Quantitative vibratory sensation measurement is related to sensory cortical thickness in MS

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Abstract

Objective: Vibratory sensation is a quantifiable measure of physical dysfunction and is often related to spinal cord pathology; however, its association with relevant brain areas has not been fully explored. Our objective was to establish a cortical structural substrate for vibration sensation.

Methods: Eighty-four individuals with multiple sclerosis (MS) (n = 54 relapsing, n = 30 progressive) and 28 controls participated in vibratory sensation threshold quantification at the great toe and a 3T MRI evaluating volume of the thalamus and cortical thickness primary and secondary sensory cortices.

Results: After controlling for age, sex, and disability level, vibratory sensation thresholds were significantly related to cortical thickness of the anterior cingulate (P = 0.041), parietal operculum (P = 0.022), and inferior frontal gyrus pars operculum (P = 0.007), and pars triangularis (P = 0.029). Within the progressive disease subtype, there were significant relationships between vibratory sensation and thalamic volume (P = 0.039) as well as reduced inferior frontal gyrus pars operculum (P = 0.014) and pars orbitalis (P = 0.005) cortical thickness.

Conclusions: The data show significant independent relationships between quantitative vibratory sensation and measures of primary and secondary sensory cortices. Quantitative clinical measurement of vibratory sensation reflects pathological changes in spatially distinct brain areas and may supplement information captured by brain atrophy measures. Without overt relapses, monitoring decline in progressive forms of MS has proved challenging; quantitative clinical assessment may provide a tool to examine pathological decline in this cohort. These data suggest that quantitative clinical assessment may be a reliable way to examine pathological decline and have broader relevance to progressive forms of MS.

Introduction

Sensory impairment significantly impacts individuals with multiple sclerosis (MS) with more than 80% reporting sensory symptoms within 1 year of diagnosis.1 Although commonly monitored by neurologists, quantitative measurement of sensation is lacking and little is known about how sensory impairment correlates with brain pathology.

Proprioception and vibration sensation, both carried by the dorsal columns, are frequently impaired in MS.2,3 Proprioceptive input contributes to balance impairment,
postural control, and falls; similarly, vibratory sensation is linked with balance and walking speed. Our group has linked tract-specific measures of the dorsal columns, spinal cord, and peripapillary retinal nerve fiber layer with vibratory sensation thresholds in MS. Although animal work shows that the primary and secondary sensory cortices and the ventral postero lateral nucleus of the somatosensory thalamus correlate with behavior during a vibrotactile detection task, and human work shows that central processing of proprioceptive input (measured with vibration to the tendons) is related to balance performance and thalamic activation is related to mental imagery of tactile stimulation, relationships among vibratory sensation and measures of cortical thickness, as well as gray, white, and thalamic volume have not been described.

Work from our group has shown that the loss of sensation affects motor function. Interventions that target sensory symptoms during rehabilitation have been shown to improve motor function and symptom severity. Augmenting sensory feedback to modulate, or prime, neural excitability has been shown to improve motor performance. In MS specifically, multiple treatments with electrical nerve stimulation (i.e., TENS) resulted in improved sensory function; however, the mechanisms responsible for these changes remain unclear. These examples highlight the potential for developing MS-specific interventions to combat the limitations that result from impaired sensation that is so common in MS.

Determining the underlying relationship between known cortical–subcortical sensory areas and their relationship with an effective behavioral measure of vibratory sensation would be useful for tracking sensory deficits over time and developing effective interventions to improve sensation in persons with MS. The objective of this cross-sectional study was to establish a cortical structural substrate for vibration sensation. We hypothesized that our clinical measure of vibratory sensation would be associated with volume of, or gray matter (GM) thickness in, primary and secondary sensory cortices.

Methods

Eighty-four individuals with clinically definite MS as defined by the 2005 McDonald criteria who had volunteered for an ongoing longitudinal parent study at the MS Center at Johns Hopkins Medical Institutions between 2008 and 2010 were recruited for this study. Twenty-eight healthy control participants who had volunteered for a strength training intervention trial were recruited for this study. A single time point (i.e., baseline visit for control participants) was used for individuals who met our study criteria. Participants with MS were included if they had received a clinical diagnosis of MS and were able to ambulate 25 feet. All participants demonstrated full understanding of the study and study-related tests. Participants with MS were excluded if they reported a relapse within three months of testing or reported a history of peripheral neuropathy or any other neurologic or cognitive condition that might interfere with sensory testing and study procedures. In a single session, EDSS, behavioral, and MRI measures were acquired.

