# A Diffusion Tensor Magnetic Resonance Imaging Study of Frontal Cortex Connections in Very-Late-Onset Schizophrenia-Like Psychosis

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**Objective:** *Onset of psychosis after the age of 60 may be associated with structural abnormalities within cerebral white matter. The authors looked within white-matter tracts, which mediate connectivity of the frontal lobes, in psychotic patients for evidence of loss of fiber integrity consistent with degenerative damage.* **Methods:** *Fourteen patients with very-late-onset schizophrenia-like psychosis and an age-matched control group underwent diffusion tensor magnetic resonance imaging. Tract maps were constructed for each subject from the imaging data, and measurements of fractional anisotropy and mean diffusivity were made within the uncinate, superior longitudinal, and inferior occipito-frontal fasciculi, and the cingulum.* **Results:** *There were no significant differences in fractional anisotropy, a measure of the ordering of axons within fiber tracts, nor in mean diffusivity, an orientationally-averaged measure of the bulk diffusivity within each voxel, between patients and control subjects.* **Conclusion:** *The lack of difference in fractional anisotropy and mean diffusivity measures between patients and controls argues against the presence of structural abnormalities within these tracts and the notion that a focal white-matter abnormality within the tracts investigated underpins the onset of psychosis.* (Am J Geriatr Psychiatry 2005; 13:1092–1099)

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Clinical,[1,2] epidemiological,[3] brain-imaging,[4] and neuropsychological[5] data all support the diagnostic concept of very-late-onset schizophrenia-like psychosis with an onset after the age of 60 years.[6] Debate continues around whether such patients have either "true" schizophrenia with an unusually delayed onset[1] or whether there is some other "neurological" basis for the development of their psychosis in later life.[7] Just as symptoms of psychosis are seen in Alzheimer disease (AD)[8–10] and dementia with Lewy bodies,[11] an as-yet unidentified neuropathology may underpin the development of psychosis in this group. Since these patients do not have diagnosable dementia at the point of presentation,[2,5] nor do they all develop dementia after several years of follow-up,[7,12,13] they provide a model for the investigation of how subtle and non-progressive degenerative brain abnormalities can give rise to schizophrenic symptoms.

Magnetic resonance imaging (MRI), particularly $T_2$-weighted imaging, is sensitive to the presence of cortical and sub-cortical infarcts and is a powerful tool for detecting sub-clinical cerebrovascular disease. The findings of such studies in very-late-onset psychosis,[14–21] however, have been inconsistent, and most have been qualitative or limited to quantified visual ratings of hyperintensities within arbitrarily-defined grey- and white-matter regions. In a quantitative assessment of $T_2$-weighted signal hyperintensities, Sachdev and Brodaty[20] found significant increases in the width of periventricular hyperintensities and in discrete hyperintense signals in the thalamus of these patients. However, a major disadvantage of such $T_2$-weighted imaging studies is that they are unable to demonstrate the individual fiber tracts that constitute white matter, and, hence, localization of hyperintensities to individual fasciculi is not possible. Furthermore, signal changes on T2-weighted images have been shown to correlate poorly with the extent of underlying tract disruption.[22]

A technique that shows great promise for obtaining information about changes in specific tracts is diffusion tensor MRI (DT-MRI).[23] Modification of a conventional MRI acquisition permits quantification of the diffusion characteristics of water molecules in vivo.[24] Within cerebral white matter, water molecules diffuse more freely along axonal bundles than across them.[25] Such directional dependence of diffusivity is termed "anisotropy," and any reduction in white-matter anisotropy indicates a reduction in the order of tissue structure within the volume of measurement. DT-MRI allows full quantification of this tissue anisotropy in vivo.[26] In such anisotropic tissue, a unidirectional measure of the effective diffusivity will depend on the direction in which it is measured. The average of the diffusivity in three orthogonal directions (mathematically equal to one-third the trace of the diffusion tensor) is described as the mean diffusivity. This measure quantifies the overall diffusivity in each voxel; it has been previously shown to be uniform throughout healthy parenchyma in spite of large variations in anisotropy, and it therefore offers a complementary index for characterizing tissue.[27]

