T1rho MRI and CSF biomarkers in diagnosis of Alzheimer’s disease

Mohammad Haris a,⁎, Santosh K. Yadav a, Arshi Rizwan c, Anup Singh b,d, Kejia Cai b,e, Deepak Kaura a, Ena Wang a, Christos Davatzikos f, John Q. Trojanowski b, Elias R. Melhem b, Francesco M. Marincola a, Arijitt Borthakur b

*Research Branch, Sidra Medical and Research Center, Doha, Qatar
†Center for Magnetic Resonance and Optical Imaging, Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA
‡All India Institute of Medical Science, Ansari Nagar East, New Delhi, Delhi 110029, India
§Center for Biomedical Image Analysis, University of Pennsylvania, Philadelphia, PA, USA
¶Section of Biomedical Image Analysis, University of Pennsylvania, Philadelphia, PA, USA
©Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA

A R T I C L E  I N F O

Article history:
Received 29 September 2014
Received in revised form 22 February 2015
Accepted 23 February 2015
Available online 26 February 2015

Keywords:
Alzheimer’s disease
Mild cognitive impairment
Medial temporal lobe
T1rho
CSF biomarkers

A B S T R A C T

In the current study, we have evaluated the performance of magnetic resonance (MR) T1rho (T1ρ) imaging and CSF biomarkers (T-tau, P-tau and Aβ42) in characterization of Alzheimer’s disease (AD) patients from mild cognitive impairment (MCI) and control subjects. With informed consent, AD (n = 27), MCI (n = 17) and control (n = 17) subjects underwent a standardized clinical assessment and brain MRI on a 1.5-T clinical-scanner. T1ρ images were obtained at four different spin-lock pulse duration (10, 20, 30 and 40 ms). T1ρ maps were generated by pixel-wise fitting of signal intensity as a function of the spin-lock pulse duration. T1ρ values from gray matter (GM) and white matter (WM) of medial temporal lobe were calculated. The binary logistic regression using T1ρ and CSF biomarkers as variables was performed to classify each group. T1ρ was able to predict 77.3% controls and 40.0% MCI while CSF biomarkers predicted 81.8% controls and 46.7% MCI. When comparing controls with AD, T1ρ predicted 68.2% controls and 73.9% AD, while CSF biomarkers predicted 77.3% controls and 78.3% for AD. Combination of T1ρ and CSF biomarkers improved the prediction rate to 81.8% for controls and 82.6% for AD. Similarly, on comparing MCI with AD, T1ρ predicted 35.3% MCI and 81.9% AD, whereas CSF biomarkers predicted 53.3% MCI and 83.0% AD. Collectively CSF biomarkers and T1ρ were able to predict 59.3% MCI and 84.6% AD. On receiver operating characteristic analysis T1ρ showed higher sensitivity while CSF biomarkers showed greater specificity in delineating MCI and AD from controls. No significant correlation between T1ρ and CSF biomarkers was observed. The combined use of T1ρ and CSF biomarkers have promise to improve early and specific diagnosis of AD. Furthermore, disease progression form MCI to AD might be easily tracked using these two parameters in combination.

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1. Introduction

Alzheimer’s is a progressive disease, where dementia symptoms gradually worsen over a number of years, and it accounts for 50–80% of dementia cases. Alzheimer’s disease (AD) is estimated to affect ~5.2 million Americans — a number expected to swell to as many as 16 million by 2050. Efforts are in progress to find better ways to treat the disease, delay its onset, and prevent it from developing. Many tools are used to look for signs of AD, including a battery of cognitive and behavioral tests (Koppel et al., 2012; Cummings, 2000; Harwood et al., 2000), cerebrospinal fluid (CSF) analysis (Hansson et al., 2006; Mattsson et al., 2009), magnetic resonance imaging (MRI) (Fayed et al., 2012; Frisoni et al., 2010; Chincarini et al., 2011) and positron emission tomography (PET) scans (Pearson and Colby, 2013; Zhang et al., 2012; Kadir et al., 2012). Imaging techniques (MRI and PET) and CSF studies have been pointed as candidates for the diagnostic biomarkers of AD.