Standard protocol approvals, registrations, and patient consents

All participants gave written informed consent prior to participation, and the Institutional Review Boards at Johns Hopkins Medical Institutions and Kennedy Krieger Institute approved all procedures.

Sensation

Vibration thresholds at the great toe were quantified bilaterally using a Vibratron II device (Physitemp, Huron, NJ). Using a two-alternative forced-choice procedure, subjects identified which of two rods was vibrating. The Vibratron is a reliable and objective quantitative measure of sensation in MS that can identify declines in sensation not detected by currently used clinical rating scales, such as the Expanded Disability Status Scale (EDSS). The same two study team members performed sensation testing on all participants. These raters have previously established excellent interrater (ICC = 0.96) and test–retest (ICC = 0.91) reliability for the Vibratron II device. Measurement of the more sensitive (best) great toe (BGT) was used for analyses.

Magnetic Resonance Imaging (MRI) acquisition

Brain MRI was performed using a 3-tesla Philips Achieva scanner (Philips Medical System, Best, the Netherlands). Two-axial whole-brain sequences without gaps were used: multi-slice fluid-attenuated inversion recovery (FLAIR); acquired resolution: 0.8 × 0.8 × 2.2 or 0.8 × 0.8 × 4.4 mm; TE: 68 msec; TR: 11s; TI: 2.8s; SENSE factor: 2; Turbo factor: 17; averages: 1; dual-echo turbo spin echo (DE-TSE); acquired resolution: 1.1 × 1.1 × 2.2 mm; reconstructed resolution: 0.8 × 0.8 × 2.2 mm; TE1: 12 msec; TE2: 80 msec; TR: 4166 msec; flip angle: 90 degrees; SENSE factor: 2; Turbo factor: 8; averages: 1; and 3-D magnetization-prepared rapid gradient echo (MPRAGE); acquired resolution: 1.1 × 1.1 × 1.2 mm; reconstructed resolution: 0.8 × 0.8 × 1.2 mm; TE: 6 msec; TR: ~10 msec; TI:
835 msec; flip angle: 8 degrees; SENSE factor: 2; averages: 1.

**MRI Analysis and measurement of volumes and cortical thickness**

The MR image analysis pipeline started with inhomogeneity correction\(^2\) of the MPRAGE, T2-w MRI (the second echo of the DE-TSE acquisition) and FLAIR scans, followed by rigid registration of the MPRAGE to the standard Montreal Neurological Institute-152 atlas resampled to 0.8 mm isotropic voxels. The T2-w MRI and FLAIR scans were also transformed to this space. A brain mask was estimated from the MPRAGE and T2-w MRI scans\(^2\) and applied to all scans. Prior to whole-brain segmentation, the skull masked MPRAGE and FLAIR images were used to delineate MS lesions.\(^2\) To allow for accurate parcellation of the remaining brain structures, lesion filling was performed using the “lesion filling” tool from FSL.\(^2\) An initial cortical and subcortical segmentation was generated by multi-atlas label fusion\(^2\) of 30 Neuromorphometrics atlases (http://www.neuromorphometrics.com/) using the ANTs software package.\(^2\) The MaCRUISE segmentation method\(^2\) was applied to reconstruct the inner and outer cortical surfaces and refine the parcellation of the cortex into 49 gyral labels. Cortical thickness was computed as the shortest distance from the outer cortical surface to inner cortical surface. The diffusion tensor images (DTI) were estimated after coregistration of the diffusion and T2-w MRI scans and distortion correction. The MPRAGE, T2-w MRI and DTI were used to segment the thalamus using the RAFTS method,\(^3\) thalamic volumes are presented in Table 1. The RAFTS method has been shown to be superior to thalamic analyses with FSL First\(^3\) and FreeSurfer\(^3\) software packages.\(^3\) All processing and segmentation results were manually reviewed by a trained observer (BD).