DT-MRI studies have shown changes in white-matter anisotropy in the brains of early-onset schizophrenia patients, as compared with age-matched comparison subjects,[28–35] but such studies have reported inconsistent results. More recently, the observation that the axis of fastest water diffusion is parallel to the dominant fiber orientation in vivo has led to the development of diffusion-tensor "tractography," in which the three-dimensional pathways of white-matter tracts are reconstructed by sequentially piecing together discrete and closely-spaced estimates of fiber orientation, to form continuous trajectories.[36–39] We have used this approach in the brains of 14 patients with very-late-onset schizophrenia-like psychosis and a group of aged healthy subjects, in order to localize measurements of mean diffusivity and diffusion anisotropy to within specific candidate tracts along their course. Since an abnormality of fronto-temporal connectivity has been suggested as an explanation for some of the symptoms of schizophrenia,[40–45] those tracts that connect the frontal lobes[46,47] were chosen for study. We hoped that such a methodological approach would allow us to demonstrate, in anatomically small regions in such patients, focal damage to those white-matter tracts that mediate functional connectivity of the frontal lobes that might not be visualized by conventional $T_2$ imaging.

## METHODS

### Subjects

*Very-late-onset schizophrenia-like psychosis subjects.* Fourteen patients with very-late-onset (>age 60

years) schizophrenia-like psychosis were recruited from the Old-Age Psychiatry Service of the South London & Maudsley NHS Trust. Criteria for very-late-onset schizophrenia-like psychosis are shown in Table 1.[6] Exclusion criteria included 1) history of head injury, cerebrovascular event, epilepsy, or other neurological illness; 2) medical conditions, including uncontrolled hypertension, congestive cardiac failure, or severe respiratory disease; 3) fulfillment of DSM-IV criteria for abuse of illicit drugs or alcohol during their lifetime; 4) any contraindications to MRI scanning, including metal implants and claustrophobia; 5) evidence of dementia, cognitive impairment greater than might be expected to accompany psychosis, or a Mini-Mental State Exam (MMSE)[48] score of less than 25 out of 30.

*Elderly comparison subjects.* Fifteen healthy, elderly volunteers (age 65 years and over) were recruited from older peoples' community clubs, residential homes, or from among the spouses of patients. Exclusion criteria were as stated for the patient group, with the additional exclusion of volunteers with past or current psychiatric or neurological illness.

Recruitment and screening of all potential participants was carried out by a geriatric psychiatrist (SR). The screening procedure included a full medical and psychiatric history, including dementia screening via the MMSE.[48] Subjects from both groups gave written consent after the procedure had been fully explained; they were accompanied to and from the scan by a geriatric psychiatrist (SR or RH). The study was approved by the local research Ethics Committee.

### Data Acquisition

Data were acquired using a GE Signa 1.5-tesla LX MRI system (General Electric, Milwaukee, WI), and an acquisition optimized for DT-MRI of white matter, providing whole-head coverage with isotropic image resolution (2.5 mm × 2.5 mm × 2.5 mm). The acquisition was peripherally gated to the cardiac cycle by use of a device placed on the subject's forefinger. Full details are provided in Jones et al.[49] After correction for image distortions introduced by the diffusion-weighting gradients, the diffusion tensor was determined in each voxel.[23]

**TABLE 1. Criteria for Very-Late-Onset Schizophrenia-Like Psychosis[6]**

| |
|---|
| Onset of symptoms over the age of 60 years |
| Presence of fantastic, persecutory, referential, or grandiose delusions, with or without hallucinations |
| Absence of primary affective disorder |
| Intellectual capacity in keeping with that of normal aging (MMSE no less than 25/30) |
| No clouding of consciousness |
| No history of neurological illness/alcohol dependence |
| Normal hematological/biochemical screen (including VDRL) |

*Note:* MMSE: Mini-Mental State Exam; VDRL: venereal disease research laboratory slide test.