It has been found that the CSF measures of total tau (T-tau) and amyloid beta (Aβ42) levels are individually sensitive though but with

Abbreviations: AD, Alzheimer’s disease; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography; T-tau, total tau; Aβ42, amyloid beta 42; T1ρ, T1rho; MTL, medial temporal lobe; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; TR, repetition time; TE, echo time; T1, total spin lock; FOV, field of view; MPRAGE, magnetization prepared rapid acquisition gradient-echo; TI, inversion time; GM, gray matter; WM, white matter; MTL, medial temporal lobe; ROC, receiver operating characteristic.

Corresponding author at: Research Branch, Sidra Medical and Research Center, P.O. Box 26999, Doha, Qatar. Tel.: +974 4012 6413; fax: +974 4404 2001.
E-mail address: mharis@sidra.org (M. Haris).
lower specificity for AD against other dementia disorders (Blennow, 2004). Moreover, the CSF Aβ1–42 levels are not easily interpreted because CSF Aβ1–42 is not exclusively brain derived and also its production and clearance are not well characterized. A number of studies have suggested that CSF markers in combination with neuroimaging and neuropsychological tools add to the accuracy of AD diagnosis (Richard et al., 2013; Schuff et al., 2009; Vernuri et al., 2010). Out of various medical imaging techniques, MRI is the most widely accepted technique to detect the pathological changes in vivo based on the tissue T1 and T2 contrast relaxation properties. However, to date none of the MRI methods has proven to be an accurate in vivo marker for early diagnosis of AD. Recently, a new MRI technique has been introduced i.e T1rho (T1ρ), the spin lattice relaxation time constant in the rotating frame, which determines the decay of transfer magnetization in presence of “spin-lock” radio-frequency field (Borthakur et al., 2004, 2006b; Wheaton et al., 2005). In biological tissues, T1ρ may have contribution from several molecular interactions. It is also possible that more than one interaction may contribute to the T1ρ signal at a time; however, their relative contributions may differ. Such interactions include chemical exchange, dipolar interaction, and J-coupling. T1ρ MRI has capability to probe the protein contents in various tissues such as brain, blood and cartilage.

T1ρ MRI has been previously used to measure the T1ρ relaxation time in the normal human brain, and showed higher range of values compared to the T2 relaxation time (Borthakur et al., 2004). Earlier, T1ρ has been used to delineate brain tumors (Aronen et al., 1999), characterize breast cancer tissue (Li et al., 2011), and monitor the level of cartilage degeneration (Regatte et al., 2004; Witschey et al., 2010). Borthakur et al. have shown the feasibility of T1ρ imaging in evaluating the plaques burden in a mouse model of AD (Borthakur et al., 2006a). Previous studies have shown higher T1ρ value in the medial temporal lobe (MTL) of AD compared to those of mild cognitive impairment (MCI) and control (Haris et al., 2011; Borthakur et al., 2008).

In the current study, we aim to evaluate the performance of T1ρ and CSF biomarkers in characterization of AD patients from MCI and control subjects. In addition, we also assess any correlation between T1ρ and CSF biomarkers.

### Table 1

Quantitative values of T1ρ relaxation times and CSF biomarkers from control, MCI and AD subjects.

| Group    | T1ρ (ms) [mean ± SE] | CSF biomarkers (pg/mL) [mean ± SE] |
|----------|----------------------|-----------------------------------|
|          | Gray matter          | White matter                      | Luminescence | Luminescence | Luminescence | Luminescence |
|          | (mean ± SE)          | (mean ± SE)                        | T-Tau        | P-Tau        | Aβ1-42       |
| Control  | 96.8 ± 1.8           | 80.3 ± 2.1                         | 56.9 ± 7.0   | 26.1 ± 3.6   | 230.4 ± 11.1 |
| MCI      | 91.9 ± 1.2           | 85.2 ± 1.4                         | 74.0 ± 12.2  | 30.6 ± 5.1   | 188.3 ± 16.0 |
| AD       | 92.3 ± 1.0           | 88.7 ± 1.9                         | 103.3 ± 10.8 | 39.0 ± 4.9   | 144.9 ± 10.4 |

ms = millisecond; SE = standard error; CSF = cerebrospinal fluid; pg = picogram; ml = milliliter; MCI = mild cognitive impairment; AD = Alzheimer’s disease.

