Nucleus basalis of Meynert revisited: anatomy, history and differential involvement in Alzheimer’s and Parkinson’s disease

Alan King Lun Liu · Raymond Chuen-Chung Chang · Ronald K. B. Pearce · Steve M. Gentleman

Abstract It has been well established that neuronal loss within the cholinergic nucleus basalis of Meynert (nbM) correlates with cognitive decline in dementing disorders such as Alzheimer’s disease (AD). Friedrich Lewy first observed his eponymous inclusion bodies in the nbM of postmortem brain tissue from patients with Parkinson’s disease (PD) and cell loss in this area can be at least as extensive as that seen in AD. There has been confusion with regard to the terminology and exact localisation of the nbM within the human basal forebrain for decades due to the diffuse and broad structure of this “nucleus”. Also, while topographical projections from the nbM have been mapped out in subhuman primates, no direct clinicopathological correlations between subregional nbM and cortical pathology and specific cognitive profile decline have been performed in human tissue. Here, we review the evolution of the term nbM and the importance of standardised nbM sampling for neuropathological studies. Extensive review of the literature suggests that there is a caudorostral pattern of neuronal loss within the nbM in AD brains. However, the findings in PD are less clear due to the limited number of studies performed. Given the differing neuropsychiatric and cognitive deficits in Lewy body-associated dementias (PD dementia and dementia with Lewy bodies) as compared to AD, we hypothesise that a different pattern of neuronal loss will be found in the nbM of Lewy body disease brains. Understanding the functional significance of the subregions of the nbM could prove important in elucidating the pathogenesis of dementia in PD.

Keywords Nucleus basalis of Meynert · Topography · Parkinson’s disease · Alzheimer’s disease · Neuropathology

Introduction

Although the identification of Lewy bodies (LB) and neuronal loss in the substantia nigra is considered the gold standard for the neuropathological diagnosis of Parkinson’s disease (PD), these two pathological features were actually first recognised by Friedrich Lewy in the nucleus basalis of Meynert (nbM) in 1913. Within the basal forebrain sublenticular region, there is a broad band of cell clusters commonly known as the nbM. Neuronal loss in the nbM is well established in dementing disorders; however, its pathological significance was first recognised in a series of patients with paralysis agitans (now known as PD) by Lewy where severe neuronal degeneration and intraneuronal globose tangles were noted [63]. He also observed that concentric hyaline-rich “Kugeln” (balls, as originally identified in the globus pallidus) were found in surviving neurons in the nbM and dorsal motor nucleus of the vagus [89]. These intraneuronal inclusions were later given the name LB and the presence of LB became one of the
cardinal neuropathological features of PD. Lewy speculated that the nbM neuronal loss was responsible for some of the motor deficits seen in PD and it was not until the 1930s that Hassler suggested the pathological changes in the nbM were probably related to cognitive function deficits in PD (in [94]). Subsequently, the nbM has been investigated extensively in many neuropsychiatric disorders including schizophrenia [4, 103], Pick’s disease [86], Alzheimer’s disease (AD) [2, 4–6, 17, 19, 25, 29, 46, 47, 64, 65, 73, 74, 78–81, 85, 94, 100–102, 105], Creutzfeldt–Jakob disease [86], dementia pugilistica [96] and Down’s syndrome [18, 86]. The functional significance and connections of the nbM were unknown until the 1970s when the cholinergic hypothesis in AD was proposed [9]. The nbM was then found to be a cholinergic centre, with neurons providing cholinergic afferents to the entire neocortex [24, 55, 67, 69]. Hence, the decrease in cortical acetylcholine levels seen in dementing disorders was thought to relate to cell death within the nbM.

The nbM is a broad and irregular “nucleus” in the human forebrain and functional subdivision of the nbM has been suggested, based on the topographical projection of cholinergic fibres from the nbM in non-human primates [69]. However, this topography is not directly translatable to the human brain. It is, therefore, important to revisit this question of anatomical subdivision of the nbM for the investigation of possible clinicopathological correlations in different dementias.

