Acta Neuropathol (1992) 84: 478 – 483

Acta Neuropathologica

Allocortical neurofibrillary changes in progressive supranuclear palsy*

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Received April 7, 1992/Revised, accepted May 10, 1992

Summary. Silver techniques for intraneuronal cytoskeleton abnormalities (neurofibrillary tangles and neuropil threads) and extracellular A4-amyloid deposits were used to examine lesions of the cerebral cortex in six cases of progressive supranuclear palsy (three were mentally unimpaired and three showed moderate degrees of dementia). Deposits of A4-amyloid protein occurred in small numbers or were absent. Neurofibrillary tangles and neuropil threads were present in all cases and were largely confined to the allocortex. A characteristic pattern of changes was found in the entorhinal cortex. The three mentally unimpaired individuals had mild cortical changes virtually confined to the transentorhinal region while all of the demented patients showed severe destruction of the superficial cellular layer in both the transentorhinal and entorhinal region. This pattern of allocortical destruction closely resembles that seen in clinically incipient Alzheimer's disease or in mentally impaired cases of Parkinson's disease. The entorhinal region receives dense input from isocortical association areas and projects via the perforant path to the hippocampal formation. The cells of origin of major portions of the perforant path are located within the superficial entorhinal cellular layer. Destruction of this layer partially or totally disconnects the hippocampus from the isocortex. The specific pattern of entorhinal destruction is considered to contribute to cognitive impairment and personality changes, frequently seen in patients with progressive supranuclear palsy.

Key words: Progressive supranuclear palsy – Steele Richardson Olszewski syndrome – Neurofibrillary changes – Entorhinal region – Dementia

Progressive supranuclear palsy (PSP) is characterized by ophthalmoplegia of the vertical gaze, pseudobulbar palsy, dysarthria, facial and axial dystonia, bradykinesia, and rigidity. The disorder is frequently associated with cognitive impairment, slowing of thought processes, and personality changes [1, 4, 19, 22, 42, 44, 52, 53]. Occurrence of intraneuronal neurofibrillary changes and neuronal loss within the pallidum, subthalamic nucleus, substantia nigra, and other subcortical nuclei are the morphological key features which most likely account for motor dysfunctions [1, 34, 37, 38]. The development of personality changes and intellectual decline is, however, poorly understood. The aim of this study is to draw attention to a circumscribed lesion of the entorhinal region. This important allocortical center of the limbic system is also involved in early stages of Alzheimer's disease (AD) and in mentally impaired cases of Parkinson's diseases (PD) [13, 14, 16, 39].

Material and methods

A total of ten brains obtained at autopsy and fixed by immersion into a 4% aqueous solution of formaldehyde were used for this study. Six brains were from individuals presenting with PSP (three males, three females, aged 56 to 73 years mean 68,3 ± years; duration of illness 3–5 years). The clinical presentation of all these cases was consistent with the diagnosis of PSP and included gait disorders, ophthalmoplegia with vertical gaze palsy, neck and trunk rigidity, dysarthria, bradykinesia, axial dystonia, and terminal pseudobulbar palsy. Depression was reported in four patients, bradyphrenia in all six. Three patients (Table 1; nos. 3–5) showed no clinical signs of dementia, one was mildly demented (no. 1), and two showed moderate to severe dementia (nos. 2 and 6), although all except case 5 presented mild memory disturbances.

Neuropathological evaluation of the six cases using routine staining methods, Bielschowsky silver impregnation, and immunohistochemistry for tau, paired helical filaments (PHF) and ubiquitin [monoclonal antibody (mAb) 3.39 reacting with ubiquitin] revealed the usual features of PSP with widespread neurofibrillary tangles (NFT), neuropil threads (NT) [17], neuronal loss and gliosis in many subcortical areas. Isocortical NFT and NT were observed in small numbers in all cases. Neuritic plaques (NP) were absent or were seen on rare occasion. Moderate numbers of amyloid deposits occurred in frontal and temporal isocortex in all cases except no. 3 (Table 1). None of the brains met the neuropath-

* Supported by grants from the Deutsche Forschungsgemeinschaft and the Bundesministerium für Forschung und Technologie

