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Regional neuropathology distribution and verbal fluency impairments in Parkinson's disease

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ABSTRACT

Background: Verbal fluency deficits are common in patients with Parkinson's disease. The association of these impairments with regional neuropathological changes is unexplored.
Objectives: Determine if patients with verbal fluency impairments have greater neuropathological burden in frontal, temporal, and limbic regions and if Lewy bodies or neurofibrillary tangles were associated with verbal fluency impairments.
Methods: Data was derived from the Arizona Study of Aging and Neurodegenerative Disorders. 47 individuals who completed phonemic and semantic verbal fluency tasks and met clinicopathological criteria for Parkinson's disease (with and without comorbid Alzheimer's disease) were included. Impairment on fluency tasks was defined by normative data, and the density of neuropathology in temporal, limbic, and frontal regions was compared between groups.
Results: Individuals with semantic fluency impairments had greater total pathology (Lewy bodies + neurofibrillary tangles) in limbic structures (W = 320.0, p = .033, r_{pb} = .33), while those who had phonemic fluency impairments had increased total neuropathology in frontal (W = 364.5, p = .011, r_{pb} = .37), temporal (W = 356.5, p = .022, r_{pb} = .34), and limbic regions (W = 357.0, p = .024, r_{pb} = .34). Greater Lewy body density was found in those with verbal fluency impairments, though trends for greater neurofibrillary tangle density were noted as well.
Conclusions: Impaired phonemic fluency was associated with higher Lewy body and tangle burden in frontal, temporal, and limbic regions, while impaired semantic fluency was associated with greater limbic pathology. Though neurofibrillary tangles trended higher in several regions in those with impaired verbal fluency, higher Lewy body density in general was associated with verbal fluency deficits. Implications for research and clinical practice are discussed.

1. Introduction

The relative contribution of neuropathological changes to cognitive decline in Parkinson's disease (PD) is a matter of some debate. Cognitive changes in PD likely reflect a complex interaction of limbic and cortical Lewy body (LB) deposition [1–3], together with many other clinical contributors [4] such as demographic, mood, and neurotransmitter effects. Further complicating matters, comorbid conditions, especially Alzheimer's disease (AD) pathology may also contribute to cognitive decline, even in those with a primary diagnosis of PD [2]. This effect may be particularly potent for neurofibrilliary tangles (NFTs), which are strongly associated with cognitive impairment in older adults [5] and those with AD [6].

To date, most studies exploring the neuropathological correlates of

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cognitive decline in PD have focused on global cognitive status, indexed by mental status exam scores or clinical state (demented or not). This method can obscure the fact that cognitive impairments in PD are quite heterogeneous [4,7], and different types of cognitive impairment are associated with differing outcomes [14]. Thus, exploring neuropathological contributions to particular cognitive impairments may help guide our understanding of cognitive decline at the level of the individual symptom.

One such common cognitive difficulty in PD is an impairment in verbal fluency (VF). VF problems are extremely common in PD [8] and are among the earliest cognitive changes in the disease [9]. Deficits on VF tasks are thought to reflect both executive and linguistic network dysfunction (in addition to a host of other cognitive processes, such as information processing speed [26], and in turn, dysfunction in the frontal and temporal regions that underlie these networks [10–15]. To date though, the association of regional distribution (frontal versus temporal/limbic) and type (NFT versus LB) of neuropathology has not been compared in those with PD with and without VF impairments. In the current study we addressed this, focusing on two main hypotheses. First, we tested whether those with VF impairments would have greater neuropathological burden in frontal, temporal, and limbic regions thought to be associated with performance on these tasks. We hypothesized that those with phonemic fluency impairments in particular would have greater neuropathology in broad fronto-temporal-limbic regions, whereas those with semantic fluency deficits would have a greater burden of pathology in temporo-limbic regions associated with semantic access. Second, we explored whether the type of pathology (LB or NFTs) in these strategic regions differed between those with and without VF impairments. We hypothesized that the overall burden of pathological changes, whether LB or NFTs in their respective brain regions, would be higher in those with VF deficits than those without.