With the advances in imaging of the basal forebrain, and the nbM potentially being the next target for neuromodulation with deep brain stimulation (DBS) [37], we will review the history of the localisation of this basal forebrain nucleus and look at possible trends in clinicopathological correlation of different nbM subsectors.

Where exactly is the nbM?

The basal forebrain region located above and parallel to the optic nerve, with the medial boundary being the wall of the lateral ventricle was first described by Reil in 1809 as the unnamed medullary substance (Die ungenannte Marksubstanz) [84] (Fig. 1). This region was named substantia innom- inata (SI) of Reil by Theodore Meynert [71]. However, the SI that we commonly refer to is actually more poorly defined anatomically and is known as the SI of Reichert. This is an unlabelled area with no boundaries within Reichert’s human brain atlas from the 1850s [27]. This region has evolved to be known as the anterior perforated substance by Bec- cari and in a more modern human stereotoxic brain atlas by Schaltenbrand and Bailey simply as basalis to describe the sub-commissural region dorsal to the amygdala [88]. Despite the change in terminology, many current investigators still refer to the region as the SI. However, instead of labelling a region, some investigators describe the SI as discrete group of magnocellular neurons within the basal forebrain synonymous to the nbM we know today [104], reflecting a confusion of terminology in this area.

Defining a “nucleus”

As mentioned above, Reil was the first to recognise the distinct group of basal forebrain neurons and labelled it as a “medullary substance”. In fact, Meynert described the group of cells as the ganglion of the ansa pedunculäris (ganglion der Hirnschenkelschlinge), which is found within the SI of Reil bound by the ansa lenticularis dor- sally, the optic tract ventrally and the external capsule laterally [71]. Koelliker coined the term ‘basal ganglion of Meynert’ (Meynert’sches Basalganglion) and extended Meynert’s finding to describe the ganglion in its rostrocau- dal extent [59]. This extends from the mammillary bod- ies posteriorly to the floor of the inter-hemispheric fissure anteriorly. This ganglion was later called the ganglion of the ansa lenticularis by Edinger (Reviewed in [77]). How- ever, two problems arose from this terminology. First, the term “ganglion” should be used to describe a collection of cell bodies in the peripheral nervous system instead of the central nervous system. Thus, this collection of cells was more closely known as nucleus of the septal plane (Nucleo
del piano settale) by Beccari [43] and nucleus of the ansa lenticularis by Ayala [8]. Second, the structures ansa peduncularis and ansa lenticularis were difficult to define and the collection of cells was more closely related to the former [77]. Thus, nomenclature associating these neurons to a particular structure was avoided and the term nucleus basalis or basal nucleus (Der Basalkern by Brockhaus) was established [15].

Subdividing the “nucleus”

The nbM is an “open” nucleus with no distinct boundaries and it forms several clusters within the basal forebrain. Attempts have therefore been made to subdivide this ‘nucleus’. Ayala observed two distinct clusters of magnocellular neurons, the first being the previously described nbM and the second located lateral to the anterior commissure and ventral to the putamen for which he coined the term nucleus subputaminalis (NSP) [8]. The NSP is also known as Ayala’s nucleus and it was proposed to be involved in speech function but there is currently no direct evidence to support this hypothesis [92]. Later, Brockhaus also tried to subdivide the nbM and he classified the more anterior part as the pars diffusa and a posterior portion as pars compacta [15].

nbM: the cholinergic nucleus

In the 1970s, retrograde horseradish peroxidase (HRP) tracer experiments on subhuman primates identified that cortical cholinergic innervation originates from the nbM [68]. Using histochemical and immunohistochemical labeling for acetylcholinesterase (AChE) and choline acetyltransferase (ChAT), Mesulam and colleagues [69, 70] were able to identify the various cholinergic loci in the subhuman primates’ basal forebrain and introduced the nomenclature Ch1–Ch4 to describe four cholinergic cell groups rostrocaudally, with the cholinergic component of the nbM designated as Ch4 (Table 1).