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Table 1. Age, sex, neuropathological stage of accumulation of amyloid deposits (A–C) and neurofibrillary changes (I–VI) according to Braak and Braak [16] and semiquantitative analysis of lobar distribution of neurofibrillary tangles (NFT) and neuropil threads (NT)

			Neuro-fibrillary changes	Amyloid deposits	Frontal		Parietal		Temporal		Occipital	
Case	Age	Sex	corresponding to AD stage		area 9		area 40		area 22		area 17	
					NFT	NT	NFT	NT	NFT	NT	NFT	NT
1 PSP	65	m	III	A	0	0	0	+	+	+		
2 PSP	67	f	IV	A	0	0	0	0	+	+	0	0
3 PSP	67	m	I	0	+	+	0	+	0	0	0	0
4 PSP	69	f	II	A	+	+	0	0	0	+	0	0
5 PSP	69	m	I	A	+	+	0		0	0	0	0
6 PSP	73	f	III	A	+	+	0	+	0	+	+	+
7 Contr	62	f	0	0	0	0	0	0	0	0	0	0
8 Contr	65	m	0	0	0	0	0	0	0	0	0	0
9 Contr	69	m	0	0	0	0	0	0	0	0	0	0
10 Contr	69	f	0	0	0	0	0	0	0	0	0	0

AD, Alzheimer's disease; Contr, control; f, female; m, male; PSP, progressive supranuclear palsy; 0, absence of changes; +, few isolated NFT and NT

ological diagnostic criteria for AD [41]. Four brains from non-demented individuals (aged 62 to 69 years; mean 66.2 ± 3 years) served as controls.

One hemisphere of case 2 was cut into three blocks in the frontal plane with the aid of a macrotome. These blocks were embedded in polyethylene glycol (PEG 1000) [51]. Large serial sections through the entire hemisphere were cut at 100 μm and every tenth of the sections was stained. Three techniques were used: (1) silver stain for neurofibrillary changes, (2) silver stain for A4-amyloid protein [15, 20, 25, 32], and (3) aldehyde-fuchsin-Darrow red for lipofuscin and basophilic material [11, 18]. Of cases 1 and 3–10, blocks including the hippocampal formation and adjoining parts of the parahippocampal gyrus and temporal isocortex were cut out at the level of the lateral geniculate body and at mid-uncus level (in most cases from both hemispheres) and processed as case 2. The uncal preparation was used to evaluate the entorhinal and transentorhinal pathology. Additional blocks of Brodmann areas 9 (frontal), 40 (parietal), 22 (temporal) and 17 (occipital) as well as numerous subcortical areas (see [37]) were embedded in paraffin, sectioned at 12 μm and stained with the above-mentioned methods (Gallyas, Campbell-Switzer, lipofuscin-Nissl and with Bodian and Bielschowsky). The number of NFT and NT were semiquantitatively determined (Table 1).

Topography and nomenclature of the entorhinal territory

The entorhinal allocortex spreads over the gyrus ambiens and anterior portions of the parahippocampal gyrus. It is formed by a broad molecular layer and cellular layers α, β, γ both of an external and internal principal stratum (Pre and Pri) [49]. Nissl preparations just permit differentiation of two outer and two inner cellular layers, while sections counterstained for lipofuscin pigment enable recognition of three outer and inner layers (Pre α, β, γ and Pri α, β, γ) [11, 12]. The lamina dissecans is a cell-sparse line separating the outer from the inner principal stratum. None of the entorhinal layers corresponds to an isocortical lamina. Most conspicuous among the layers is Pre-α which mainly consists of islands of large multipolar projection cells (modified pyramidal cells).

Located between the proper entorhinal region and the adjoining temporal isocortex is the transentorhinal region. It is burried for the most part in the depth of the rhinal sulcus. The region is mainly characterized by the conspicuous descent of the superficial entorhinal cellular layer Pre-α which follows an oblique course through the outer cortical layers [11, 12].

Entorhinal and transentorhinal pathology easily escape recognition if only a single block of tissue is cut out at the level of the lateral geniculate body. This block displays the classical view of the hippocampal formation. Entorhinal and transentorhinal regions are missing at this level or present with only remnants of their posterior poles. The classical hippocampus preparation, therefore, does not allow evaluation of transentorhinal or entorhinal changes.