2. Methods

2.1. Participants

Data was abstracted from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) database (www.brainandbodydonationprogram.org). The overarching purposes and methodology of this study are described in detail elsewhere [16]. All study procedures were reviewed by the local institutional review board for AZSAND, with written informed consent obtained for all participants. The details of clinical examination, neuropathological procedures, and diagnostic criteria utilized elsewhere are described in detail elsewhere [16] and are only briefly reviewed here. For the current study, we reviewed 1210 cases from the database. We included individuals with a clinicopathologically confirmed diagnosis of PD (referred to below as the PD group) and did not exclude individuals with an additional clinicopathological diagnosis of AD (referred to below as the PD + AD group). However, we did exclude individuals who met criteria for other neurodegenerative conditions (i.e. atypical parkinsonian conditions, dementia with Lewy bodies, other tauopathies., etc.). Next, individuals who did not have VF scores from within 2 years of their autopsy or had missing variables from their autopsy or clinical findings relevant to this study (N = 4) were excluded. Finally, we excluded those who were left handed as neuropathological ratings are obtained from the left hemisphere in the AZSAND database, and a subset of those who are left handed may have atypical language lateralization. This left 47 cases for the current analysis.

2.2. Neuropsychological examination

Neuropsychologists and trained staff in AZSAND examine enrollees with a core neuropsychological battery (see 16). Pertinent to the current study, all participants completed the Controlled Oral Word Association test to assess phonemic fluency [17]. Participants are asked to state as many words as possible with a target letter in 60 seconds. Proper nouns and similar words with different endings are excluded. Three trials are given with different letters for each trial. Semantic or category fluency is assessed by the participant naming as many different animals as possible in 60 s, with total correct (non-rule violation or non-repetition errors) being counted as correct. For the current study, phonemic and semantic verbal fluency performances were transformed into Z-scores using age and education adjusted normative data for older adults that is commonly used in clinical practice [18]. For the primary analyses, impairment was defined as performances at or below one standard deviation below the age/education adjusted means. As current diagnostic schema for PD MCI suggest scores ranging from 1 to 2 standard deviations below the mean be used to define impairment [12], we repeated the analyses with a 1.5 standard deviation below the mean cut point and present that information in supplemental tables. Age at the time of neuropsychological evaluation was calculated by subtracting the difference between the year of autopsy and year of neuropsychological examination from the listed age at death. For those over the age of 90, age was transformed to 90 for comparison (this was the case for 3 of the participants).

2.3. Other instruments

Motor impairments were defined by part three of the Unified Parkinson's Disease Rating Scale (UPDRS [19]. Overall dementia severity was staged by clinician ratings on the Functional Assessment Staging Test (FAST), a clinician rating of dementia severity based upon caregiver report and observations [20]. Scores range from 1 (normal) to 7 (profound dementia). In addition, global cognitive abilities were assessed by the Mini Mental State Examination (MMSE [21];

2.4. Statistical analysis

Clinical and demographic variables were compared between the PD and PD + AD groups using Welch's *t*-test for unequal sample sizes or chi-square as appropriate. Cohen's d is reported for effect size. For the primary hypotheses, we created anatomical distribution summary scores from the semi-quantitative neuropathological ratings included in the AZSAND database. Summary scores were created by adding together the neuropathological ratings of pathology density in particular regions. The limbic pathology score consisted of LB densities within the amygdala, cingulate cortex, transentorhinal cortex as well as AD tangle pathology within the hippocampus and entorhinal regions. The frontal pathology score included the sum of frontal Lewy bodies as well as frontal tangles. The temporal pathology score consisted of temporal lobe Lewy bodies and temporal lobe tangles. These global measures are considered the primary variables for our analyses. However, as our second hypothesis sought to evaluate the relative contribution of LB versus NFT pathology, we also explored individual pathology score differences in these locations as well.

After categorizing subject performances on the fluency measures into impaired and unimpaired groups on the basis of normative data, we compared pathological burden using one sided (hypothesizing greater pathological burden always associated with worse cognitive performance) Wilcoxon Mann Whitney tests (reporting Wilcoxon W statistics rather than U statistics), which are robust to violations of normality and uneven sample sizes. Effect sizes are reported in terms of rank biserial correlations. These analyses were repeated in those who met criteria for PD alone and PD + AD groups. Analyses were repeated for particular groups of interest: those without a generalized dementia syndrome defined by MMSE ≥ 25 [27], and comparing those with selected fluency impairments versus those who did not exhibit those findings. Analyses were conducted in JASP [22].