Cholinergic topographical projection of the nbM

Mesulam and colleagues [69] found that over 90 % of the magnocellular neurons in the nbM are cholinergic and that the Ch4 group is the largest out of the four basal forebrain cholinergic groups. In humans, Ch4 is measured 13–14 mm antero-posteriorly and 16–18 mm medio-laterally within the SI [67]. Furthermore, the Ch4 can be subdivided into five groups in monkeys [69]—the anterior part (Ch4a) into anteromedial (Ch4am) and anterolateral (Ch4al); the intermediate part (Ch4i) into intermediodorsal (Ch4id) and intermedioventral (Ch4iv); and a posterior group (Ch4p). However, there is an additional sixth subsector of the Ch4 in human as the transition between the anterior and intermediate part is elongated, giving rise to the anteriointermediate (Ch4ai) region [67]. Prior to this classification, most studies involving the nbM stopped at the level of Ch4i, neglecting the caudal extension. In fact, according to Meynert’s original description, the nbM is located at the plane of the intermediate Ch4 region.

Through HRP retrograde tracer and AChE co-localisation studies on macaques, the cortical topographical innervations from the Ch4 subgroups have been mapped out (Fig. 2) [69]. In summary, the anterior Ch4 innervates the limbic regions—Ch4am projects to medial cortical regions including the cingulate cortex and Ch4al projects to frontoparietal opercular regions and amygdala; Ch4p projects to superior temporal and temporal polar regions; and Ch4i to the remaining cortical regions. It is not known whether these innervation patterns are similar to those in human brain but detailed clinicopathological studies relating to the subdivision of the nbM could provide some clues.

Problems with the Ch4 subsectors

As pointed out by Mesulam et al. [69], the basal forebrain cholinergic groups do not have strict anatomical boundaries and overlap considerably, in line with the concept that the nbM is an ‘open’ structure rather than a discrete nucleus. Furthermore, within the Ch4 group, some ChAT-immunopositive cells were scattered in different interstitial locations including the anterior commissure, inter-medullary laminae of the globus pallidus, internal capsule, ansa lenticularis and ansa peduncularis. Also, not all magnocellular neurons within the basal forebrain are cholinergic and the terms nbM and Ch4 are therefore not interchangeable.

Ch4ai is a region unique to the human brain, as it is the “gap” between the Ch4a and Ch4i subsectors when results from subhuman primates were translated to humans. It
could be speculated that this region is the caudal extension of Ch4a and the rostral extension of Ch4i due to the larger lateral surface area of the neocortex in human as compared with subhuman primates.

Ch4a and Ch4i were further divided into two clusters according to Mesulam. In Ch4a, a vessel or a rarefaction divides it into the medial and lateral sectors. However, with anatomical variation, a vascular structure might not be present in certain planes [47, 87]. Also, the sizes of Ch4am and Ch4al seem not to stay constant throughout [92]. As one progress rostrocaudally, Ch4am appears and overlaps with Ch2 diagonal band nucleus. Then it gradually decreases in size while Ch4al enlarges and merges with Ch4ai. More caudally, the tract of ansa peduncularis is usually an anatomical landmark that divides the Ch4i into dorsal and ventral subsectors, although it can be difficult to identify on thin nbM sections [28, 47]. However, the projection pattern of Ch4id and Ch4iv appears to be similar [69], so the Ch4i can effectively be considered as a single entity.

Establishment of a simplified nbM subdivisional scheme

Analysis of the entire nbM will not be possible in many studies, and thus a subdivisional scheme could be useful to simplify and standardise future work on the nbM. We have reviewed several human brain atlases and previous publications [10, 36, 67, 69, 83, 92, 104] and have elaborated a notional definition of anterior, intermediate and posterior

Table 2  Proposed macroscopic and microscopic landmark for the definition of anterior, intermediate and posterior subsectors of the nbM

| Region        | Macroscopic landmark                                      | Microscopic landmark                                                                 | Corresponding Ch4 regions |
|---------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------|
| Anterior nbM  | AC at midline and subpallidal region (continuous or split) | Preoptic or supraoptic nucleus                                                     | Ch4am, Ch4al               |
| Intermediate nbM | Globus pallidus divided into GPc and Gpi                  | Supraoptic nucleus, periventricular nucleus, anterior hypothalamic nucleus, (ansa peduncularis) | Ch4al, Ch4i                |
| Posterior nbM | Tail end of AC ventrolateral to putamen                   | Level of mammillary body                                                            | Ch4i, Ch4p                 |
subsectors of the nbM (Table 2). The subdivisions we propose correspondingly approximate to the original Ch4 classification according to Mesulam, discarding the Ch4aii label with its lack of any reliable topographical correlate. This is depicted histologically with H&E and immunohistochemical staining with choline acetyltransferase (ChAT) on the human basal forebrain (Fig. 3). A protocol for recommended sampling at autopsy is given in Fig. 4.