Results

All PSP cases revealed the characteristic subcortical pathology with widespread NFT, NT, neuronal loss and gliosis in many nuclei [1, 33, 37, 38, 48, 53].

The cerebral cortex remained either devoid of extracellular A4-amyloid (case 3) or showed only a few deposits in frontal, temporal or parietal isocortical association areas (all PSP cases except no. 3; Fig. 2a). A few NP with argyrophilic neurites and amyloid cores were seen in only cases 1, 2 and 6. All cases exhibited the presence of NFT and NT in variable, but usually small amounts in isocortical layers II, III and V (Fig. 2b). Moderate numbers of globular tangles occurred in the granule cells of the fascia dentata, while the first Ammon's horn sector displayed only a few flame-shaped NFT within pyramidal cells. Other sectors of the Ammon's horn, the subiculum, presubiculum and parasubiculum remained devoid of changes. In contrast, the entorhinal territories were vastly affected. The impact of the destruction was carried by the superficial layer Pre-α with very large numbers of prominent NFT and numerous NT (Figs. 1, 2c, d). Most of the NFT were star shaped and extended widely into the proximal dendrites. The presence of many "ghost tangles" was also noted in layer Pre-α. Cases 2 and 6 even displayed an involvement of layers Pri-α and Pre-β (Figs. 1, 2c, d).