### Fiber-Tracking

Full details of the tractography method used in the current study are provided elsewhere,[39] but a brief description follows. Diffusion anisotropy and mean diffusivity measurements were localized to specific fasciculi by use of the technique of fiber-tracking or tractography.[36–38] This technique, by following the pathway of least resistance to the diffusion of water molecules, creates three-dimensional reconstructions of white-matter tracts non-invasively. First, we defined locations for the initiation of the tracking algorithm (referred to here as seedpoints). By cross-referencing neuroanatomical works,[46,47] one of the authors (MC) who was blind to individual subjects' group status, defined 3-D regions of interests (ROIs) believed to contain a section of the desired fasciculus on an image showing fractional anisotropy (FA). FA is a diffusion tensor-derived quantitative measure of water diffusion directionality on a scale from *0* to *1*, with *0* corresponding to isotropic diffusion; that is, no preferred orientation, and *1* corresponding to the case where diffusion occurs only along one axis.[26] At each seedpoint, the fiber orientation was determined (from the diffusion tensor), and the tracking algorithm moved a distance of 0.5 mm along this direction. The diffusion tensor and, hence, fiber orientation was determined at the new location, and the algorithm moved a further 0.5 mm along this direction. A pathway was traced out in this manner until the fractional anisotropy fell below an arbitrary threshold (set to 0.15). The procedure was then repeated by tracking from the seedpoint in the opposite direction to the first step, in order to reconstruct the whole tract passing through the seedpoint. One ROI was defined for fasciculi whose boundaries were clearly delineated on the fractional anisotropy image. In tracts such as the superior longitudinal fasciculus and cingulum, there are no other fasciculi in the neighborhood of

their central portions, and so it was straightforward to define a single ROI that included only fibers belonging to that particular tract. However, in regions where fasciculi run closely to one another (e.g., the uncinate and inferior fronto-occipital fasciculi), definition of a single ROI that includes the fibers of only one of the fasciculi is difficult. To overcome this problem, a second ROI was defined, at a distance from the first ROI, such that it contained at least a section of the desired fasciculus but no fibers of the undesired fasciculi. Only those pathways that were launched from the first ROI and passed through the second ROI were retained for analysis.[37,39]

### Deriving Tract-Specific Measurements

As it was necessary to determine the diffusion tensor at the end of each incremental (0.5-mm) step in the reconstruction of tracts in order to determine the fiber orientation (and hence the direction in which to take the next step), we were able to determine the mean diffusivity and fractional anisotropy at 0.5-mm intervals along each fasciculus. These measures were stored as the tracking process continued, and at the termination of tracking, the average fractional anisotropy and average mean diffusivity for the particular tract were determined (which we refer to as the 'tract-averaged' measures). In this way, measurements of anisotropy and mean diffusivity were confined to within the fasciculus of interest.[50] This approach makes it possible to extract measurements from the entire length of tracts that follow a tortuous route, which would be extremely difficult to extract with the more conventional approach of manually placing a region of interest on two-dimensional slices.

### Statistical Analysis

Data were analyzed with the Statistical Package for Social Sciences (SPSS 10.0). Age differences between the two groups were investigated by the use of a *t*-test for independent samples. The study was designed such that there were eight measures for fractional anisotropy (FA) and mean diffusivity (MD) for each subject (four fasciculi, each with right and left measures). As these measures are potentially highly interrelated, it was necessary to use a repeated-measures model to examine analysis of covariance (ANCOVA). The model included within-subject factors (FA or MD measures in all eight tracts) and between-subject factors (belonging to patient or comparison group). Because previous studies have reported an age-related dependence of various indices of diffusion within the adult brain,[43–54] age was included as a covariate. In order to rule out the potential confounding effects of antipsychotic treatment on tract measures, post-hoc analyses were carried out, using mean daily dose (chlorpromazine [CPZ] mg equiv) as a covariate in the ANCOVA. An alpha level of 0.01 was applied to the models, to control for multiple testing.

## RESULTS

The $T_2$-weighted images that were collected as part of the DT-MRI acquisition from all subjects were checked by a neuroradiologist for gross focal and structural abnormalities, and all of the scans were reported as normal. Two patients and three comparison subjects were unable to remain still during image acquisition, and these subjects were excluded because of the poor quality of the resulting image data. Tract maps of the uncinate, superior longitudinal, and inferior fronto-occipital fasciculi and the cingulum within the right and left hemispheres were successfully constructed in the remaining participants. Figure 1 shows an example of reconstructed trajectories of the candidate white-matter tracts that constitute the longitudinal association fiber system in the left hemisphere of a single subject. Reference to standard anatomical texts[46,47] shows that these reconstructions closely match descriptions from post-mortem studies.