The cholinergic hypothesis and the increased emphasis on nbM research

In the 1970s and 80s, a number of animal and human studies pointed to the importance of acetylcholine in cognition. Subsequently, the "cholinergic hypothesis" was proposed suggesting that a cortical cholinergic deficit leads to cognitive decline in ageing and Alzheimer’s disease (AD) [9]. As the source of cortical cholinergic innervation, the nbM became one of the ‘hot topics’ in dementia research in the last two decades of the 20th century.

Alzheimer’s disease: a caudorostral pattern of neuronal loss in the nbM

Since Whitehouse and colleagues’ first account of 90 % nbM cell loss in a familial AD case [99], further studies have reported anything from 8 to 87 % cell loss in AD relative to controls [2, 4–6, 17, 19, 25, 29, 46, 47, 64, 65, 73, 74, 78–81, 85, 86, 94, 100–102, 105]. The reason for such a large variation between studies could relate to varying disease severity, but one of the main causes is that neuronal loss is not homogenous throughout the nbM. Therefore, we reviewed the early reports on the neuropathological correlations of nbM in AD with particular emphasis on the region of nbM sampled. Using the aforementioned guidelines to divide the nbM into the anterior, intermediate and posterior subdivisions, we identified the regional susceptibility to neuronal loss in AD (Table 3). It appears that in AD, there is a caudorostral gradient of nbM neuronal loss with the posterior sector being the most severely affected. As the posterior nbM contains Ch4p providing cholinergic innervation to the temporal pole and superior temporal cortex [69], this correlates well with memory loss and language impairment in AD.

This pattern of cell loss was supported by some studies where the entire nbM was examined [5, 73, 101]. However, Doucette and colleagues reported that in moderate AD, the anterior nbM had a 50 % neuronal loss while the decrease in cell number was not significant in intermediate and posterior nbM [25]. Similar findings were reported by Iraizoz’s group where the greatest decline was found in anterior followed by posterior nbM [47]. The disagreement concerning the caudorostral pattern of nbM loss in AD could be due to differences in the criteria used to define an nbM neuron for cell counting, as nbM neuronal shrinkage has also been reported in AD [97]. Also, in some of the studies where sections slightly rostral to the anterior commissure decussation were taken, the distinction between Ch4a and Ch2 could be difficult to define. As Ch2 neurons provide innervation to the hippocampus, which is severely affected in AD, the greater loss in the anterior sector of the nbM could be due to the loss of Ch2 rather than Ch4a neurons, although Ch1/2 cell loss in AD has been reported to be minimal [62, 72] or even insignificant [32] compared with age-matched controls.

Revisiting the nbM in Parkinson’s disease

As mentioned previously, cell loss in the nbM was first identified in PD by Lewy, early in the 20th century. However, quantification of neuronal loss was not attempted until the 1980s where studies reported up to 80 % depletion in the nbM of PD cases (Table 4). When directly comparing PD and AD cases, the loss is comparable [86] or more extensive in PD than in AD [17, 20, 79] and the loss was more apparent among PD with dementia (PDD) cases. Therefore, it is perhaps not be surprising that PDD patients have good neuropsychiatric responses to anticholinesterase medication such as rivastigmine and galantamine (review by [1]). Furthermore, recent imaging studies using cholinergic markers to label acetylcholinesterase have reported significant cortical cholinergic deficits in PD and PDD patients [11–13, 44, 60, 90, 91]. This suggests that apart from the dopaminergic deficit, a decrease in cholinergic tone also contributes to cognitive impairment in PD, as supported by the dual syndrome hypothesis where executive dysfunction and visuospatial impairment in PD correspond to dopaminergic and cholinergic deficits, respectively [53].