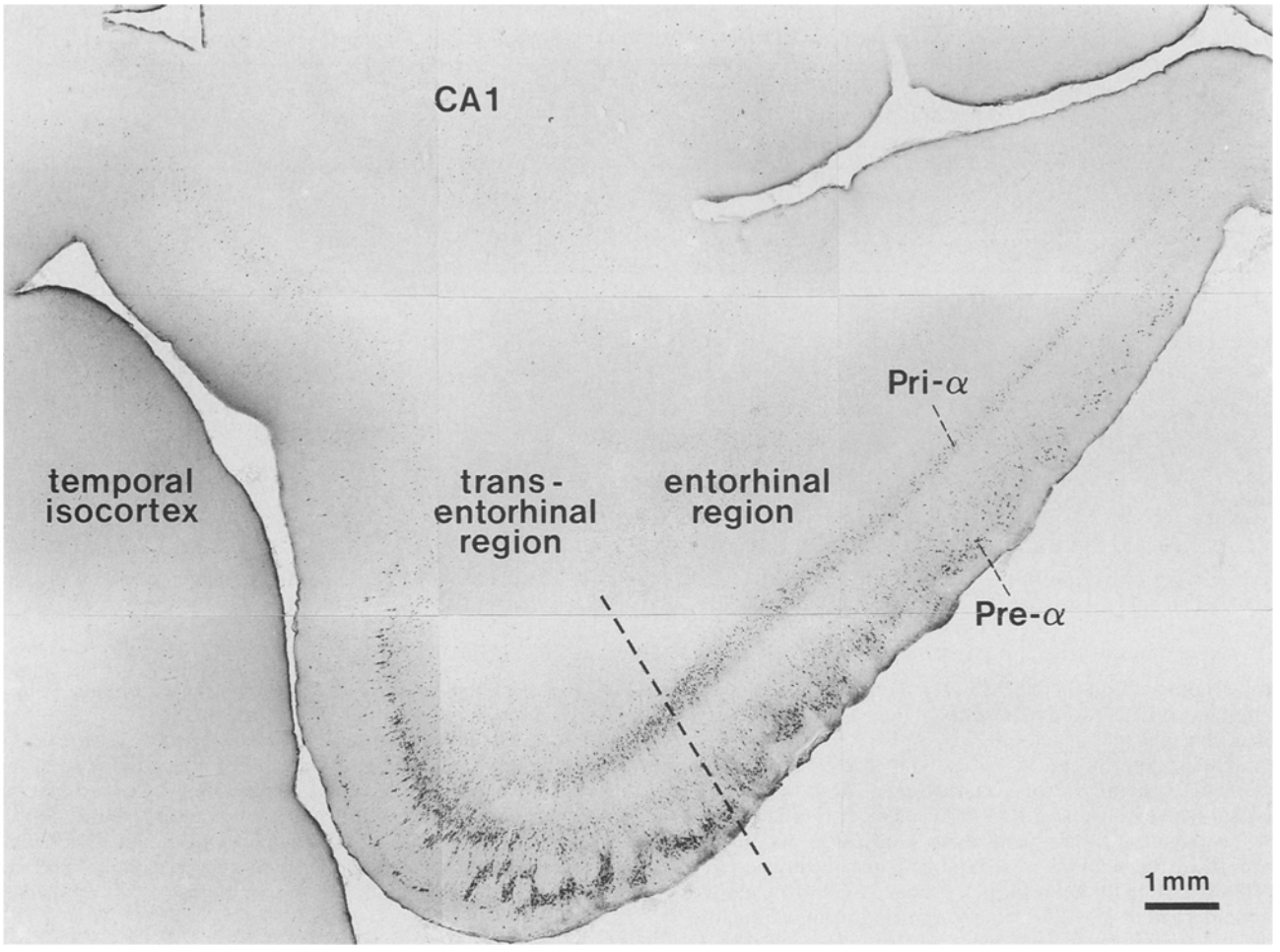

Fig. 1. Anterior parahippocampal gyrus at mid-uncal level. The superficial entorhinal cellular layer Pre-α shows severe destruction with many neurofibrillary tangles (NFT) and neuropil threads (NT) in both the transentorhinal and entorhinal region. Large numbers of NFT can also be observed in the deep layer Pri-α. The hippocampal formation (CA1 = first sector of the Ammon's horn) and the isocortex show only mild involvement with very low densities of NFT and NT. PSP with severe dementia (case 2), 100 μm PEG, Gallyas silver stain for neurofibrillary changes

The severity of entorhinal affection varied among individuals but three of the six cases showed severe destruction of layer Pre-α (Table 1: nos. 1, 2, 6) and clinically signs of moderate (nos 1 and 6) to severe dementia (case 2) were noted. The mildly affected cases had pathological changes virtually confined to the transentorhinal region (Table 1: nos. 3–5). None of these patients had been demented.

Discussion

Previous studies have not mentioned major destruction of the cerebral cortex in PSP [1, 19, 26, 48, 53] or have noted only mild changes of isocortical areas and hippocampus [9, 27, 33, 37, 38, 56]. Therefore, cognitive impairment in PSP was largely related to subcortical pathology, in particular to disconnections of ascending fiber tracts to the orbitofrontal cortex [3, 4, 22, 24, 39a]. However, recent studies demonstrated large numbers of NFT and NT in primary motor cortex with less-severe involvement of isocortical association areas [27]. In six other cases of PSP with some degree of dementia, NFT formation was found to be largely confined to the hippocampal formation and primary motor cortex with only mild involvement of isocortical association areas that are predominantly involved in AD [28]. Two other cases of PSP with severe dementia exhibited severe involvement of the limbic system with much lesser affection of the isocortex [43, 55].

The present report also draws attention to a distinct involvement of the cerebral cortex. Severe changes are virtually confined to a small but important part of the allocortex, the transentorhinal and entorhinal region. The question arises whether such a circumscribed cortical lesion sufficiently explains the personality changes (apathy, inertia), bradyphrenia, memory dysfunctions, and intellectual deterioration frequently seen in PSP.

The transentorhinal region receives a dense input from isocortical association areas. Additionally, limbic thalamic nuclei project upon the entorhinal cortex via

