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EEG microstate-source coupling is spatially preserved in ALS

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Abstract - EEG microstates are thought to reflect rapid transitions between brain-wide states and show disrupted temporal dynamics across neurological and psychiatric conditions, including ALS, yet the neural sources generating these states remain incompletely understood. Here, we introduce a source-resolved framework that links time-resolved microstate activations to estimated regional brain signals, enabling estimation of the neural sources underlying canonical microstate classes.

Resting-state EEG from a large cohort of healthy controls (HC, $n = 122$) and individuals with amyotrophic lateral sclerosis (ALS, $n = 121$) was analysed. Canonical microstates were derived from pooled data, and time-resolved microstate activation time series were estimated via projection-based decomposition of scalp potentials. In parallel, EEG source activity was reconstructed using beamformer-based inverse modelling and parcellated into 90 cortical regions. Microstate-source coupling was quantified using ridge regression linking microstate activations to reconstructed regional timecourses, producing spatially resolved coupling maps for each microstate class.

In HC, reproducible and spatially distinct microstate-source coupling patterns were observed, consistent with structured mapping between scalp-defined brain states and distributed neural systems. Spatial reproducibility was confirmed using permutation-based null models that preserved temporal autocorrelation within microstate sequences and accounted for spatial dependence across regions. In HC, microstate-source coupling was spatially reproducible across independent subgroups for the four canonical microstates (A-D; $r \geq 0.90$, $q < 0.05$).

In ALS, coupling topography was preserved relative to HC for all four microstate classes ($r \geq 0.90$, $q < 0.05$), and cluster-based permutation testing revealed no significant group differences in coupling magnitude for any microstate class, a null result robust to sex and riluzole status. Microstate-source coupling was preserved, suggesting stability of canonical microstate organisation across sensor and source space.

Overall, these findings demonstrate that canonical EEG microstates have stable, reproducible coupling with distributed brain sources, and that this coupling organisation is preserved in ALS despite known alterations in microstate temporal characteristics. This dissociation suggests that spatial and temporal organisation of microstates may be governed by partially independent mechanisms, with spatial organisation buffered against ALS-related change, potentially through degeneracy or local compensatory mechanisms, while temporal engagement remains more directly sensitive to disease.

Keywords—ALS, EEG microstates, electrical source imaging, resting-state networks

1. INTRODUCTION

Measuring the brain's neuro-electric activity using resting-state electroencephalography has shown potential as a method to differentiate ALS patients from healthy controls (HC) (Dukic et al., 2019; Nasserroleslami et al., 2019). Nasserroleslami et al. (Nasserroleslami et al., 2019) revealed persistent differences in resting-state EEG measures between ALS patients and healthy controls, focusing on theta-band spectral power and functional connectivity (theta and high gamma-band coherence) at the sensor level. Building on this approach, Dukic et al. (Dukic et al., 2019) conducted source localisation of EEG signals, identifying specific brain regions contributing to the recorded signals. Spatial patterns revealed disease-specific alterations in motor and non-motor networks, characterised by increased theta-band co-modulation in central, posterior, and frontal regions, and reduced beta-band synchrony in frontotemporal and sensorimotor areas (Dukic et al., 2019) which were reported to persist longitudinally (Metzger, Dukic, McMackin, Giglia, Mitchell, Bista, Costello, Peelo, Tadjine, Sirenko, McManus, et al., 2024a).

Beyond spectral and spatial analyses, examining the temporal dynamics of EEG signals has provided further insights into ALS-related brain changes. In particular, microstate analysis, based on distinct,

recurrent scalp electrical potential topographies, has been shown to differentiate ALS patients from controls (Metzger, Dukic, McMackin, Giglia, Mitchell, Bista, Costello, Peelo, Tadjine, Sirenko, Plaitano, et al., 2024; Notturmo et al., 2022). The investigation of four canonical microstate classes (A–D) revealed consistent topographies across groups, but significant differences in parameters such as coverage, occurrence, duration, and transition probabilities. Specific microstate features were linked to clinical measures: microstate B duration and microstate C coverage correlated with lower limb decline, while transition probabilities ($A \rightarrow D$, $C \rightarrow B$) were associated with cognitive decline. Altered microstate properties in ALS suggest disruptions in both sensory and higher-order networks (Metzger, Dukic, McMackin, Giglia, Mitchell, Bista, Costello, Peelo, Tadjine, Sirenko, Plaitano, et al., 2024).