The cognitive picture of PDD is commonly considered as a “subcortical” type since patients typically present with dysexecutive signs without significant impairment in storage memory as in “cortical” AD-type dementia [20, 23]. Hence, with varying cortical regions affected in PD and AD the differing clinical profiles may correlate with neuronal loss in particular nbM subsectors. However, only a small number of studies have investigated PDD separately and the different subregions within the nbM have not been compared in PDD cases. We reviewed the literature, estimated the regions sampled in various studies as mentioned before (Table 5) and found a slightly greater deficit in the intermediate nbM region. This supports a recent imaging study [58] which reported a posterior–anterior gradient of cortical cholinergic deficit and this could be due to the extensive
**Fig. 3** Formalin-fixed, paraffin-embedded basal forebrain sections available from the Parkinson’s UK Tissue Bank at Imperial College, London, stained with H&E (a–c; g–i) and serial sections stained with choline acetyltransferase (ChAT) immunohistochemistry (Millipore AB144P, 1:100 with pressure cooker pretreatment in pH 6.0 citrate buffer) (d–f; j–l). Six subdivisions of the basal forebrain were defined and arranged rostrally (top left) to caudally (bottom right). a, d Level at nucleus accumbens. This level is defined by the absence of anterior commissure and the presence of a large caudate head with nucleus accumbens. b, e Pre-anterior nbM level. Anterior commissure appears in this section but it is located ventral to the globus pallidus and is rostral to decussation level. A large ventral striatum could be seen clearly with ChAT immunohistochemistry. c, f Most rostral anterior nbM level. This level is defined by the decussation of the anterior commissure. Ch4 neurons are defined by their location being lateral to the supraoptic nucleus and they are orientated at the medial–lateral axis parallel to the basal border of the section. g, j Most caudal anterior nbM level. The anterior commissure is split into two parts with medial end still decussating and lateral end located ventral to the globus pallidus. h, k Intermediate nbM level. At this level, the globus pallidus is split into the external and internal components by an inter-medullary lamina. The anterior commissure is located ventral to the putamen and sometimes the infundibulum could be seen. i, l Posterior nbM level. This is defined by the presence of mamillary body, small or absence of caudate and internal capsule occupying the medial half of the tissue. Asterisk denotes area of maximal density of ChAT-immunopositive cells in the nbM. Zoomed-in figure showing the ChAT-immunopositive neurons in the nbM at ×10 objectives. AC anterior commissure, Cd caudate, fx fornix, GP globus pallidus, GPe globus pallidus externa, GPi globus pallidus interna, ic internal capsule, inf infundibulum, mb mamillary body, nAcc nucleus accumbens, ot optic tract, Pt putamen, son supraoptic nucleus, VS ventral stratum
cell loss in the Ch4i affecting the cholinergic innervation to occipital–parietal cortical regions.

**A dichotomous pattern of nbM cell loss in PD and AD**

Amyloid-beta (Aβ) plaques and tau neurofibrillary tangles (NFT) are hallmark neuropathological features of AD, the latter being more closely associated with cognitive decline [7]. It has been well recognised that LB- and AD-type pathologies frequently co-exist in the brains of PDD and dementia with Lewy bodies (DLB) [49] and that there may be synergistic relationships between the two types of pathologies in the development of dementia [21, 48].

Cullen and Halliday [22] proposed that the cause of neuronal loss in the nbM could differ between PD and AD. They studied cell loss and NFT pathology within the nbM of AD and LB disease with concomitant AD. Severe cell loss in the nbM of AD cases was accompanied by abundant extraneuronal NFT pathology. However, cases of LB disease with AD have equally severe nbM depletion, despite relatively little or no cortical AD-type pathology [34]. They concluded that cortical AD pathologies did not seem to affect the reduction of cholinergic cortical afferents in PD. In addition, Nakano and Hirano reported that neuronal loss in the nbM of PD is not associated with NFT in the cortex, hippocampus or in the nbM [76]. Therefore, in order to study nbM loss in ‘pure’ PD, cases with severe AD pathologies should be excluded. In the studies we reviewed (Tables 4, 5), most [17, 19, 20, 34, 79, 80, 95] but not all [4, 86, 98, 105] have excluded cases with severe co-existing AD pathologies.