### 2. Materials and methods

#### 2.1. Participants

Institutional Review Board of the University of Pennsylvania approved the current study protocol. In this study, we have included 27 AD patients (mean age ± SD = 76.8 ± 9.1 years), 17 MCI patients (mean age ± SD = 71.93 ± 8.7 years), and 17 age-matched control subjects (mean age ± SD = 70.2 ± 9.4 years). A standardized clinical assessment including medical history, physical and neurological examination, psychometric evaluation, and brain MRI was performed in all patients. The general cognitive function in each patient was assessed using Mini-Mental State Examination (MMSE) score. Diagnoses were made by a team consisting of neurologist, neuropsychologist, and psychiatrist who performed extensive behavioral, neuropsychological, and neuroimaging assessments. Diagnoses of MCI was made according to the Petersen criteria for MCI (Petersen et al., 2001), while the AD patients were diagnosed according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association criteria (NINDS–ADRDA) for probable AD (McKhan et al., 1984). Patients with history of irritable bowel syndrome, chronic diarrhea, peptic ulcer, or gastrointestinal reflux disease; cardiac disease; significant electrocardiographic abnormalities; hemotologic disorders; hepatic or renal disease; active malignancy within 5 years; or clinically important depressive, neuropsychiatric, cerebrovascular, or respiratory disease were excluded from this study. The control group consisted of patients, who presented to our memory clinic with subjective complaints, and underwent exactly the same diagnostic work-up as the MCI and AD patients.

#### 2.2. Collection of CSF

CSF samples were obtained from all subjects by lumbar puncture following an overnight fast. Spinal fluid was withdrawn by experienced physician through an atraumatic 25-gauge sprotte needle and immediately transferred to a bar code-labeled polypropylene vial and placed in −80 °C freezer.

#### 2.3. Biomarker analysis using multiplex xMAP (Luminex) technology

The 42 β-amyloid (Aβ1–42), T-tau and P-tau181p levels were measured in sample aliquots using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics immunoassay kit-based reagents (INNO-BIA AlzBio3, Ghent, Belgium). Full details of this combination immunoassay have been previously published (Vanderstichele, 2012; Reijn et al., 2007). Briefly, the Innogenetics kit reagents included well characterized capture monoclonal antibodies specific for Aβ1–42 (4D7A3), T-tau (AT120) and P-tau181p (AT270), each chemically bonded to unique sets of color-coded beads, and analyte specific detector antibodies (HT7, 3D6). Calibration curves were produced for each biomarker using aqueous buffered solutions that contained the

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**Fig. 1.** T1rho (T1ρ) contrast from medial temporal lobe overlaid on anatomic fluid attenuated T1ρ weighted images of control (A), medial cognitive impairment (MCI, B), and Alzheimer’s disease (AD, C) patients. A progressive increase in T1ρ contrast in medial temporal lobe (MTL) region was observed from control to MCI to AD. No T1ρ contrast from CSF was depicted.
of 3 biomarkers at concentrations ranging from 56 to 1948 pg/mL for recombinant tau, 27–1574 pg/mL for synthetic Aβ1-42 peptide and 8–230 pg/mL for a tau synthetic peptide phosphorylated at the threonine 181 position (i.e. the p-tau181p standard).

2.4. MRI protocol

Written informed consent was obtained from each patient before they underwent for MRI. Brain imaging was performed on a 1.5-Tesla Siemens Sonata clinical-scanner (Siemens Medical Systems, Malvern, PA, USA) using a vendor-supplied head coil. T1ρ images were acquired using a fluid-attenuated T1ρ prepared Turbo Spin-Echo pulse sequence (Borthakur et al., 2004; 2008). The imaging parameters were: TR/TE = 2000 ms/12 ms, TSL (duration of spin lock pulse) = 10, 20, 30, 40 ms, spin lock pulse amplitude of 500 Hz, slice thickness = 2 mm, FOV = 24 × 24 cm², matrix size = 256 × 128, bandwidth = 130 Hz/pixel, and echo train length = 4 for a total imaging time of 6 min for four T1ρ weighted images. To remove the contribution from CSF to T1ρ signal, an inversion time (TI) of 860 ms was used. An oblique coronal image of a slice perpendicular to the anterior/posterior commissure (AC/PC) plane was obtained. The slice was chosen to include the head of hippocampus. Immediately after T1ρ MRI, the entire volume of each subject’s brain was imaged in the coronal plane using a T1-weighted 3D volumetric magnetization prepared rapid acquisition gradient-echo (MPRAGE) pulse sequence with 160 continuous slices. The parameters were TR/TE = 3000 ms/3.5 ms, slice thickness = 1.2 mm, FOV of 240 × 240 cm² and 192 phase encode steps, and flip angle = 8° for a total imaging time of 10 min.