However, interpretations of microstates remain largely paradigm-based typically relying on comparisons of microstate parameters between conditions (e.g., states of consciousness or patient vs. control groups), without direct anatomical associations (Tarailis et al., 2023). Estimating the neural generators of microstates can provide critical insight into their functional significance, allowing dynamic EEG patterns to be interpreted in terms of underlying brain structure and functional organisation (Abreu et al., 2021; Bréchet et al., 2020; Britz et al., 2010; Custo et al., 2017a; Valt et al., 2024).

Sensor-level microstate analyses are limited in their ability to disentangle the distributed cortical and subcortical generators underlying scalp topographies, particularly in ALS where widespread and overlapping network involvement is common (Dukic et al., 2019, 2022). Source-space approaches address this limitation by improving anatomical specificity and enabling clearer interpretation of whether microstate abnormalities reflect focal regional dysfunction or broader network reorganisation.

Previous studies have linked the four canonical microstates and known functional MRI (fMRI) networks using simultaneous recording of EEG and fMRI (Abreu et al., 2021; Britz et al., 2010). However, the temporal resolution of fMRI makes it suboptimal for capturing microstate rhythms, which typically occur on a timescale of 50 to 100 ms. To preserve the temporal resolution of EEG, alternative approaches estimate microstate sources directly from EEG using linear inverse solutions (Bréchet et al., 2020; Custo et al., 2017b; Hücke et al., 2021).

A key challenge in microstate research remains that their hypothetical neural generators vary across studies, reflecting distributed and partially overlapping networks that depend on methodological and modelling choices (Bagdasarov et al., 2022; Britz et al., 2010; Custo et al., 2017b; Mishra et al., 2020; Musso et al., 2010). This variability limits a unified interpretation of microstates as fixed representations of specific brain regions or networks. Establishing more direct links between microstates and their neural generators is therefore crucial, particularly in ALS, where this may help clarify mechanisms of distributed network dysfunction.

The present study introduced an EEG microstate-source coupling framework to investigate the brain sources associated with canonical EEG microstates, and applied this framework, for the first time, to a large cohort of individuals with ALS alongside healthy controls. We first characterised microstate-source coupling patterns in healthy participants and assessed their reproducibility across independent subgroups. Having previously shown that the temporal dynamics of microstates are altered in ALS, we next compared microstate-source coupling patterns between groups to determine whether neurodegeneration also alters the neural generators underlying canonical microstates.

2. METHODS

2.1. Participants

Ethical approval was obtained from the St. James's Hospital / Tallaght University Hospital Joint Research Ethics Committee - Dublin [2014 Chairman's Action 7; 2019-05 List 17 (01); 2019-07 Chairman's Action (22)]. Experiments were performed in accordance with the Declaration of Helsinki. All participants provided informed written consent to the procedures before undergoing assessment.

Individuals diagnosed with ALS and ALS-frontotemporal dementia (ALS-FTD), according to the revised El Escorial criteria (Ludolph et al., 2015) and the Strong criteria (Strong et al., 2017) were recruited from the Irish National ALS Clinic at Beaumont Hospital in Dublin, Ireland. Those with primary lateral sclerosis, progressive muscular atrophy, flail arm/leg syndromes, other medical conditions, or neurological/neuropsychiatric symptoms were excluded. Age-matched healthy controls

(HC), without diagnosed neurological or neuropsychiatric disorders, were recruited from an existing volunteer database (Burke et al., 2017). Details of the demographics can be found in Table 1.

Table 1: Demographic profile for controls and patients. The table details the gender proportions, the average ages at recording and, when applicable, disease durations, delays between sessions, site of onset and the number of patients with FTD comorbidity. Numbers show mean $\pm$ standard deviation.

Groups	N	Male (%)	Age (years)	Disease duration (months)	ALSFRS-R scores	Site of onset (N)				ALS-FTD diagnosis (N)
						Bulbar	Spinal	Thoracic	Cog/Beh	
Controls	122	44	60 $\pm$ 11	/	/	/	/	/	/	/
ALS	121	74	62 $\pm$ 7	18 $\pm$ 6	38 $\pm$ 7	23	90	6	2	4

2.2. Experimental setting

High-density (128 channels) resting-state EEG data was recorded from 121 ALS patients and 122 age-matched HC. Data collection was conducted at the Clinical Research Facility in St. James's Hospital, Dublin. EEG recordings took place in a specially designed room, isolated by a Faraday cage to shield against external electric interference. Electrode offsets were maintained within the range of $\pm$ 25mV. Participants were instructed to sit comfortably with their eyes open during the recording session. A large letter X (measuring 6x8 cm², printed in black on white) served as a focal point for their gaze. EEG signals were captured at a sampling rate of 512 Hz using a 128-channel BioSemi ActiveTwo system from Amsterdam, Netherlands (Honsbeek et al., 1998). A recording was performed in three blocks, each lasting two minutes. The participants' alertness and overall well-being were assessed by the experimenter in brief intervals between each block.