Striatal Aβ has been suggested to contribute to the development of dementia in PD and DLB, independently of comorbid AD pathologies [51, 52]. Although a couple of studies reported striatal Aβ as specific to DLB not PDD [39, 50], and subsequently concluded Aβ load in the striatum affects the temporal relationship between dementia and PD motor symptoms rather than presence of dementia, controversies remain as to whether the severity of striatal Aβ could differentiate PDD from DLB.

Other basal forebrain cholinergic nuclei such as the medial septal nucleus (Ch1) and the vertical limb of the diagonal band nucleus (Ch2) also show differential susceptibility in AD and LB disorders. Fujishiro and colleagues reported the loss of Ch1 and Ch2 ChAT-positive neurons in DLB but not AD cases compared with controls [32]. However, a recent study reported no significant change in Ch1 and Ch2 ChAT-positive neurons in PD and PDD [38]. So further work is needed to identify the potentially subtle pathological differences between PDD and DLB. One
further consideration, as mentioned previously, is that other neurotransmitter deficits could contribute to cognitive decline in PD. Cell loss in the nbM happens in parallel with dopaminergic neuronal loss in the substantia nigra and ventral tegmental area; and noradrenergic neuronal loss in the locus coeruleus [54]. Hence, the basal forebrain depletion

| Study                      | n  | Anterior nbM % | Intermediate nbM % | Posterior nbM % | Not specified/Entire nbM % |
|----------------------------|----|----------------|--------------------|----------------|---------------------------|
| Whitehouse et al. [99]    | 1  | 90 % (Ch4)     |                    |                |                           |
| Perry et al. [81]         | 6  | 33 %           |                    |                |                           |
| Whitehouse et al. [100]   | 5  | 73 % (Max density) | 79 % (Mean density)|                |                           |
| Arendt et al. [4]         | 14 | 54 % (Max density) | 71.7 % (Mean density)|                |                           |
| Candy et al. [17]         | 5  | 35 %           |                    |                |                           |
| Nagai et al. [75]         | 3  | 66 % (Ch4)     |                    |                |                           |
| Tagliavini and Pilleri [94]| 9  | 63 %           |                    |                |                           |
| Wilcock et al. [102]      | 6  | 49 % (Ch4a or Ch4i) |                |                |                           |
| Mann et al. [64]          | 22 | 58.9 %         |                    |                |                           |
| McGee et al. [65]         | 6  | 33-69.7 % (Ch4) |                    |                |                           |
| ● Arendt et al. [5]       | 5  | 46 % (Ch4am)   | 51.4 % (Ch4al)    | 62.6 %         | 57 % (Ch1–Ch4)            |
| Perry et al. [79]b        | 8  | 8 % (Moderate AD) |                |                |                           |
| ● Rogers et al. [86]      | 3  | 64.7 % (Total cell count/section) | 74.9 % (Total cell count/section) |        |                           |
|● Doucette et al. [25]     | 8  | 50 % (Moderate AD) | n.s. (Moderate AD) | n.s. (Moderate AD) | |
|● Etienne et al. [29]      | 10 | 73 %           | 87 %              |                |                           |
| Rinne et al. [85]         | 7  | 22 %           | 64 %              |                |                           |
| Allen et al. [2]          | 7  | 61 % (Nissl; Ch4i or Ch4p) | 29 % (Neuron specific enolase staining; Ch4i or Ch4p) |        |                           |
| Chan-Palay et al. [19]c   | 12 | 24 % (Ch4a or Ch4i) |                |                |                           |
| ● Wilcock et al. [101]    | 13 | 13 % (n.s.) (Ch4am) | 41 %              | 57 %           |                           |
|● Mufson et al. [73]d      | 7  | 35.1 % in (Ch4am) | 62.1 %            | 76.5 %         |                           |
| Iraizoz et al. [47]       | 6  | 43 %           | 25 %              | 30.5 %         | 31 % (Ch4)               |
| Perry et al. [80]         | 4  | 39.3 % (Not specified) |                | 63.7–86.6 % (Ch4) | |
| Arendt et al. [6]         | 64 | 64 %           | 40 %              | 56 %           | 40 % (Ch4)               |
| Iraizoz et al. [46]       | 21 | 48 %           | 40 %              | 56 %           | 40 % (Ch4)               |
| Zarow et al. [105]        | 86 | 41.1 %         |                   | 8–86.6 %       |                           |