Table 1
Demographic, clinical, and cognitive characteristics of the sample.

	Variable	Parkinson's Disease Only (N = 34)		Parkinson's + Alzheimer's Disease (N = 13)		Difference
		Mean(SD)	Frequency	Mean(SD)	Frequency	
Demographics	Age	78.2(7.0)	–	81.8(4.2)	–	$t(36.13) = 2.16$ df = 36.13, $p = .038$, $d = .63$
	Education (years)	15.3(2.7)	–	14.4(2.1)	–	Ns
	Gender- Male		64.7%		53.8%	Ns
Motor Symptoms	UPDRS- Part 3	34.6(16.3)	–	31.3(14.8)		Ns
Cognitive Variables	FAST Stage- 1	–	11.8%	–	0%	χ^2 (8) = 16.23, $p = .039$
	2	–	11.8%	–	0%	
	3	–	11.8%	–	7.7%	
	4	–	26.5%	–	69.2%	
	5+	–	38.2%	–	15.4%	
	MMSE	24.7(3.9)	–	22.8(3.2)	–	Ns
	Animal Fluency (Z-Score)	−1.2(1.2)	–	−1.9(.8)	–	$t(33.18) = -2.24$, $p = .03$, d = −.66
	% Impaired	–	50.0%	–	84.6%	Ns
	Phonemic Fluency (Z-Score)	−0.8(1.3)	–	−1.6(0.7)		$t(41.12) = -2.88$, $p = .006$, $d = -.805$
	% Impaired	–	61.8%	–	84.6%	χ^2 (1) = 4.7, $p = .03$

Note: Ns = not statistically significant.

3. Results

3.1. Demographics and clinical characteristics

Descriptive measures for the sample are found in Table 1, with comparisons between individuals who were found to have PD only as their final pathological diagnosis, versus also having an additional diagnosis of Alzheimer's disease (PD + AD). Individuals with PD only were younger than those with PD + AD. There were no other demographic differences between the pathologically defined groups. All of the PD only group and 92.3% of the PD + AD group were Caucasian. 68% of the UPDRS scales were administered to patients in their "off" medication state. There were no significant differences in UPDRS ratings between the groups. The distribution of FAST scores between the groups was different, with the PD + AD group mainly being in stages 4 and 5 of dementia, while the PD group had more individuals in the milder stages of cognitive decline and early dementia (stages 1–3). However, there was no significant difference between the MMSE scores between the PD and PD + AD groups.

3.2. Neuropathological differences between those with and without semantic fluency impairments

Table 2 describes LB and NFT density and distribution between individuals with and without semantic fluency impairments. The two groups differed significantly only in terms of total limbic pathology when using the pathology summary scores. When individual pathological densities were explored, greater densities of LB in the transentorhinal cortex were found in those with impaired semantic fluency relative to those without such impairments. Trends (defined as $p < .10$) were noted for increased LB pathology in the amygdala and NFT within the hippocampus in those with impaired semantic fluency. Frontal and neocortical temporal lobe pathology was not found to differ significantly between the two groups.

When individuals who did not meet criteria for comorbid AD (N = 34, 21 with impaired semantic fluency performance and 13 without) were considered separately, the same pattern held true. There was an overall difference in limbic pathology (W = 191.5; $p = .025$, $r_{pb} = .40$), with greater density of LB in the amygdala (W = 177, $p = .04$, $r_{pb} = .297$) and transentorhinal cortex (W = 199, $p = .003$ $r_{pb} = .53$), in those with impaired semantic fluency. Within the PD + AD group (n = 13) there were only two cases in which semantic fluency measures were unimpaired, precluding further analysis.

3.3. Neuropathological differences between those with and without phonemic fluency impairments

Table 3 describes pathological distributions in individuals with and without phonemic fluency impairments. The presence of impaired phonemic fluency was associated with greater total frontal, temporal,

Table 2
Comparison of Lewy bodies and Alzheimer's pathology density and distribution between individuals with and without semantic fluency impairments.