2.3. EEG pre-processing

Continuous EEG data were first detrended and demeaned to remove linear offsets. A two-pass (zero-phase) band-pass filter (filter order 2) between 1 and 98 Hz was applied to attenuate slow drifts and high-frequency noise.

Bad channels were identified using criteria based on PREP pipeline principles, including excess high-frequency noise (threshold = 20), low correlation with neighbouring channels (threshold = 0.3), and temporal instability (bad time fraction > 0.02). Detected channels were iteratively interpolated using neighbouring electrodes (weighted interpolation), and the data were re-referenced after each iteration. This process was repeated until convergence or a maximum of 10 iterations. A final detection pass using stricter temporal criteria (bad time threshold = 0.01) was applied.

For artifact detection, the continuous data were segmented into non-overlapping epochs of 2 s. Jump artifacts were detected using a z-score-based method (cutoff = 30), incorporating median filtering and absolute signal differences to enhance sensitivity to abrupt changes. Muscle artifacts were identified using a band-pass filter between 110–140 Hz (single pass seventh-order Butterworth), followed by Hilbert transform-based envelope estimation and z-score thresholding (cutoff = 10), with detection restricted to temporo-parietal channels known to capture high-frequency muscle activity. A temporal padding of 0.5 s ($\pm$ 0.25 s) was applied to each detected artefact to ensure complete coverage of artifact periods. Independent Component Analysis (ICA) decomposition was used to identify and remove components associated with ocular artifacts.

Artifact and channel detection were performed automatically, but results were visually inspected and corrected as needed. Samples marked as artifacts were removed, and the remaining clean data were segmented into non-overlapping 2-second epochs. Only artifact-free segments were retained. Identified bad channels were then interpolated using spline interpolation of neighbouring electrodes. Finally, the data were re-referenced to the common average.

Following preprocessing, the analysis pipeline consisted of four stages: (i) sensor-level microstate estimation, (ii) source reconstruction of ROI activity, (iii) participant-level regression linking microstate activations to ROI dynamics, and (iv) group-level spatial statistical analyses (Figure 1).

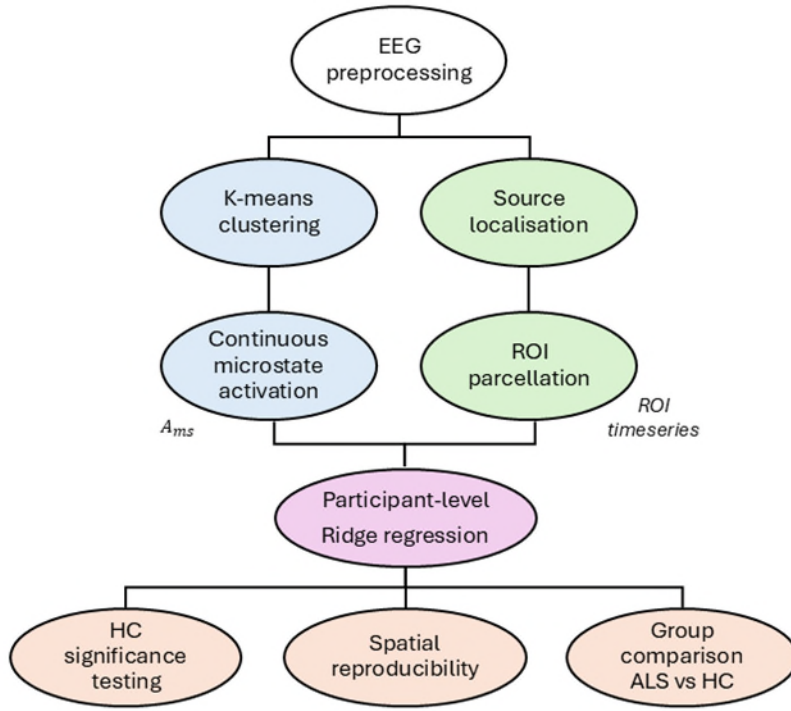


Figure 1: Illustration of the microstate-source coupling pipeline.

2.4. Microstates estimation

Microstates were computed using the Microstate EEGLAB toolbox (Poulsen et al., 2018), as described in our microstate study at sensor-level (Metzger, Dukic, McMackin, Giglia, Mitchell, Bista, Costello, Peelo, Tadjine, Sirenko, Plaitano, et al., 2024). In brief, we identified microstates based on quasi-stable topographies of resting-state EEG (1-30 Hz; a 30 Hz low-pass, two-pass linear-phase FIR, was applied).