2.5. Data processing

Images were transformed to a G4 PowerBook computer (Apple Corp., Cupertino, CA) and processed with programs written in the IDL programming language (RSI Corp., Boulder, CO). T1ρ weighted data corresponding to different TSLs were fitted pixel-wise to a mono-exponential decay expression $S(TSL) = S(0) \times \exp \left(-\frac{TSL}{T1p}\right)$ (Borthakur et al., 2004; Borthakur et al., 2008). Pixels whose intensities correlated poorly ($R^2 < 0.95$) with the fitting equation were set to zero. Pixels outside of the brain were also set to zero. T1p values were automatically calculated from gray matter (GM) and white matter (WM) of the left and right MTL. For brain segmentation, a previously developed method was used to partition the volumetric MPRAGE scans into 92 regions of interest (ROIs) incorporating all major cortical and subcortical regions (Davatzikos et al., 2008). For quantitative analysis, 4 regions of interest (ROIs) were defined on T1ρ images i.e. left and right temporal lobes WM and GM. A program written in IDL was used to automatically calculate T1p values only from pixels that were classified as GM and WM located either in the left or right MTL.

2.6. Statistical analyses

For statistical analysis T1p values from left and right MTL were averaged (separately for GM and WM). Descriptive statistics was performed to calculate the mean value of T1p, and CSF biomarkers for different cohorts (controls, MCI and AD patients). Mann Whitney U-test was performed to see the difference for T1p and CSF biomarkers between controls, MCI and AD patients. Logistic regression with enter method was performed to measure the prediction rate of T1p and CSF biomarkers in classification of AD, MCI and controls. Receiver operating characteristic (ROC) analysis was performed to measure the sensitivity and specificity. We used a default cutoff 0.5 to predict the event. Additionally, discriminant analysis using T1p and CSF biomarkers was performed when three groups taken together. Pearson correlations between T1p versus CSF biomarkers, T1p versus age and between T1p versus MMSE scores were also performed. p value equal or less than 0.05 was considered statistically significant. All the statistical computations were performed using the Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, USA).

### Results

The mean MMSE scores in control (29.53 ± 1.19), MCI (25.11 ± 2.68) and AD (19.16 ± 5.57) were significantly ($p = 0.001$, $p < 0.001$, $p = 0.002$) different among groups. Mean T1p and CSF biomarkers values in three groups (control, MCI and AD) are reported in Table 1.

Fig. 1 shows the overlaid T1p maps from MTL region (in color) on fluid-attenuated brain T1ρ weighted images of control, MCI, and AD patients. Pixels with higher T1p (red) are more prominent in MTL of AD patient. The mean T1rho values in control (0.80 ± 0.06), MCI (0.83 ± 0.07), and AD (0.83 ± 0.06) were different among groups. ** Indicates the significance difference ($p < 0.05$) for the mean T1ρ values between two groups.

