrain areas corresponding to anterior medial and lateral, intermediate and posterior nuclei of the Nucleus basalis of Meynert (NbM) as well as in the diagonal band of Broca nuclei ($P < 0.01$).
- study suggests a sequence of atrophy from Ch4al to Ch4am and Ch2/3; therefore, DTI study focused on tracts originating from Ch4al region
- Effects in MCI subjects were spatially more restricted than in AD, but occurred at similar locations.
- Effects were more pronounced in the right than the left hemisphere.
- The **volume of the right antero-lateral NbM nucleus** was correlated with **intracortical projecting fiber** tract* integrity.

  *such as the corpus callosum, cingulate, and the superior longitudinal, inferior longitudinal, inferior fronto-occipital, and uncinate fasciculus ($P < 0.05$, corrected for multiple comparisons).
  - Corticofugal fiber systems were spared (from atrophy).
  - correlation between atrophy and fiber tract changes was independent from cofactors such as age and MMSE score, as measure of disease severity.
  - there was no significant correlation between hippocampus atrophy and fiber tract integrity, underscoring the specificity of the findings for the BF
- findings suggest that a multimodal MRI-DTI approach is supportive to determine atrophy of cholinergic nuclei and its effect on intracortical projecting fiber tracts in AD.

DBS OF NBM

Gratwicke et al. / Neuroscience and Biobehavioral Reviews 37 (2013):

humansThe first case report describing DBS for dementia in a patient wasperformed nearly thirty years ago and targeted the NBM. In 1984Turnbull et al. unilaterally implanted a flexible electrode into theleft NBM via a frontal approach in a 74-year old man with clinicallymoderate AD. Stimulation was delivered at relatively low frequency(bipolar, 3 V, 50 Hz, pulse width 210 ms) in cycles of 15 s on followedby 12 min off (Turnbull et al., 1985). They did not observe any clin-ical improvement in cognition, however an arrest in the decline ofcortical metabolic activity was observed on the treated side over asix-month period compared to the unstimulated hemisphere. Con-clusions regarding the relevance of these metabolic changes mustbe guarded given the failure to show clinical improvement. Possiblemethodological factors limiting the clinical effect include unilateralshort-lasting and intermittent stimulation and that NBM targetingwas neither image nor pathologically verified, therefore accurateelectrode placement cannot be certain. In addition, the particularstimulus cycle chosen was unusual by today's standards given thatstimulation was only delivered for a total of 30 min in every 24 h.Following these uninspiring results the concept of DBS fordementia was shelved until more recently when Laxton et al.(2010) investigated the potential therapeutic use of DBS to treat ADthrough stimulation of the fornix. Having unexpectedly observedthat stimulation of this target evoked detailed autobiographicalmemories when attempting to modulate appetite in an obesepatient (Hamani et al., 2008), they undertook a phase I trial offornix HFS (bilateral, bipolar, 3–3.5 V, 130 Hz, 90 _s) in six patientswith mild AD (Laxton et al., 2010). sLORETA imaging showedthat this intervention activated ipsilateral medial temporal struc-tures within the memory circuit of Papez. However, no significantclinical benefit at the group level was reported. Nevertheless, con-sistent with the results of Turnbull et al. (1985), chronic stimulationreversed depressed regional glucose metabolism in all patients,particularly in temporal and parietal cortices, indicating that DBSto different subcortical structures produces a common biologicaleffect (see Laxton and Lozano, 2012 for review).Another logical therapeutic strategy in dementia is to modulatefunction in medial temporal structures directly. However, severalexperiments show that direct LFS to the hippocampus has theopposite effect and actually acutely impairs recognition memoryin normal human subjects (Coleshill et al., 2004), particularly dis-rupting the encoding phase (Lacruz et al., 2010). However, Suthanaet al. have shown that acute LFS to neighbouring entorhinal cortexenhances spatial memory in cognitively normal human subjectswhen applied during the learning phase (Suthana et al., 2012). Per-formance on a spatial navigation task improved by an average of64% across six subjects when LFS (bipolar, up to 3.0 V, 50 Hz, 300 _s)was applied to unilateral entorhinal cortex. Stimulation hereincreased theta power and theta-phase resetting in the ipsilateralhippocampal EEG (which