A three-fold cross-validation identified four microstate classes as optimal in a subset of 4-9 microstate classes based on HC data.

To ensure direct comparability between groups and reduce bias introduced by separate clustering solutions, a common microstate template set was derived from pooled ALS and HC data. For the combined ALS and HC group, the EEG signals were clustered at peak times of global mean field power (GFP) (where the topographies are the most stable (Michel & Koenig, 2018)) using modified k-means clustering to obtain four microstate templates (Poulsen et al., 2018).

The modified algorithm differs from the standard k-means algorithm in that it treats topographies of opposite polarity (identical spatial configurations in which the sign of the scalp potential is reversed at every electrode) as belonging to the same microstate class. This polarity invariance reflects the fact that the same neural generators can produce scalp potentials of either polarity depending on the phase of the underlying oscillation. A Gaussian-weighted moving average was added to the GFP signal as a smoothing method (window of five timepoints) (Al Zoubi et al., 2019).

Time-resolved microstate activation coefficients were estimated by projecting normalised EEG scalp maps onto the microstate templates using the Moore-Penrose pseudoinverse, similarly to the TESS framework described by Custo et al (Custo et al., 2014). At each timepoint, this provides the least-squares coefficients that best reconstruct the instantaneous topography as a weighted linear combination of the microstate templates. The resulting activation coefficients were then scaled by the square root of GFP in order to preserve signal strength information and subsequently z-scored (within participant and microstate class). This procedure resulted in time-resolved (i.e., non-discretised) microstate activation time series for each participant and each microstate class, denoted A_{ms} .

2.5. Microstate-ROI coupling

In parallel with the microstate processing, the EEG sources were localised using the method described by Dukic *et al* (Dukic et al., 2019), applied to the full EEG recordings. The source localisation analysis included the use of a linearly constrained minimum variance (LCMV) beamformer and an ICBM152 MRI template-based head model (Fonov et al., 2009) for source localization. Source time courses were reconstructed for 90 cortical and subcortical regions (excluding cerebellum) using the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002), and each ROI time series was z-scored.

The resulting EEG sources (ROI time series) and the microstate activation timeseries share an identical sampling rate and length, they can be related sample-by-sample, which allows for a direct estimation of the brain regions associated with each microstate topography. To estimate the association of microstate activity with regional source signal, ridge regression (L2-regularised) was applied separately for each participant and ROI:

$$y_r = A_{ms} \cdot \beta_r$$

The regularisation parameter ($\lambda = 10^4$) was selected using 5-fold participant-level cross-validation to minimise prediction error while stabilising estimates under multicollinearity (details in Supplementary Materials).

Because EEG microstate topographies are polarity-ambiguous by definition, the sign of the regression coefficients is arbitrary and not directly physiologically interpretable. We therefore use the absolute values of the regression coefficients ($|\beta|$) as a polarity-invariant measure of coupling strength between microstate activity and ROI sources, focusing on association magnitude rather than direction. Group-level microstate-ROI coupling maps were computed by averaging regression coefficients ($|\beta|$) across participants.

2.6. Statistical significance of the microstate source coupling in HC group

HC analyses were used to establish microstate contributor maps prior to between-group comparisons. To assess the statistical significance of the association between microstate activity and ROI time series, a non-parametric permutation procedure was performed at the level of individual participants and ROIs. EEG microstate sequences exhibit substantial temporal structure and autocorrelation rather than random temporal organization (von Wegner et al., 2016, 2017). To construct a null model that preserves local temporal dependencies within microstate dynamics while disrupting their temporal alignment with ROI activity, surrogate microstate time series were generated using a block permutation procedure. Specifically, each microstate activation coefficient was segmented into contiguous temporal blocks of length $N/20$ (with N being the number of timepoints), and these blocks were randomly permuted while preserving their internal temporal order. This procedure maintains local autocorrelation structure and multivariate relationships across microstate classes, while disrupting long-range temporal alignment between microstate dynamics and ROI time series. For each permutation ($n = 1000$), ridge regression was recomputed using the block-permuted microstate time series, yielding null distributions of regression coefficients for each microstate class and ROI. The resulting null distributions were used to assess whether the observed regression coefficients (from the HC group) exceeded those expected under a temporally structured but misaligned null model.

2.7. Spatial reproducibility

Spatial similarity between microstate contributor maps were assessed between HC subgroups (HC1, $n_1 = 61$ vs HC2, $n_2 = 61$) and between ALS and HC groups, using Spearman correlations combined with Moran spectral randomisation ($n = 10,000$ permutations) to account for spatial autocorrelation. Observed correlations between microstate contributor maps were compared against the null distributions obtained from the surrogate maps to derive empirical one-tailed p-values. Multiple comparisons were controlled using adaptive false discovery rate (FDR) correction (one-tailed hypothesis, FDR correction, $q < 0.05$).