**Statistical analyses**

Statistical analyses were performed using the R Software. Multiple linear regression was used to investigate the association of each region of interest (ROI) based measure with best vibration while controlling for confounders including age, sex, and EDSS. Finally, similar analyses were performed within each disease subtype group to find possible associations of brain measurements with best vibration within each disease subtype.

Appropriate cortices were matched to the side corresponding to the BGT. Although MaCRUISE output provides 49 gyral labels in each hemisphere, we a priori chose to examine only primary and secondary sensory areas. Thus, in addition to thalamic volume, we examined cortical thickness in primary and secondary cortical areas that have been shown to be related to sensory function: postcentral gyrus, precentral gyrus, superior parietal lobe, parietal operculum, supramarginal gyrus, inferior frontal gyrus (including pars opercularis, pars triangularis and pars orbitalis), middle frontal gyrus, and anterior cingulate gyrus.\(^1,4,15,34–41\) Differences among controls and individuals with MS and among relapsing and progressive subgroups were examined with Mann–Whitney tests. Volume measures were normalized using intracranial volume (ICV) for all analyses. Given the small number of predictors in each model, we did not adjust for multiple comparisons.

**Results**

**Study population**

Eighty-four individuals with MS and 28 healthy controls participated in this study. Subjects were sub-grouped by diagnosis, and baseline characteristics are shown in Table 1. Five individuals with MS and two healthy controls failed quality control for thalamic analyses; thus, their data were removed.

**MS versus control analyses**

We compared vibratory sensation and brain volumes in individuals with MS and healthy controls and between MS subtypes (Table 1). There was no significant difference between individuals with MS and controls in sex or ICV, but controls demonstrated significantly better (i.e., lower vibratory threshold) vibratory sensation than those with MS as well as significantly higher thalamic and cerebral WM volumes (Table 1). These results were maintained when comparing controls to individuals with progressive MS; however, when comparing controls to individuals with relapsing MS, there was no significant difference between groups on vibratory sensation.

**Whole-group analyses**

We examined relationships among brain areas in both individuals with MS and healthy controls using heat maps of Pearson correlations (Fig. 1A–D). There were strong relationships among many of the brain areas, with correlations greater than 0.6 indicated in yellow (Fig. 1A and B). In individuals with MS, all brain areas were minimally correlated with age, symptom duration, sex, EDSS, and ICV, but the strongest confounder related to thalamic volume was lesion volume (Fig. 1C). Thalamus volume was notably not correlated with any of the brain areas in either MS or controls.
In individuals with MS, after controlling for age, sex, and EDSS, there was a significant relationship among BGT and cortical thickness of the anterior cingulate \((P = 0.041, R^2 = 0.204, \text{adjusted } R^2 = 0.156)\), inferior frontal gyrus, pars operculum \((P = 0.044, R^2 = 0.108, \text{adjusted } R^2 = 0.055)\), inferior frontal gyrus pars orbitalis \((P = 0.006, R^2 = 0.297, \text{adjusted } R^2 = 0.254)\), inferior frontal gyrus pars triangularis \((P = 0.029; R^2 = 0.146, \text{adjusted } R^2 = 0.095)\), and parietal operculum \((P = 0.023, R^2 = 0.149, \text{adjusted } R^2 = 0.098)\). However, after controlling for age, subtype, and EDSS, normalized thalamic volume was not a significant predictor of BGT performance \((P = 0.239, R^2 = 0.264, \text{adjusted } R^2 = 0.217)\) (Table 2).

Relapsing versus progressive analyses

Individuals with relapsing disease were significantly younger, with shorter symptom duration, and lower EDSS scores than individuals with progressive disease. Additionally, individuals with progressive disease demonstrated significantly lower cerebral WM volume and performed significantly worse than those with relapsing MS on vibration testing \((P < 0.0001)\) (Table 1).

To further examine the relationships of these cortical measures to vibration sensation within disease subtype, we explored these relationships independently in both relapsing and progressive disease subtypes. In both cases, we controlled for age, sex, and EDSS. There were no significant relationships within the relapsing subtype \((P > 0.05\) for all measures). Interestingly in the progressive subtype, there were significant relationships among BGT performance and thalamic volume \((\beta = 0.0000, P = 0.039)\) as well as reduced cortical thickness in the inferior frontal gyrus pars operculum \((\beta = -0.0112, P = 0.014)\) and pars orbitalis \((\beta = -0.0102, P = 0.005)\). The regression coefficients presented show, for example, that an increase in cortical thickness in the inferior frontal gyrus pars orbitalis by 1 mm³ results in a decrease in BGT of 0.0102 microns, indicating that increased cortical thickness is associated with better vibration perception. (Table 2; Fig. 2).