Demographic characteristics of the remaining sample are shown in Table 2. There were 12 subjects in each group. There were no significant differences in the age-distribution between patients (mean: 78.1 years; standard deviation [SD]: 7.4) and comparison subjects (mean: 82.3 years; SD: 9.7; $t_{[22]} = 1.18$; $p = 0.25$). The two groups were also similar with respect to other characteristics, including gender, education level, and handedness. The mean duration of illness in patients was 1.3 years (range: <1 year to 5 years). Nine patients (75%) were prescribed antipsychotic treatment at the following daily dose: risperidone, 1 mg (2 patients); olanzapine, 5 mg–10 mg (5 patients); trifluoperazine, 5 mg (1 patient); and amisulpiride, 50 mg (1 patient). For the purposes of sta-

tistical analysis, this was converted to CPZ mg equivalents: mean: 59.4; SD: 50; range: 0–125).

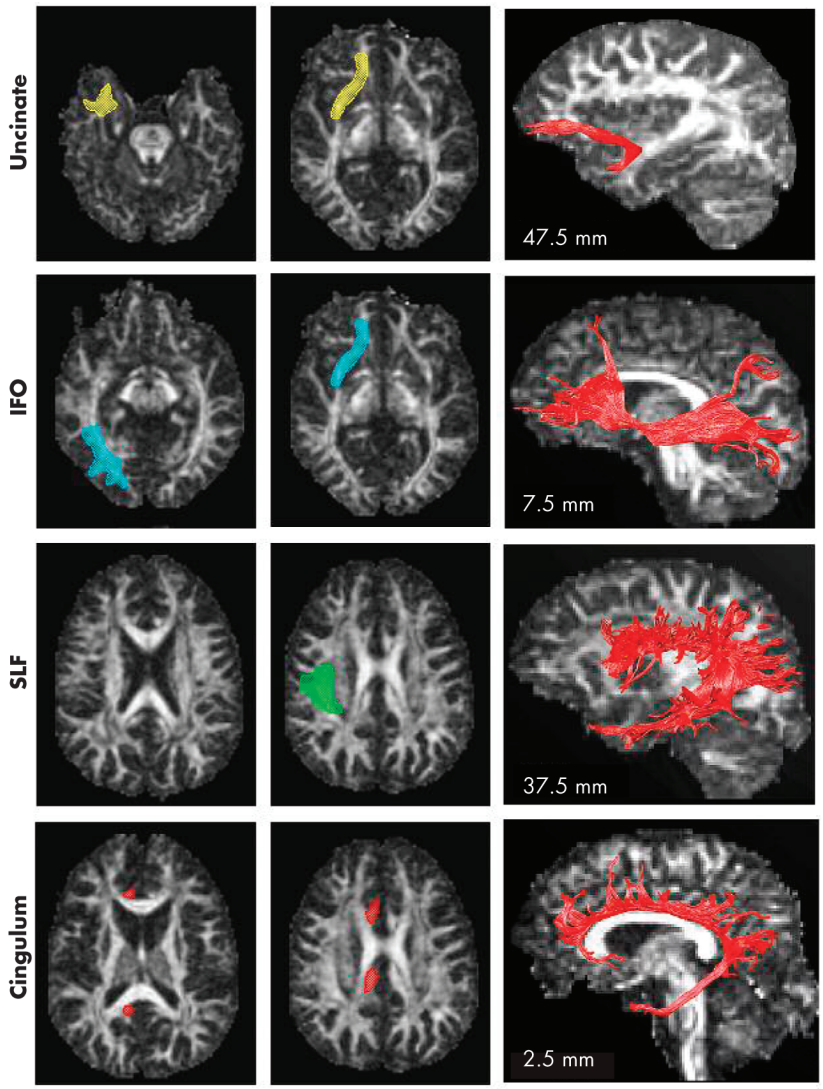
### Fractional Anisotropy

A repeated-measures ANCOVA revealed a significant negative effect of age on FA measures ($F_{[1, 20]} = 7.88$; $p = 0.011$), but no effect of group membership ($F_{[1, 20]} = 0.59$; $p = 0.45$) and no interaction of age × group ($F_{[1, 20]} = 0.67$; $p = 0.42$). When the effects of age were examined in relation to individual tracts, only FA measures obtained from the right uncinate fasciculus were significantly associated with age ($t = -3.69$; $p = 0.001$; Figure 2). A post-hoc analysis showed no significant effect of mean daily drug dosage on FA measures ($F_{[1, 75]} = 2.39$; $p = 0.13$).