2.8. Statistical comparison between ALS and HC groups

To assess group differences in microstate source contributions, we performed non-parametric cluster-based permutation testing. For each microstate class, individual participant regression coefficients $|\beta|$ quantified the magnitude of microstate contribution across ROIs. Spatial neighbours were defined based

on the Euclidean distance between ROI centroids, enabling spatial clustering across adjacent regions (< 40 mm). Group differences in the magnitude of microstate contributions between ALS and healthy controls were evaluated using an independent-samples t-statistic within a Monte Carlo permutation framework (10 000 permutations). Cluster-level inference was performed using a threshold of $p < 0.05$, whereby adjacent ROIs exceeding this threshold were grouped into spatial clusters. For each cluster, the sum of t-values (cluster mass) was computed, and statistical significance was assessed using a permutation-derived null distribution of the maximum cluster mass.

Both positive and negative clusters (i.e., regions where coupling magnitude was greater or smaller in ALS than in controls) were assessed using a two-tailed test ($\alpha = 0.05$). This approach identifies spatially contiguous sets of brain regions showing consistent group differences in microstate source contributions, while controlling for multiple comparisons at the level of brain regions. To ensure that the observed results were not confounded by demographic or clinical factors, we conducted additional control analyses examining the potential influence of gender and riluzole medication on microstate-source coupling, the details and results of which are reported in the Supplementary Material (Sections 3.1 and 3.2).

3. RESULTS

The clustering algorithm revealed four optimal microstate prototypes for the HC and ALS groups. Across all timepoints, these four maps respectively explained on average 47% ($\pm 0.07\%$) of the global variance for the HC group and 47% ($\pm 0.07\%$) of the global variance for the ALS group (mean $\pm$ SD). Figure 1 shows the four topographies of the microstate prototypes, each representing one cluster of maps. Similar to what is commonly described in the literature, the topographies are reliably observed across conditions.

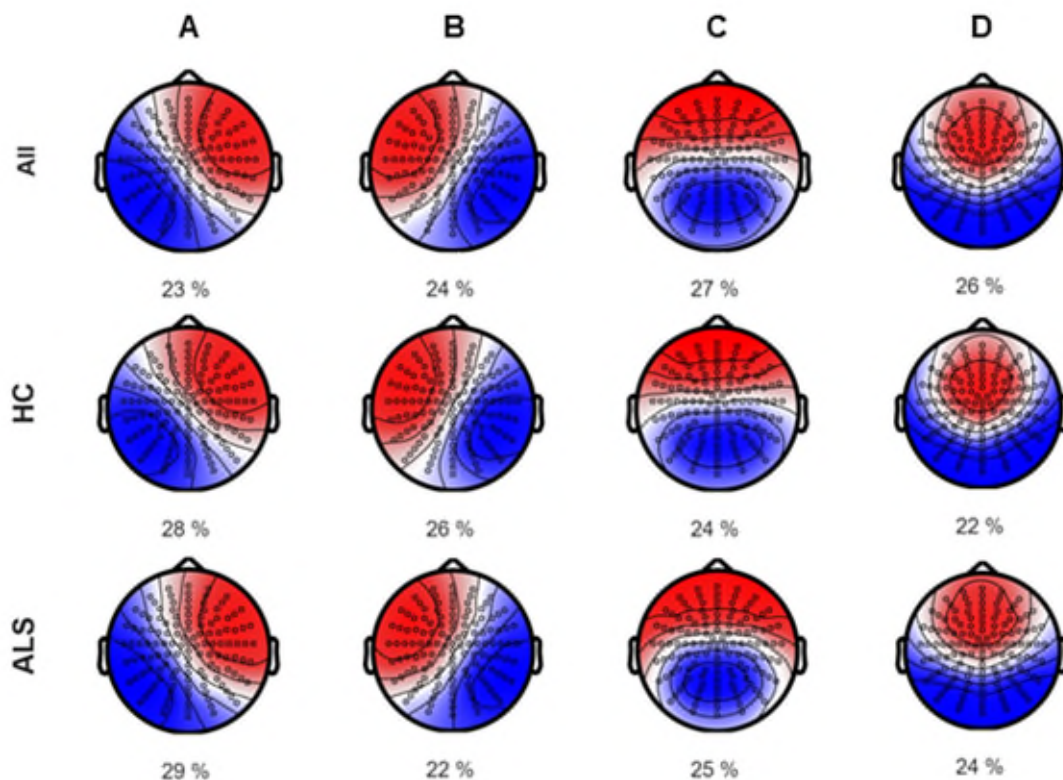


Figure 2: The spatial configurations of microstate classes A-D were examined for the ALS, HC and combined groups, disregarding polarity. To align with existing literature, the microstate maps were rearranged based on their topographies. The proportional contribution of each class to the sequence of microstates is expressed as a percentage below.