	Normal Semantic Fluency (N = 15)	Impaired Semantic Fluency (N = 32)	Difference
	Mean(SD)	Mean(SD)	
Frontal Lobe Pathology	**1.6(1.5)**	**1.5(1.1)**	**Ns**
Frontal Lewy Body	1.2(1.1)	1.3(.9)	Ns
Frontal Tangles	.4(.7)	.2(.5)	Ns
Temporal Lobe Pathology	**2.2(1.5)**	**2.4(1.3)**	**Ns**
Temporal Lewy Bodies	1.3(0.9)	1.5(.8)	Ns
Temporal Tangles	0.9(0.9)	0.9(.8)	Ns
Limbic Pathology	**13.1(2.6)**	**14.4(3.3)**	**W = 320.0, $p = .033$, r_{pb}, = .33**
LB Transentorhinal	2.6(0.8)	3.2(.9)	W = 332.0, $p = .007$, $r_{pb} = .428$
LB Amygdala	3.5(0.5)	3.7(.7)	Ns(A)
LB Cingulate	2.3(1.2)	2.6(1.0)	Ns
Tangle Hippocampal	2.0(0.8)	2.3(.7)	Ns(B)
Tangle Entorhinal	2.6(0.6)	2.7(.6)	Ns

Note: Ns = not statistically significant (A)Trend noted, W = 292.5, p = .069, $r_{pb} = .219$ (B) Trend noted, W = 295.0, $p = .09$, $r_{pb} = .229$.

Table 3
Comparison of Lewy bodies and Alzheimer's pathology density and distribution between individuals with and without phonemic fluency impairments.

	Normal Phonemic Fluency (N = 19)	Impaired Phonemic Fluency (N = 28)	Difference
	Mean(SD)	Mean(SD)	
Frontal Lobe Pathology	**1.1(1.2)**	**1.8(1.2)**	**W = 364.5, p = .011, r_{pb} = .37**
Frontal Lewy Body	.9(1.0)	1.5(0.9)	W = 364.5, p = .009, rank biserial = 0.37
Frontal Tangles	0.2(0.5)	0.3(0.2)	Ns
Temporal Lobe Pathology	**1.8(1.1)**	**2.7(1.4)**	**W = 356.5, p = .022, r_{pb} = .34**
Temporal Lewy Bodies	1.6(0.8)	1.6(0.8)	Ns
Temporal Tangles	0.6(0.6)	1.1(0.9)	W = 355.5, p = .016, $r_{pb=}$.336
Limbic Pathology	**12.9(3.2)**	**14.7(2.8)**	**W = 357.0, p = .024, r_{pb} = .34**
LB Transentorhinal	2.6(1.1)	3.3(0.7)	W = 350.5, p = .013, r_{pb} = .37
LB Amygdala	3.5(0.8)	3.8(0.5)	Ns(a)
LB Cingulate	2.4(1.2)	2.6(0.9)	Ns
Tangle Hippocampal	2.1(0.8)	2.4(0.7)	Ns
Tangle Entorhinal	2.5(0.7)	2.8(0.5)	Ns(b)

Note: NS = not statistically significant; A) Trend, W = 320.5, p = .07, r_{pb} = .205; B) Trend, W = 306.5, p = .057, r_{pb} = .216).

and limbic pathology, with a broad mix of locations and types of pathology being associated with impaired performance on this measure.

When the 34 individuals with PD only were considered, individuals with (n = 17) and without (n = 17) phonemic fluency impairments differed only in terms of limbic area pathological densities (p = .03), though again there was a noted trend for differences in frontal (p = .08) and temporal (p = .086) regions as well. In those with impaired phonemic fluency, LB pathologic burden was higher in within the frontal lobe (p = .04), transentorhinal cortex (p = .01), and amygdala (p = .046). Again, only 2 individuals with PD + AD did not have impaired phonemic fluency, which precluded looking specifically within the PD + AD group for associations with performances.