n.s. Not significant

a Familial AD
b Moderate AD
c Poor definition of nbM region. According to diagram in the study, area included indicates Ch4a and Ch4i
d NGFR immunohistochemistry as marker for cholinergic neurons in the nbM
could also be associated with the decrease in dopaminergic and noradrenergic innervation in PD. Finally, serotonergic dysfunction, dysregulation of excitatory amino acid and purinergic interactions in PD [93] should not be neglected as they might also contribute to non-motor symptoms including cognitive impairment in PD.

Table 4  Studies of the nbM in PD

| Study                      | n  | % Loss relative to control |
|----------------------------|----|----------------------------|
|                            |    | Anterior nbM | Intermediate nbM | Posterior nbM | Not specified/entire nbM |
| Arendt et al. [4]a         | 5  | 87 % (Total count) | 70 % (Max density) |              |                         |
| Candy et al. [17]          | 3  |              |                  |              |                         |
| Whitehouse et al. [98]     | 4  | 33.4 % (n.s.) |                  | Greater loss in PD than AD |
| Gaspar and Gray [34]       | 14 | 32 % (Mean cell count) | 34 % (Mean density) |              |                         |
| Nakano and Hirano [76]     | 11 | 60.0 % (Mean density) | 52.2 % (Max density) |              |                         |
| Tagliavini et al. [95]     | 3  | 39.8 % |                  |              |                         |
| Perry et al. [79]          | 4  |              |                  | 17.3 % (Ch4) |                         |
| Rogers et al. [86]         | 1  | 39.8 % (Total cell count/ section) | 39.7 % (Total cell count/ section) |              |                         |
| Chan-Palay et al. [19]     | 3  |              |                  | 7.7 % (Ch4a or Ch4i) |                         |
| Perry et al. [80]          | 7  |              |                  | 67.9 % (Not specified) |                         |
| Zarow et al. [105]a        | 19 | 37.3 % |                  |              |                         |
| Range                      | 19.0–39.8 % | 32.8–87 % | – | 7.7–74.7 % |

n.s. Not significant
a Did not distinguish PDD from PD

Table 5  Studies of the nbM in PDD

| Study                      | n  | % Loss relative to control |
|----------------------------|----|----------------------------|
|                            |    | Anterior nbM | Intermediate nbM | Posterior nbM | Not specified/entire nbM |
| Whitehouse et al. [98]     | 2  | 77.1 % (Total cell count) | 53.1 % (Max density) |              |                         |
| Gaspar and Gray [34]       | 18 | 60 % (Mean cell count) | 58 % (Mean density) |              |                         |
| Perry et al. [79]          | 10 |              |                  | 72.2 % (Ch4; PDD and DLB not distinguished) | 74.7 % (Ch4; PD with AD) |
| Rogers et al. [86]         | 3  | 44.3 % (Total cell count/ section) | 72.3 % (Total cell count/ section) |              |                         |
| Chui et al. [20]           | 3  | 66.1 % |                  |              |                         |
| Chan-Palay et al. [19]     | 6  |              |                  | 47.4 % (Ch4a or Ch4i) |                         |
| Perry et al. [80]          | 14 |              |                  | 41.7 % (Ch4; PDD and DLB not distinguished) |                         |
| Range                      | 36.5–66.1 % | 53.1–77.1 % | – | 41.7–74.7 % |