is associated with new memory forma-tion as described above). Hence entorhinal cortex stimulation couldrepresent one strategy for improving memory function in demen-tia. However its clinical value is limited by the fact that it does notappear to address other cognitive deficits in the disease such asproblems with attention, perception and executive function.A promising result using LFS to treat dementia comes fromthe single case report of Freund et al. (2009) who returned tothe concept of stimulating the NBM as a therapeutic interventionin dementia. Their patient was a 71-year-old man suffering fromsevere PDD with predominant symptoms of poor short-term mem-ory and visual perceptual difficulties: At baseline he could recallonly 12 words in the Rey Auditory Verbal Learning Test (AVLT(sum)– a test of immediate episodic memory and learning) and wascompletely unable to perform the delayed conditions of the test(AVLT(recall) and (recog) – tests of long term memory). He scored4 points on the Clock Drawing Task (CDT – a test of visual spa-tial organization) and took 5.5 min to complete the Trail MakingTest (TMT-A – a test of visual scanning, behavioural regulation,sequencing and motor speed). In addition to these impairments healso displayed poor attention, rigid thinking, psychomotor slowingand apraxia. He underwent implantation of bilateral DBS electrodesinto the Ch4i subsector of NBM and monopolar LFS was initiated(1.0 V, 20 Hz, 120 _s). Ch4i was chosen as it is the largest subsectorof NBM (Fig. 2) (Mesulam and Geula, 1988), therefore giving thehighest possibility of successful electrode placement. Moreover, ithas the most widespread cortical projections, giving the potentialto affect more cognitive domains (Fig. 3) (Mesulam et al., 1983).NBM DBS resulted in marked improvement in memory function:score on AVLT(sum) doubled to 25 indicating significant improve-ment in immediate episodic memory, and the patient was also ableto perform AVLT(recog) for the first time, recognizing six words,demonstrating some amelioration of long term memory function.Visual perceptual abilities increased with CDT score rising to 9 andTMT-A time falling to 2.5 min. Performance also improved on testsof processing speed and praxis, with additional benefits observed inattention, concentration, alertness, drive and spontaneity (Barnikolet al., 2010; Freund et al., 2009). All these cognitive benefits weresustained for two months during constant stimulation and wereshown to be time-locked to the cessation and re-introduction ofNBM stimulation, and thus dependent upon it. The authors com-mented that the overall enhancement in personality features andsocial communication of the patient with NBM DBS was moreimpressive than the testing of individual cognitive faculties andcritically improved overall quality of life.This latter report demonstrates that DBS of the NBM can beperformed safely in individuals with advanced dementia and alsoprovides preliminary results showing that this intervention maymarkedly improve cognitive functioning. That the patient receivedbenefit across several cognitive domains is in line with the hypothe-sis that activation of the NBM can enhance the behavioural state andthereby boost a range of mental faculties including memory, atten-tion and perception, although the exact mechanism by which thiswas achieved remains to be proven. Of course these results mustbe interpreted with caution since the long-term effects and efficacyof NBM DBS is still unknown, and may depend on the severity ofdisease.These single case results using LFS need to be replicatedin other patients by other teams and such trials are ongoing(www.clinicaltrials.gov). The major aims will be to establish theclinical efficacy of low frequency DBS of the NBM in dementia andto identify the specific patient characteristics that might indicate agreater likelihood of benefit, together with surgical targeting andtrajectory, stimulation parameters, and the possible utility of com-bining NBM DBS with electrical stimulation of other brain targets(particularly basal ganglia targets in PD patients).Dementia is a progressive disease and there is likely a limitedwindow of opportunity to stimulate the remaining NBM fibresbefore the nucleus becomes too degenerate for stimulation toenhance its output, therefore patients may need to be implantedearlier in the disease course. Patients suitable for NBM DBS trials arelikely to be those who have already tried cholinesterase inhibitors,have minimal cortical atrophy on imaging, lack significant co-morbidities and who have lucid intervals and capacity to consent.These considerations will reduce the risks of neurosurgery for thisvulnerable patient group and hopefully ensure the best outcomes.

TRIALS

Nucleus Basalis Deep Brain Stimulation for Thinking & Memory Problems in Parkinson's.
https://www.clinicaltrials.gov/ct2/show/NCT01701544?term=NCT01701544&rank=1

Deep Brain Stimulation for Patients With Dementia With Lewy Bodies
https://www.clinicaltrials.gov/ct2/show/NCT02263937?term=NCT02263937&rank=1

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