3.4. Repeating the analyses with a stricter cutpoint for defining impairment

As noted above, current recommendations for defining cognitive impairment in PD [12] suggest a cut point anywhere from 1 to 2 standard deviations below demographically matched normative data as defining impairment. As a 1.5 standard deviation below the mean cutpoint is also commonly employed clinically, the above analyses were repeated using this definition of impairment. For the semantic fluency analyses, results were essentially unchanged (see Supplemental Tables 1 and 2). Three individuals were reclassified from impaired to unimpaired. These three individuals had PD only, and their performances were 1 standard deviation below their demographic controls. The overall pattern of results was the same, with the group defined as impaired having greater limbic pathology (W = 352.0; p = .023, r_{pb} = .35). Though overall frontal pathology did not differ between the groups, Lewy bodies in the frontal lobe were now significantly different between the two groups (W = 334.0; p = .038, r_{pb} = .28).

For phonemic fluency, 3 individuals were reclassified from impaired to unimpaired with the change in the cut score. In contrast to the semantic fluency results, these three individuals had PD + AD diagnoses, with phonemic fluency performances that fell very close to the 1.5 standard deviation cutpoint (−1.2 Z, −1.4Z and −1.4Z for each of these cases). In 2/3 cases, neuropathological scores were greater than the average for the other impaired individuals in this domain. After adjusting the cutpoint, there were no significant differences found for overall neuropathology summary scores between impaired and unimpaired groups, though impaired participants still had greater neurofibrillary tangles overall in temporal and entorhinal corticies (see Supplemental Tables 3 and 4).

3.5. Exploring the impact of dementia severity and selective verbal fluency impairments

Two other analyses were undertaken to better tease apart the influence of the more generalized dementia syndrome on the findings and a second to evaluate the impact of selective verbal fluency deficits. These analyses are considered exploratory due to the small nature of the sample sizes in these subgroups.

In terms of dementia severity, we repeated the analysis using only individuals with an MMSE ≥ 25 (N = 22) [27] to rule out those with a more significant generalized cognitive impairment. Using the total neuropathology scores, those with impaired phonemic fluency (N = 6) had greater total neuropathological burden in temporal (W = 81.0; p = .006, r_{pb} = .688) and frontal (W = 75.00; p = .020, r_{pb} = .563) cortices, with a trend for greater limbic burden as well (W = 69.5, p = .059, r_{pb} = .448). When individuals without dementia but with (N = 7) and without (N = 15) semantic fluency impairments were compared on total neuropathological burden, no significant differences were found between the groups.

To evaluate the impact of selective weaknesses in verbal fluency impairments, we utilized the entire sample and a definition of 1 standard deviation below the mean to define impairment on each task. When individuals with selective impairments in semantic verbal fluency (N = 10) were compared with those who had no verbal fluency impairment on either task (N = 14), there remained a significant difference between the groups on total neuropathological burden in limbic structures (W = 99.5, p = .043, r_{pb} = .421), with trends for greater pathological burden in temporal (W = 93.00, p = .085, r_{pb} = .329) and frontal regions (W = 94.5, p = .072, r_{pb} = .35). Selective impairments in COWA performance were infrequent (N = 5), but when compared to the 14 individuals with no impairments on either task (N = 14), greater pathological burden was observed in limbic structures (W = 57.5, p = .020, r_{pb} = .643), and temporal (W = 55.00, p = .029, r_{pb} = .571) regions, with a trend noted for frontal regions as well (W = 49.0, p = .091, r_{pb} = .40). When individuals who only had an impaired semantic fluency performance (not COWA; N = 10) were compared against those who only showed an impaired COWA performance (N = 5), no significant differences in temporal, frontal, or limbic pathological distribution were found.

4. Conclusion

In the current study, impairments in verbal fluency tasks were associated with greater pathology in a range of limbic and neocortical regions, with the pattern of association differing depending on the task used to define impairment.

Phonemic fluency impairments were associated with greater pathological burden across frontal, temporal, and limbic regions. In keeping with prior research [11], this likely reflects the fact that phonemic fluency puts greater demands on executive control of lexical search, thought to be underpinned by fronto-subcortical circuits.

However, because this task still requires access to lexical and semantic word knowledge, impairments are also related to greater neuropathological burden in the broader temporolimbic semantic network. This effect held even when individuals who had selected deficits in phonemic fluency were compared against individuals without impairments, and even when those without a more significant dementia syndrome were compared.