3.1. Microstate-source coupling patterns in healthy controls

Patterns of microstate-ROI coupling revealed distributed and partially overlapping cortical and subcortical profiles across the four canonical microstates (Figure 3). Microstate A was characterised by prominent involvement of occipital regions, including the calcarine cortex and lingual gyrus bilaterally, alongside ventral temporal areas and right-lateralised limbic and subcortical structures, including the hippocampus, parahippocampal gyrus, amygdala, and thalamus, as well as posterior cingulate cortex. Microstate B showed a similar occipito-temporal profile, with additional engagement of left-lateralised limbic and subcortical regions, including hippocampus, basal ganglia, and thalamus, together with insular and posterior cingulate contributions.

Microstate C exhibited a shift towards a more anterior and sensorimotor profile, involving right supplementary motor area, precentral and opercular regions, as well as superior temporal cortex, anterior insula, and mid-cingulate cortex, accompanied by right-lateralised subcortical structures. Microstate D displayed a more heterogeneous pattern, combining occipital and temporal regions with posterior cingulate cortex and thalamic involvement, alongside limited sensorimotor contributions.

Across microstates, subcortical regions (particularly thalamus and hippocampus) and posterior cingulate cortex were consistently represented, indicating that microstate dynamics are associated with widespread cortico-subcortical interactions rather than isolated cortical regions (Figure 4). Lists of the AAL ROIs associated with each microstate and contributing to the overlap across microstates are provided in Supplementary Note 4.

The permutation-based null model confirmed significant microstate-source coupling across all regions and microstate classes (FDR, $q < 0.05$) beyond autocorrelation structure (detailed information available in the Supplementary material, section 2).