### Mean Diffusivity

A repeated-measures ANCOVA revealed a significant positive effect of age on MD measures ($F_{[1, 20]} = 29.09$; $p < 0.0001$), but no significant effect of group ($F_{[1, 20]} = 4.21$; $p = 0.054$), and no interaction in age × group ($F_{[1, 20]} = 3.77$; $p = 0.067$). When the effects of age were examined in individual tracts, MD measures in all except the left cingulum were found

**FIGURE 1. Reconstructed Major Association Fasciculi of the Left Frontal Lobe**



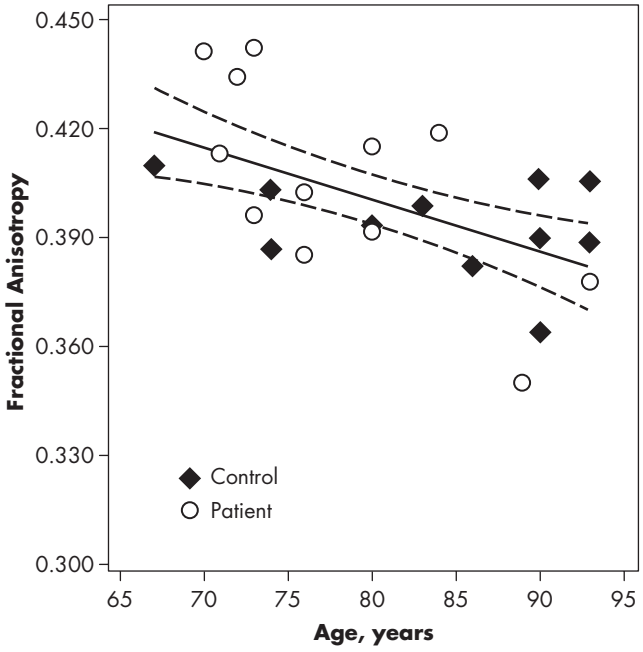

*Note:* The backdrop shows the fractional anisotropy image (distance from the mid-line is given in mm). IFO: inferior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus.

**TABLE 2. Demographic Characteristics of Patient and Comparison Groups**

| | Patient Group (n = 12) | Comparison Group (n = 12) |
|---|---|---|
| Age, years | 78.1 (7.4) | 82.3 (9.7) |
| Education level, years | 9.1 (1.3) | 9.2 (0.8) |
| Women, N (%) | 10 (83) | 10 (83) |
| Right-handed subjects, N (%) | 11 (92) | 10 (83) |
| Duration of illness, years | 1.3 (1.5) | NA |
| Patients on antipsychotic treatment, N (%) | 10 (83) | NA |
| Daily dose of antipsychotic (CPZ mg equiv.) | 59.4 (50.0) | NA |

*Note:* Values are mean (standard deviation), unless otherwise indicated.

**FIGURE 2. Regression Line: Fractional Anisotropy (FA) Measures (95% confidence intervals) in the Right Uncinate Fasciculus by Age**




*Note:* Note that at age 67 years, there are two data points for the comparison subjects. One subject has an FA value of 0.410; the other, 0.412.

to increase significantly with age (Table 3). A post-hoc analysis showed no significant effect of drug dose ($F_{[1, 8]} = 2.17$; $p = 0.18$) on MD measures.

## DISCUSSION

This is the first study to report DT-MRI data from patients with very-late-onset schizophrenia-like psychosis. By restricting our measures to regions within specifically-generated three-dimensional maps of the major fasciculi that mediate connectivity of the frontal lobes, we hoped to localize any disruption of the microstructure of fiber pathways that might accompany onset of psychosis in late life. Similar strategies have allowed the demonstration of reduced left-greater-than-right asymmetry in a small portion of the uncinate fasciculus[33] and white-matter directionality in the left superior longitudinal and uncinate fasciculi[34] in schizophrenia and increased white-matter directionality within portions of the superior longitudinal fasciculus and corpus callosum in schizophrenia patients with auditory hallucinations.[35] Fractional anisotropy is a measure of the degree of diffusion directionality of water within tissue microstructure, whereas mean diffusivity quantifies non-directional, random movement of water within tissue. Reductions in fractional anisotropy reported from various white-matter areas in schizophrenia patients[28–35] and in the white matter of the right superior frontal gyrus of elderly depressed patients[55] have been interpreted as evidence for disruption of microstructure within the axonal bundles that constitute neural circuits.