Discussion

These data establish a cortical substrate for vibration sensation, measured with an objective and clinically available instrument and builds upon recent work demonstrating links between brain pathology and clinical measurement in persons with MS.\textsuperscript{42,43} We hypothesized that vibration sensation on the Vibratron II would correlate with cortical thickness in the primary and secondary sensory cortices. Whole-group analysis shows that vibratory
Figure 1. Heat map demonstrating correlations among primary and secondary sensory areas in (A) individuals with MS and (B) healthy controls, and primary and secondary sensory areas and potential confounders in (C) individuals with MS and (D) healthy controls. EDSS: Expanded Disability Status Scale; IFG: inferior frontal gyrus; ICV: intracranial volume. Using the color scale, a correlation of 1 is white and progressive darkening of colors to dark red indicates poorer correlations.

Table 2. Associations among clinical vibratory testing and cortical brain areas in persons with MS.

| Brain Area                        | All MS Participants | RRMS                             | Progressive MS                              |
|----------------------------------|---------------------|----------------------------------|--------------------------------------------|
|                                  | β                   | P-value                          | β                                          | P-value |
| Thalamus volume                  | −0.0000890456       | 0.239                            | −0.000161132                               | 0.908   |
|                                  | −0.0000244647       | 0.039                            |                                            |         |
| Anterior cingulate               | −0.0054             | 0.041                            | −0.0069                                    | 0.079   |
|                                  | −0.00063            | 0.151                            |                                            |         |
| Middle frontal gyrus             | −0.0042             | 0.138                            | −0.002                                     | 0.622   |
|                                  | −0.0073             | 0.136                            |                                            |         |
| Inferior frontal gyrus pars operculum | −0.0057     | 0.044                            | 0.0003                                    | 0.948   |
|                                  | −0.0112             | 0.014                            |                                            |         |
| Inferior frontal gyrus pars orbitalis | −0.0069   | 0.007                            | −0.005                                    | 0.228   |
|                                  | −0.0102             | 0.005                            |                                            |         |
| Parietal operculum               | −0.0045             | 0.022                            | −0.0053                                    | 0.076   |
|                                  | −0.0056             | 0.089                            |                                            |         |
| Postcentral gyrus                | −0.0017             | 0.645                            | −0.0035                                    | 0.447   |
|                                  | −0.00049            | 0.446                            |                                            |         |
| Precentral gyrus                 | −0.0034             | 0.255                            | −0.0005                                    | 0.876   |
|                                  | −0.01               | 0.093                            |                                            |         |
| Supramarginal gyrus              | 0.0012              | 0.712                            | −0.0009                                    | 0.837   |
|                                  | −0.0028             | 0.607                            |                                            |         |
| Superior parietal lobule         | −0.0032             | 0.382                            | −0.00042                                   | 0.418   |
|                                  | −0.00043            | 0.457                            |                                            |         |
| Inferior frontal gyrus pars triangularis | −0.0059 | 0.029                            | −0.0052                                    | 0.227   |
|                                  | −0.0065             | 0.125                            |                                            |         |

β indicates the regression coefficient; all confounders include age, sex, and EDSS. Bolded values indicate significance at P < 0.05.
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sensation (BGT) is associated with the cortical thickness of the anterior cingulate \((P = 0.041\)), inferior frontal gyrus pars operculum \((P = 0.004\)) and pars triangularis \((P = 0.021\)) as well as the parietal operculum \((P = 0.021\)). The progressive MS subgroup appears to be the largest contributor to these relationships, as there were no significant findings among the relapsing subgroup (Table 2). We also show strong correlations among primary and secondary sensory cortices (Fig. 1). A key finding is that clinical vibratory sensation is significantly correlated with secondary cortices (specifically thalamic volume) in individuals with progressive disease, and not correlated with the whole-group sample. Although a strong relationship among vibratory sensation and postcentral gyrus was expected, our data show no significant relationship in either the relapsing or progressive groups. However, appreciation of vibratory sensation may require additional processing in the secondary sensory cortices. This is consistent with animal studies showing selectivity of cortical areas for in response to different types of touch. Much of the work to predict future disability has focused on relapsing-remitting MS. Without overt relapses, monitoring decline in progressive forms of MS has proved challenging; however, our work suggests that vibratory sensation is a clinical measure that can reflect pathological differences in a spatially distinct CNS area and may supplement information captured by brain atrophy measures alone, particularly in individuals with progressive disease.