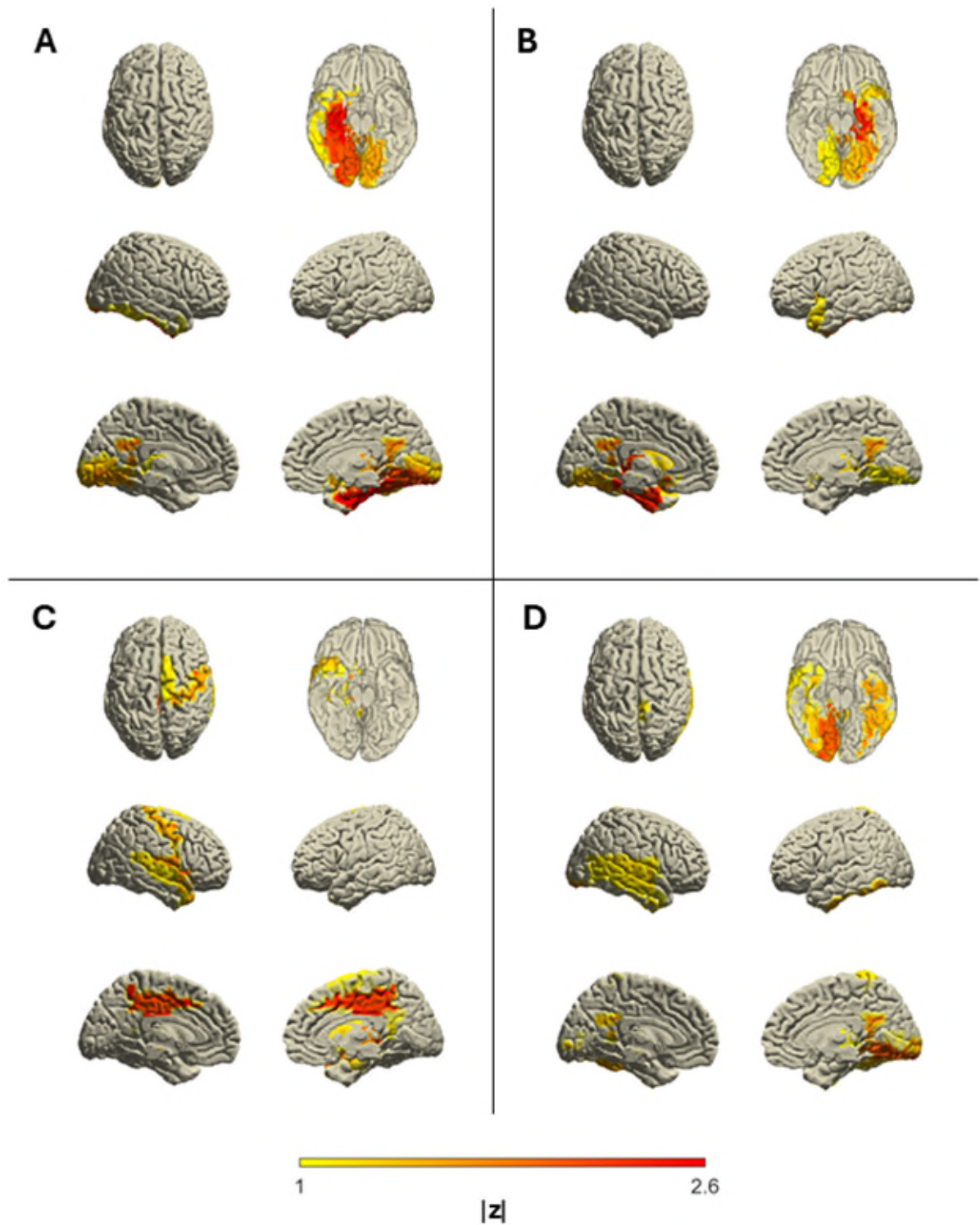


Figure 3: Microstate-ROI coupling for each microstate class (A-D) in the HC group ($n = 122$). EEG microstate timecourses were related to source reconstructed timecourses (90 AAL ROIs) using ridge regression. Polarity-invariant microstate-ROI coupling strengths ($|\beta|$) were obtained by averaging absolute values of the coefficients across participants. The zscores of the coupling strength are thresholded at $|z| > 1$ and visualized on 3D brain maps for each microstate class. Microstate-ROI coupling patterns revealed distinct but overlapping spatial profiles, with microstates A and B dominated by occipito-temporal and limbic/subcortical regions, microstate C showing anterior and sensorimotor involvement, and microstate D exhibiting an heterogeneous combination of occipital, temporal, cingulate, and thalamic contributions.

3.2. Stability of microstate-source coupling across groups

We then compared the microstate sources from two HC subgroups and from the ALS versus the HC group. In HC subgroups (Group 1: $n = 61$, age 60.15 ± 10.56 years, 34F/27M; Group 2: $n = 61$, age 59.77 ± 11.90 years, 34F/27M; age t-test, $p = 0.853$; gender χ^2 , $p = 1.000$), we observed strong and statistically significant diagonal spatial correlations between corresponding microstate coupling maps for microstates A-D ($r \geq 0.90$, FDR-corrected $q < 0.05$), while off-diagonal associations were not significant (Figure 5a). ALS versus HC comparisons revealed significant spatial correlations for all corresponding microstates A-D ($r \geq 0.90$, FDR-corrected $q < 0.05$), indicating a robust preservation of microstate source topography across groups (Figure 5b). Importantly, these effects were observed after controlling for spatial autocorrelation using Moran spectral randomization, suggesting that the observed similarities are not driven by spatial smoothness alone.

3.3. Microstate source coupling do not differ significantly between ALS and healthy controls across brain regions

Cluster-based permutation testing revealed no significant difference in spatial clusters for any of the microstate classes when comparing microstate source contributions between ALS patients and healthy controls. Although positive and negative clusters were identified, none survived the permutation-derived significance threshold ($\alpha = 0.05$), indicating that the magnitude of microstate-source coupling across ROIs did not differ systematically between groups. These null results were consistent across both the maximum and weighted cluster mass statistics. The lack of group differences in microstate-source coupling was not attributable to gender or riluzole medication status, as confirmed by control analyses (Supplementary Sections 3.1 and 3.2).