Our finding of significant associations between age and both FA and MD measures are consistent with previously published data obtained from healthy volunteers.[51–54] We found no significant differences between patients and comparison subjects in relation to FA or MD measures. Hence, we found no evidence to suggest that microstructural abnormalities within the cingulum or superior longitudinal, inferior fronto-occipital, and uncinate fasciculi are more prevalent in the brains of patients with very-late-onset schizophrenia-like psychosis than in their healthy aged peers. This negative finding is perhaps not surprising, since the importance of focal structural brain abnormalities in this group has not been consistently established, and a wide range of factors,[6] including female gender, premorbid social functioning, sensory deficit, and migrant status,[56] appear to contribute to increased risk. Of course, our study does not exclude the possibility that other tracts may be abnormal, and this is an area for future investigation. It is unlikely that chronic exposure to antipsychotic medication might have confounded our results, as patients were generally recruited to the study within a year following first contact with psychiatric services, and there

**TABLE 3. Relationship Between Mean Diffusivity and Age in Individual Tracts**

| Tract | β | SE | *t* | p | Partial $\eta^2$ |
|---|---|---|---|---|---|
| Right cingulum | 0.003 | 0.001 | 3.40 | 0.003 | 0.37 |
| Left cingulum | 0.002 | 0.001 | 1.33 | 0.198 | 0.08 |
| Right IFO | 0.006 | 0.002 | 3.44 | 0.003 | 0.37 |
| Left IFO | 0.005 | 0.001 | 3.31 | 0.004 | 0.35 |
| Right SLF | 0.003 | 0.001 | 3.31 | 0.003 | 0.35 |
| Left SLF | 0.003 | 0.001 | 2.62 | 0.016 | 0.26 |
| Right uncinate | 0.006 | 0.001 | 4.74 | 0.000 | 0.53 |
| Left uncinate | 0.005 | 0.001 | 5.28 | 0.000 | 0.58 |

*Note:* β: slope of the regression line (units: $10^{-3}$ $mm^2s^{-1}year^{-1}$); SE: standard error (units: $10^{-3}$ $mm^2s^{-1}year^{-1}$); partial $\eta^2$: proportion of variance in fractional anisotropy measures accounted for by age; IFO: inferior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus.

was no significant association between mean daily dose of antipsychotic medication and tract measures.

This was a small-scale, exploratory study, and it is, of course, possible that we lacked statistical power to demonstrate any small differences in FA and MD between patients and comparison subjects. Performing a power calculation was problematic because we did not have an a priori expectation of the size of the effect we expected to see, and this is the first DT-MRI study of late-onset schizophrenia-like psychosis ever to have been attempted. Furthermore, the use of the tractography approach proposed here is novel; hence, comparative data are non-existent. Negative findings in brain-imaging studies can be as informative as positive ones, however. Consistent failure by workers in the field to demonstrate the presence of focal structural abnormalities in the brains of such patients without significant cognitive impairment continues to suggest both that we have to continue to look and that the importance of other etiological factors should not be underestimated. Future research in this area should perhaps focus on the influence of age and gender on tract-specific diffusion measures in healthy individuals, because these are believed to be important risk factors for the disorder. The demonstration of a structural, neurodegenerative etiology for very-late-onset schizophrenia-like psychosis would have important implications for prevention, treatment, and prognosis for sufferers and their caregivers.

*Part of this work was made possible through a visit made by DKJ to the Section on Tissue Biophysics and Biomimetics, National Institute of Child Health and Human Development, Bethesda, MD.*

*This work was supported by The Wellcome Trust (Grant #054030/2/98). SSS was supported by a Wellcome Trust Research Training Fellowship.*

*Finally, we thank the anonymous reviewers for their substantive helpful comments and suggestions.*

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