Possible functional correlate to subdivisional neuronal loss in the nbM in PD

Correlation relating specific cognitive deficits in PD with subsector pathology in the nbM has not been achieved, in part because of a lack of detailed neuropsychological
testing in extant postmortem brain studies. An exception is from one study by Chui and co-workers in which three neuropathologically confirmed PD cases with dementia had undergone extensive neuropsychiatric tests before death and detailed cognitive profiles for the patients were available [20]. Their cognitive impairment included the presence of hallucination, visuospatial impairment and attentional deficits typical in PD cases. When the cell count of nbM (apparently Ch4a) was compared against AD cases, a greater decrease in mean density was observed in PDD (66.1% loss) than in AD (61.9% loss). On the other hand, the correlation between cognitive impairment in LB disorders and regional cortical involvement has been well supported by various functional imaging studies. In particular, atrophy and hypometabolism in the occipito-parietal region and, to a lesser extent, the frontal cortex in PDD patients relative to controls have been reported [35]. One study has compared the specific cognitive impairment in PD with regional fluorodeoxyglucose (FDG) uptake [33]. The degree of executive dysfunction in PD patients correlated positively to hypometabolism score in the frontal lobe, whereas visuospatial function impairment correlated to occipito-parietal reduction in FDG uptake.

Hence, one could speculate that pathology in Ch4a correlates with executive dysfunction in PDD due to frontal and limbic cortical innervation from the anterior Ch4 area. Moreover, anosmia in PD and PDD has been shown to be associated with limbic cortical cholinergic denervation, which could again correlate with Ch4a pathology [14]. Similarly, visuospatial impairment in PDD or even in early PD would possibly be due to neuronal loss in the Ch4i subsector. As PD/PDD patients typically have a less amnestic profile than AD, we would expect Ch4p to be relatively spared. However, visual hallucination in PD is a more complex phenomenon which might be due to a combination of occipito-parietal hypometabolism [45] and the presence of LB in the temporal lobe [40]. Therefore, pathology in the Ch4i and Ch4p regions may play a role in this characteristic element of cognitive dysfunction in PDD/LBD, along with other brain centres.

In addition, in earlier studies, no distinction was made between PDD and DLB [79, 80], as DLB is a more recently established clinical entity [66], and it would be of interest to investigate whether the pattern of cell loss within the nbM subregions differs in PDD and DLB.

**Conclusion and future work**

Following our literature review on the studies of the nbM above, we also revisited the original work by Friedrich Lewy [30] and found that the area he defined as the nbM was from the optic tract to septum pellucidum. This would equate to the anterior/intermediate Ch4 region according to modern classification and thus historical evidence illustrates that LB and severe neuronal depletion were first described in the anterior portion of nbM. Along with the collective evidence and our speculation that there is a relative sparing of posterior nbM involvement in PD patients, it could be hypothesised that pathology in the nbM begins...
in the anterior portion and progresses caudally in PD. This anatomical progression supports the prion-like propagation hypothesis [3, 16, 26, 31] and the dual-hit hypothesis of alpha-synuclein [41, 42] where pathology starts in the olfactory bulb and spreads towards the basal forebrain region (Fig. 5). However, further studies investigating the topographical innervation pattern from different subsectors of the human nbM to target regions and reciprocal connectivity are needed, particularly with the advancement in tractography and other high-resolution imaging techniques.

With the increasing number of imaging studies focusing on basal forebrain changes [56, 57] there is a need for this nucleus to be revisited in pathological studies. The potential for neuromodulatory treatment targeting the nbM is now being realised, in particular deep brain stimulation in dementia [37, 61] and stereotactic gene delivery of trophic factors [82]. However, it is important to note that there are many caveats to consider, including distinctly varying pathogenesis of dementia in PD and AD. Better clinicopathological correlations have to be established, especially in relation to the different subregions of the nbM. This will improve our understanding of the pathological basis for different forms of dementia disorders and the role of forebrain cholinergic mechanisms in normal cognition as well as in the setting of cognitive decline.

Acknowledgments The authors would like to thank Parkinson’s UK, registered charity 258197, for their continual support as well as the donors and family for their invaluable donation of brain tissue to the Parkinson’s UK Tissue Bank. The work in Laboratory of Neurodegenerative Diseases is supported by HKU Alzheimer’s Disease Research Network under Strategic Research Theme of Healthy Aging and the source are credited.

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