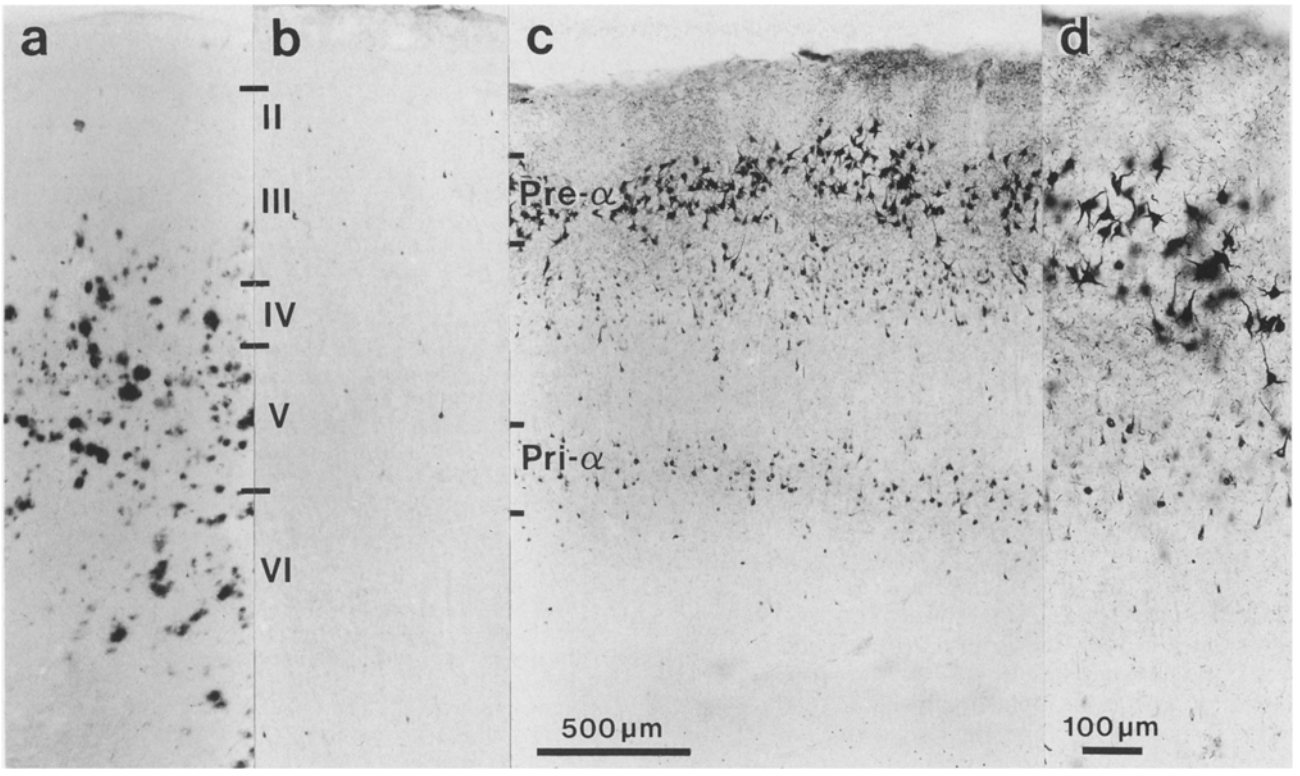

Fig. 2. **a** A relatively small number of amyloid deposits is encountered in isocortical association areas (medial portion of the temporal lobe). **b** The same area displays only a few NFT and NT scattered throughout cortical layers II, III and V. **c, d** The same case shows severe involvement of the entorhinal region. Most severe changes are seen in the superficial cellular layer Pre-α with large numbers of conspicuous star-shaped NFT. NT form dense networks within and above the islands of Pre-α. Note the additional involvement of one of the deep layers (Pri-α) and even layer Pre-β (small pyramid-shaped NFT subjacent Pre-α). *Bar* in **c** is also valid for **a** and **b.** PSP (case 2), 100 µm PEG, Gallyas silver stain for neurofibrillary changes

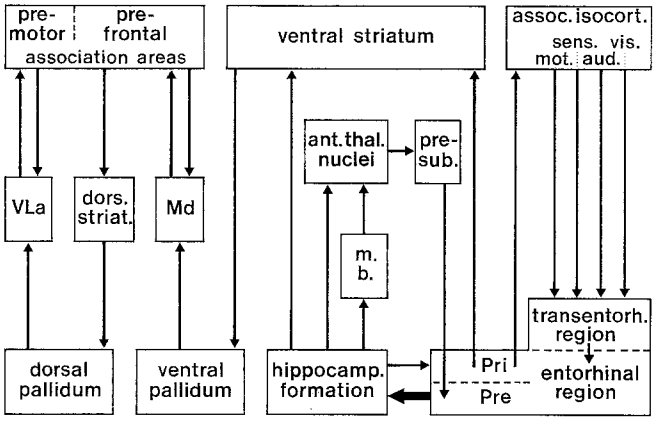

Fig. 3. Schematic representation of isocortical and limbic input to the entorhinal region, connections between entorhinal region and hippocampal formation, and output to ventral striatum and motor system. Note that destructions seen in PSP severely impair the flow of information running between the entorhinal region and the hippocampal formation. In addition, the lesion partially or totally disconnects prefrontal association cortex from limbic influence. *ant. thal. nuclei,* anterior thalamic nuclei; *assoc. isocort. (mot. sens. aud. vis.),* isocortical association areas (somato-motor, somato-sensory, auditory, visual); *m. b.,* mamillary body; *Md,* mediodorsal thalamic nuclei; *presub.,* presubiculum; *VLa,* anterior ventrolateral thalamic nucleus