Vibratory sensation has been shown to distinguish among individuals with MS with and without walking impairment, and greater postural sway (i.e., proprioceptive impairment) has been linked with cerebellar and spinal cord atrophy. Our results show that vibration sensation among subtypes was significantly different, with individuals in the progressive cohort having worse vibratory sensation (Table 1), which is in agreement with previous work from our laboratory. Further, individuals with relapsing MS demonstrated no significant difference in vibratory sensation from healthy controls. This may be due to the relatively low disability of the relapsing group (average EDSS 2.5) or age-related changes in the control group, which was, on average, slightly older than the relapsing MS group. In the progressive cohort, reduced vibratory sensation was significantly positively associated with reduced thalamic volume as well as cortical thickness in the inferior frontal gyrus pars operculum and pars orbitalis, and marginally associated with reduced cortical thickness in the anterior cingulate \((P = 0.041)\), inferior frontal gyrus pars operculum \((P = 0.014)\); and inferior frontal gyrus pars orbitalis \((P = 0.004)\) and pars triangularis \((P = 0.021)\) as well as the parietal operculum \((P = 0.021)\). The progressive MS subgroup appears to be the largest contributor to these relationships, as there were no significant findings among the relapsing subgroup (Table 2). We also show strong correlations among primary and secondary sensory cortices (Fig. 1). A key finding is that clinical vibratory sensation is significantly correlated with secondary cortices (specifically thalamic volume) in individuals with progressive disease, and not correlated with the whole-group sample. Although a strong relationship among vibratory sensation and postcentral gyrus was expected, our data show no significant relationship in either the relapsing or progressive groups. However, appreciation of vibratory sensation may require additional processing in the secondary sensory cortices. This is consistent with animal studies showing selectivity of cortical areas for in response to different types of touch. Much of the work to predict future disability has focused on relapsing-remitting MS. Without overt relapses, monitoring decline in progressive forms of MS has proved challenging; however, our work suggests that vibratory sensation is a clinical measure that can reflect pathological differences in a spatially distinct CNS area and may supplement information captured by brain atrophy measures alone, particularly in individuals with progressive disease.

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thickness in the precentral gyrus and parietal operculum (Fig. 2). The precentral gyrus has been implicated in sustained attention toward sensation, while the inferior frontal gyrus has been implicated in working memory for sensory processing. Thus, it is possible that performance on the vibration task may be mediated by memory and/or attention in individuals with progressive MS compared to those with relapsing-remitting MS.

The thalamus relays sensory information to higher cortical centers that influence cognition, so it is perhaps not surprising that thalamic atrophy has been linked with clinical and cognitive performance in both relapsing-remitting MS and in advanced disease stages. The Vibratron requires individuals to make a forced-choice decision about which of two rods is vibrating. Thus, individuals must compare the two rods, holding the information in working memory while they make a decision. The neural correlates of vibrotactile decision-making have been studied extensively using single-unit recordings in nonhuman primates, as well as neuroimaging and transcranial magnetic stimulation (TMS) studies in humans. These studies confirm relationships among primary and secondary sensory areas with working memory areas such as dorsal–lateral frontal cortex during vibrotactile decision-making processes. Thus, the interplay of sensory and cognitive performance may be important to consider in future studies. In addition, an important next step would be to evaluate longitudinal relationships among sensory deficits, cognitive impairment, and imaging correlates of GM volume.