In contrast, individuals with semantic fluency impairments demonstrated greater density of pathology, particularly Lewy body pathology, in the limbic system. The effect size was largest for LB densities in the transentorhinal cortex, with trends noted for higher densities of LB pathology in the amygdala and AD tangles in the hippocampus as well. Though these limbic structures are most often thought of as being involved with episodic memory, limbic circuits have been increasingly implicated in semantic access in conditions such as epilepsy [23] as well as in fMRI studies in patients without neurological conditions [24]. This effect was significant in the sample as a whole, though was not strongly identified in those with no underlying dementia syndrome.

A meta-analysis of verbal fluency difficulties in PD revealed more impairment on semantic fluency than phonemic fluency at a group level [8]. Furthermore, at the level of the individual, the presence of semantic fluency deficits in PD has been identified as a potent risk factor of the development of PD related dementia, with these impairments thought to reflect the spread of PD pathology to posterior temporal networks [14]. Our findings are complementary with this formulation. Mean verbal fluency scores were weaker for semantic than phonemic fluency in both PD and PD + AD groups. Furthermore, the presence of semantic fluency impairment was indeed associated with greater pathological burden in particularly the limbic system. Thus these findings suggest that verbal fluency impairments in particular may represent important cognitive markers to help track disease progression through varied cortical and limbic structures.

Given that semantic fluency impairments are also common in those with AD [15], concern might be raised that AD pathology was driving the impairments we observed. However, greater LB density was observed in limbic and cortical structures in those with impaired VF, with regional findings varying depending on the task involved. AD tangles though did trend higher in many of the same regions. Thus, similar to other studies that did not find clinical differences between those with PD vs. PD + AD [25], our results lead to caution in interpreting cognitive scores as markers of specific underlying disease processes. In those with PD, our analyses suggest that overall pathological burden in particular neuroanatomical structures is associated with cognitive symptoms, and this pattern can be seen for both LB and AD pathology.

The current results provide further empirical support to cognitive theories of the underlying networks assessed by VF tasks and cast caution on interpreting VF tasks interchangeably. For example, while current PD mild cognitive impairment criteria cite the use of phonemic or semantic type of verbal fluency task as a marker of executive dysfunction [12], it may be helpful for clinicians and researchers to utilize phonemic rather than semantic fluency if the intention is to index frontal lobe involvement, given that impairment on phonemic fluency is associated with greater frontal lobe pathology. However, it should be recognized that impairment on phonemic fluency is also associated with greater pathological density in temporal and limbic systems as well. Different scoring techniques which help to tease apart sematic clustering and executive switching components of verbal fluency tasks [26] may help to aide interpretation of impairments on these tasks to help index “pure” executive dysfunction. Results also further the hypothesis that difficulty with semantic access may serve as a marker of “posterior” network involvement in PD [14], with the caveat that semantic fluency impairments may reflect posterior neocortical as well as limbic spread of PD as well as the presence of other neuropathological conditions in these regions. In addition, the relationship of semantic fluency with limbic pathological burden was at least somewhat influenced by the presence of overall dementia severity.

Another issue raised by the current findings is the impact of psychometric definition of impairment on the results. Current clinical guidance suggests a definition of impairment between 1 and 2 standard deviations below demographically matched controls, in addition to other methods [12]. In the current study, changing to a more stringent cutpoint had little effect on semantic fluency findings, but did change the associations with phonemic fluency impairments. This change appeared to occur because these “borderline” impairment cases actually had pathological burdens greater than others in the impairment group and were near the cutpoint defining impairment. Understanding what degree of pathological burden is associated with cognitive impairment in particular (and conversely, studying those with high pathological burdens but no measurable cognitive impairment) is an important venue for future studies.

Although these findings are intriguing, the generalizability may be limited due to our small, well educated, and older sample size which may not be reflective of other samples. Additionally, it is important to note that our current study did not explore the relationship of other factors (i.e. neurochemical changes, comorbid depression, etc.) which may impact cognitive test performances. Effect sizes were small to moderate, and more fine-grained analysis of pathology in specific cortical regions was not available which may be helpful to explore in future studies. It is also important to note that verbal fluency measures involve other cognitive constructs, such as speeded processing and general verbal intellectual abilities, and our results also highlight the role of global dementia severity on cognitive/pathological relationships. Further work to understand this complex interplay will be necessary.

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Appendix A. Supplementary data

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