the presubiculum [7, 46, 57]. External entorhinal layers, particularly layer Pre-α generate the perforant path and via this fiber tract both the isocortical and limbic data are transported to the hippocampal formation. In turn, the internal entorhinal layers receive input from the hippocampal subiculum and project back to isocortical association areas (Fig. 3). The structural preservation of the medial temporal lobe, particularly of the hippocampus and entorhinal cortex, is considered important for the maintainance of memory functions [31, 58]. Hippocampus and deep entorhinal layers also generate projections to the ventral striatum which in turn controls via ventral pallidum and mediodorsal thalamus the activity of prefrontal association areas. The limbic system thereby provides input to cortical areas and subcortical nuclei involved in the initiation, execution and control of movements (Fig. 3) [5, 6].

The conspicuous destruction of layer Pre-α in PSP certainly hampers the information transport via the perforant path. The lesion partially or totally disconnects the isocortex from the hippocampus and, additionally, destroys important limbic circuits [8, 12, 14, 16, 29, 30, 31, 40, 47, 58]. The hippocampal feedback to the entorhinal cortex is impaired by involvement of the deep layer Pri-α. The specific pattern of entorhinal pathology

in PSP, therefore, most likely contributes to the development of personality changes and mental deterioration (Fig. 3). Moreover, disturbances within the limbic circuits also hamper the entorhinal and hippocampal output to the ventral striatum. Destruction of the ventral pallidum adds to the partial or total disconnection of the limbic system from mediodorsal thalamic nuclei and prefrontal association cortex (Fig. 3). A decreased limbic stimulation of prefrontal isocortex may eventually result in the development of apathy, inertia and other personality changes [10, 21]. The mild changes seen in other isocortical association areas explain the absence of apraxia, aphasia, and agnosia.

The initial stages of AD show a similar type of involvement [14, 16]. As in PSP, NFT and NT exhibit a pronounced predilection for certain areas, layers, and neuronal types. In AD, the projection cells of the transentorhinal layer Pre-α are among the first neurons of the entire brain which develop NFT and NT. From this predilection site the destructive process spreads into other parts of the cortex. Stages I and II of AD exhibit involvement of only the transentorhinal Pre-α. At stage III, the destruction extends into the proper entorhinal region with additional involvement of the deep layer Pri-α at stage IV. The final stages V and VI are characterized by very severe destruction of the isocortex [16]. PSP cases with mild changes are comparable to AD stages I or II, while those with more severe alterations correspond to AD stages III or IV (Table 1). The distribution pattern of entorhinal pathology in PSP does not differ from that seen in the initial stages of AD.

A similar pattern of entorhinal involvement with the appearance of abundant NFT and NT in layer Pre-α (corresponding to AD stages III–IV) is also seen in mentally impaired cases of PD [14, 39]. In PD, cognitive impairment and personality changes generally remain unaccompanied by isocortical dysfunctions such as apraxia, aphasia, and agnosia [2, 45], a clinical constellation which corresponds well to the pattern of entorhinal pathology.

These limbic system changes and the recently observed isocortical lesions in PSP [27, 28, 33] may be combined with or paralleled by dysfunctions of the cholinergic magnocellular nuclei of the basal forebrain, also considerably affected in PSP [54] and in PD [23, 35, 36]. Despite important subcortical pathology in both PSP and PD with particular impact to subcortico-cortical systems [23, 39a, 50], the presence of severe entorhinal pathology in both disorders calls for a reconsideration of the concept of "subcortical dementia" [4, 21].

Acknowledgements. The authors would like to thank Ms. Babl, Fertig, and Schneider (preparations), and Ms. Szasz (drawings).

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