Although it is known that individuals with sustained disease progression over 5 years demonstrate whole-brain, cortical, and thalamic atrophy, which is associated with increased T2 lesion burden and WM damage, our data surprisingly showed no significant difference in thalamic volume, lesion volume, or ICV among subtypes (Table 1). Recent work suggests that vibratory sensation detects subcortical changes early in the disease course, and is particularly sensitive to changes in the relapsing-remitting cohort. However, in this cross-sectional study, the relationship of vibratory sensation and thalamic volume is strongest for individuals with progressive MS. While the relapsing-remitting cohort did demonstrate poorer vibratory sensation than controls, this difference was not significant, perhaps as a result of a larger variance and smaller sample size in the relapsing cohort than prior work, or as a result of age-related changes in vibration sensation given the age difference between the relapsing-remitting cohort and the control group. While this dataset does not provide information about the relationship of cortical thickness to sensation over time, vibration sensation could be capturing changes in both sensation and cognitive function, such as working memory for sensory processing, which are apparent in individuals with progressive disease. There is evidence that pathogenic mechanisms in MS evolve independently in the brain and spinal cord, supporting the idea that distinct mechanisms may affect areas of the CNS differentially by disease subtype. We found a significant relationship among thalamic volume and vibratory sensation among those with progressive disease. The thalamus is highly connected to sensory cortex; thus, it is not surprising that we can capture this relationship with a clinical measure of vibratory sensation. Future work exploring relationships among specific thalamic nuclei and vibratory sensation may strengthen this finding for individuals with relapsing MS.

There are several limitations in this study. First, our findings show significant associations among vibratory sensation and cortical brain areas in persons with MS, with the progressive MS subgroup as the largest contributor. It is possible that these statistically significant changes may not reflect a true biological effect. However, the results of this study may assist with hypothesis generation for future, larger, confirmatory studies. Given the paucity of clinically relevant markers for progression in Progressive MS, vibratory sensation holds promise as a potential outcome for clinical trials and warrants further investigation. Next, there were a larger number of individuals in the relapsing-remitting cohort as compared to the progressive cohort; however, this is representative of our clinical population. A level of cognitive processing is required to participate in the Vibratron testing; individuals unable to follow study-related commands were excluded from this study; therefore, we did not incorporate individuals with severe cognitive dysfunction. Although quantitative measures of proprioception have been developed for both the upper and lower limbs, both require extensive laboratory equipment; the Vibratron II is a tool that is clinically accessible would be more useful to clinicians assessing individuals with MS. Our testing was conducted only on the great toe, as we were using vibratory sensation as a proxy for quantitative proprioceptive testing to probe balance and gait. Future work should examine vibratory testing in the index finger and relationships with primary and secondary sensory cortices. We did not acquire spinal cord images; examining spinal cord lesions and pathology could help to explain the variance in the associations between vibration and GM structure and distinguish among MS subtypes. As prior data from our laboratory have shown that spinal cord MRI can explain variability in vibration sensation among persons with MS, it is currently not feasible to parse the contributions of individual thalamic nuclei, therefore we only quantified whole thalamic volume. We anticipate that a more refined measure of thalamic nuclei would...
strengthen the structure–function relationships discussed here. Finally, this study was limited to cross-sectional data and cannot draw conclusions about the change in relationships among vibration performance and cortical brain areas over time.

Conclusions

The current study demonstrates significant independent relationships between quantitative vibratory sensation and measures of primary as well as secondary sensory cortices, after adjusting for confounding variables in a diverse sample of individuals with MS. Our data highlight the utility of quantitative vibratory sensation in improving our understanding of relationships uniting structure and function in MS. This is an important step toward using this accessible clinical measure for monitoring the efficacy of pharmacologic interventions, and for developing targeted treatments for individuals with progressive MS. A longitudinal expansion of this dataset will examine the progression of volumetric as well as cortical thickness measures in primary and sensory cortices and will quantify the degree to which these changes track with the clinical measure of vibratory sensation over time.

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Conflict of Interest

Dr. Fritz, Dr. Eloyan, Mr. Glaister, Mr. Dewey, Dr. Al-Louzi, Dr. Costello, Dr. Chen, and Dr. Prince report no disclosures. Dr. Calabresi has received research funding from MedImmune, Biogen, Sanofi, and Novartis, and consulting fees from Disarm Therapeutics, unrelated to the current study. Dr. Zackowski reports research funding from Acorda, Sun Pharmaceuticals and Biogen, unrelated to the current study.

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