### Table 2

| Group          | Biomarker | AUC  | SE  | Sensitivity % | Specificity % | 95% CI         | p value |
|---------------|-----------|------|-----|--------------|---------------|----------------|---------|
| Control vs    | T1rho     | 0.65 | 0.09| 0.60         | 0.77          | 0.49, 0.82      | 0.09    |
| MCI           | CSF       | 0.67 | 0.09| 0.53         | 0.82          | 0.50, 0.85      | 0.05    |
| Control vs    | T1rho     | 0.80 | 0.07| 0.82         | 0.71          | 0.65, 0.94      | 0.001   |
| AD            | CSF       | 0.83 | 0.06| 0.77         | 0.79          | 0.72, 0.95      | 0.001   |

ROC = receiver operating characteristic; MCI = mild cognitive impairment; AD = Alzheimer’s disease; CSF = cerebrospinal fluid; AUC = area under curve; SE = standard error; CI = confidence interval; LB = lower bond; UP = upper bond.
Increased sulcal space in AD patient suggests greater degree of brain atrophy. A lack of signal from CSF implies that the higher $T_1\rho$ values in AD patients are not due to free fluid. The error bars show mean WM $T_1\rho$ and GM $T_1\rho$ values in controls, MCI and AD patients (Table 1). On comparative analysis, MCI subjects showed higher $T_1\rho$, T-tau, P-tau and lower $A\beta_{1-42}$ compared to control subjects. However, only increase in WM $T_1\rho$ ($p = 0.05$) reached to the statistical significant level (Table 1, Fig. 2). AD patients showed significantly increased GM $T_1\rho$ ($p = 0.041$), WM $T_1\rho$ ($p = 0.005$), T-tau ($p = 0.001$), P-tau ($p = 0.025$) and significantly decreased $A\beta_{1-42}$ ($p < 0.001$) compared to control subjects. Binary logistic regression showed that $T_1\rho$ (GM and WM) was able to predict 77.3% controls and 40.0% MCI subjects, whereas CSF biomarkers (T-tau, P-tau and $A\beta_{1-42}$) predicted 81.8% controls and 46.7% MCI subjects accurately. Combination of $T_1\rho$ and CSF biomarkers were able to predict 86.4% controls and 66.7% MCI subjects.

T-tau concentration was significantly ($p = 0.05$) increased over MCI subjects. The scattered maps between age and CSF biomarkers show no significant change in the CSF biomarkers with age.

Fig. 3. The scattered maps between age and $T_1\rho$ values for controls, MCI subjects and AD patients show no significant correlations.
T₁ρ predicted 35.3% MCI subjects and 81.9% AD patients, while the prediction rate was 53.3% for MCI subjects and 83.0% for AD patients using the CSF biomarkers. Combined CSF biomarkers and T₁ρ were able to predict 57.3% MCI subjects and 84.6% AD patients.

When combined three groups together, T₁ρ and CSF biomarkers were able to classify 54.5% controls, 40% MCI subjects and 65.2% AD patients. These two biomarkers misclassified 31.8% controls as MCI subjects and 13.6% controls as AD patients, while 33.3% MCI subjects were falsely predicted as controls and 26.7% MCI subjects as AD patients. There were false prediction of 8.7% AD patients as controls and 26.1% AD patients as MCI subjects.

On ROC analysis, T₁ρ showed greater sensitivity (60%) and less specificity (77%) than CSF biomarkers (53% and 82%) in discriminating MCI from control (Table 2). When delineating AD from control T₁ρ showed 82% sensitivity and 71% specificity while CSF biomarkers showed 77% sensitivity and 79% specificity (Table 2).

In all three cohorts, scattered maps between age and T₁ρ showed no significant change in T₁ρ values with age (Fig. 3). However, WM T₁ρ in MCI subjects and both GM T₁ρ and WM T₁ρ in AD patients showed an increasing trend with age (Fig. 3). No significant correlation of CSF biomarkers with age and T₁ρ was observed (Figs. 4–5). A negative correlation trend between Aβ1-42 and T₁ρ was observed in controls and MCI subjects, while in AD patients this correlation showed a positive trend. On the other hand, correlation between P-tau and T₁ρ showed a negative trend both in MCI subjects and AD patients.

4. Discussion

In the current study, significantly higher WM T₁ρ and GM T₁ρ in MTL in brain of AD was observed compared to that of controls, which is in agreement with the previous studies (Haris et al., 2011; Borthakur et al., 2008). MCI subjects showed significantly higher WM T₁ρ compared to controls, which suggests that abnormality occur earlier in WM than GM. Significantly higher GM and WM T₁ρ in AD compared to controls imply that in AD abnormality persist both in GM and WM. Higher changes in WM T₁ρ compared to GM T₁ρ suggest greater abnormality in WM than GM.

Earlier, Borthakur et al., have shown decreased T₁ρ with increased plaques burden in mouse model of AD (Borthakur et al., 2006a). Over the last two decades, a number of transgenic AD mouse models have been created which differ in their biochemical profiles and disease progression rates (Elder et al., 2010; Chin, 2011). To date it is debatable which model closely relates with the human AD pathology (Elder et al., 2010; Chin, 2011). It is possible that the mouse model used earlier by Borthakur et al., may not clearly depict the human AD pathology. Further, an explanation for higher T₁ρ in the human AD patients as observed in the current study and other previous studies (Haris et al., 2011; Borthakur et al., 2008) is only due to the plaques burden is not sufficient. Moreover, in AD, hyperphosphorylation of tau protein leads to the accumulation of neurofibrillary tangles, which results in loss of neurons. Till date no study has been performed to evaluate any relation.

Fig. 5. The scattered maps between T₁ρ values and CSF biomarkers depict no significant correlation in any group.
between phosphorylated tau protein and T1ρ in AD brain. A postmortem study may help to assess correlation between plaques burden, biochemical changes and T1ρ relaxation time in the human brain, and may provide a more precise explanation for increased T1ρ values in the human AD patients.

Majority of studies have reported decreased Aβ1-42, and increased T-tau and P-tau levels in CSF of MCI and AD patients (Hansson et al., 2006; Mattsson et al., 2009; Andreasen et al., 2001, 2003) and our findings are in conformity with those studies. It is widely believed that increased CSF T-tau level reflects neuronal and axonal damage. However, clinical studies have shown that the elevated CSF T-tau level is not specific to AD as it may also be elevated in other neurodegenerative diseases (Arai et al., 1997; Urakami et al., 2001). In a recent study, Hampel’s group reported that when compared with T-tau, P-tau showed better specificity for AD (Hampel, and Blennow, 2004). It has also been shown that the P-tau’s level consistently increased in AD when compared with frontotemporal dementia (FTD), Lewy body dementia (LBD), and control (Parnetti et al., 2001). An adequate explanation for decreased concentration of Aβ1-42 in CSF of AD patients is still lacking. The suggested explanation is that it is due to accumulation of Aβ1-42 in plaques is not sufficient, as decreased Aβ1-42 concentration in CSF of patients with Creutzfeldt–Jakob disease without apparent plaque formation has been reported previously (Wiltfang et al., 2003; Otto et al., 2000). Moreover, considerable uncertainty exists with respect to the influence of ageing on CSF biomarkers levels (de Leon et al., 2004; Hulstaert et al., 1999). Normal ageing studies have depicted both positive and negative age effects (Andreasen et al., 2001; de Leon et al., 2004; Hulstaert et al., 1999). In the current study, no age related changes in CSF biomarkers were observed.

Medial temporal lobe (MTA) atrophy as observed on MRI is considered to be an early and sensitive marker for AD, and is assumed that it reflects underlying neuronal loss in hippocampus and temporal lobe (Clerox et al., 2013; Jack et al., 1997; Duara et al., 2008). However, MTA may also be present in other types of dementia (Tam et al., 2005; Barber et al., 1999) and absence of MTA does not exclude the diagnosis of AD especially in the early stage. Studies have been performed to investigate the cross-sectional relation between CSF biomarkers and atrophy on MRI. Some observed no relation between CSF tau or Aβ1-42 and whole-brain atrophy (Sluimer et al., 2010), while others found a significant inverse relationship between CSF P-tau and hippocampal volume (Barber et al., 1999) and absence of MTA does not exclude the diagnosis of AD. In the current study, no correlation between T1ρ and CSF biomarkers showed better prediction rate for MCI (66.7%). Similarly, the relative value of these markers in tracking changes along the clinical continuum of AD. In conclusion, both CSF biomarkers and T1ρ MRI seem to have incremental value in diagnosis of AD. By applying them together diagnostic accuracy might be increased.

Acknowledgments

This work was performed at a NIH supported research center (NIH RR02305) and from a grant from the Pennsylvania State Tobacco Settlement grant (SAP4100027296).

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