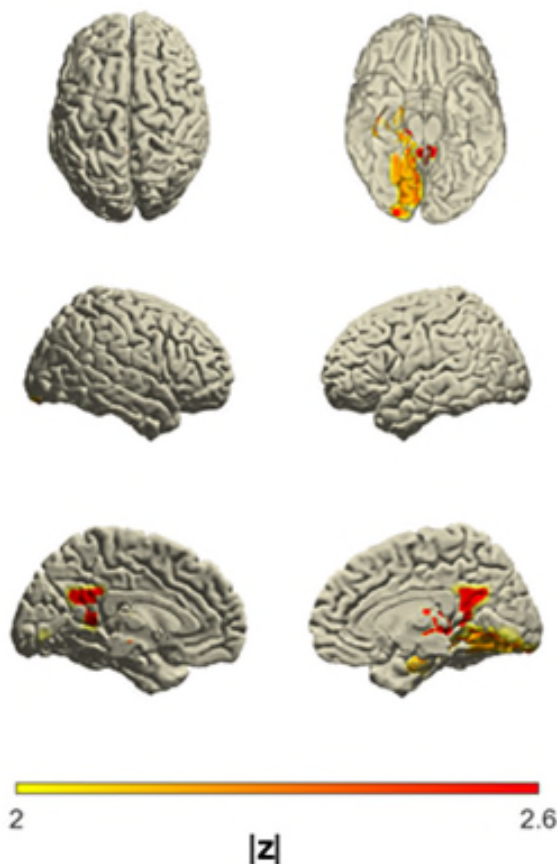


Figure 4: Overlap of the four estimated brain sources of microstates.
The combined zscore across microstate of the microstate-ROI coupling strength was computed for the HC group ($z > 2$). The overlapping regions indicate partial engagement of a posterior Default Mode Network core, centred on the bilateral posterior cingulate cortex and hippocampus, alongside visual and thalamo- limbic contributions.

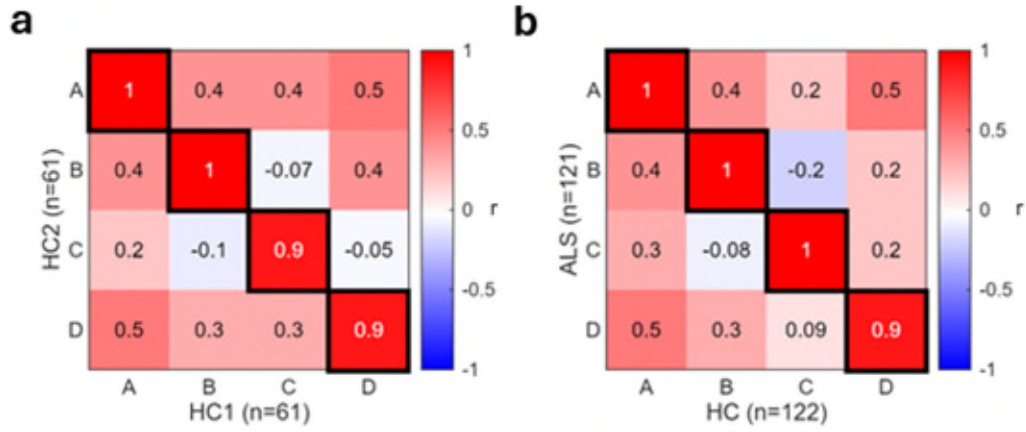


Figure 5: Spatial correlations of the microstate brain sources estimated in HC subgroups (a) and in ALS versus HC groups (b). **a.** Significant spatial correlations were observed between corresponding microstate sources (A – D; $r \geq 0.90$, FDR-corrected $q < 0.05$) in HC subgroups, while non-matching pairs showed no consistent associations. **b.** In ALS versus HC, significant spatial correlations were observed for all corresponding microstates (A–D; $r \geq 0.90$; FDR-corrected $q < 0.05$), indicating preserved spatial similarity of microstate source distributions across groups. Spatial autocorrelation was preserved in the null models using Moran spectral randomization.

4. DISCUSSION

EEG microstates, reflecting macroscopic electrical fields arising from phase-locked synchronized oscillations (Seeber & Michel, 2021) among spatially distinct sources, are known to exhibit differences in properties such as coverage, duration, and transition probabilities between individuals with ALS and healthy controls, showing correlations with both motor and cognitive decline in ALS (Metzger, Dukic, McMackin, Giglia, Mitchell, Bista, Costello, Peelo, Tadjine, Sirenko, Plaitano, et al., 2024). A deeper understanding of the relationship between microstates and their underlying brain sources would enhance our comprehension of these phenomena and of the mechanisms driving their alterations in ALS. In previous studies, simultaneous EEG-fMRI investigations identified specific brain regions associated with the four canonical microstates (related to auditory, visual, salience, and dorsal attention networks) (Britz et al., 2010; Michel & Koenig, 2018). This study aimed to refine the identification of brain areas contributing to microstates in both healthy individuals and those with ALS, using source localisation methods applied to EEG data (Custo et al., 2017a), thereby providing a more direct measure of brain activity. The study primarily demonstrates preservation of microstate-source coupling in ALS.

We observed distinct brain sources associated with the four canonical microstates in the HC group (Figure 2).

In our group of 122 healthy participants, microstates A and B both demonstrated predominantly posterior source coupling. Microstate B showed convergence with previous EEG-fMRI findings, exhibiting dominant occipital and occipito-temporal involvement demonstrating overlap with regions previously associated with the visual network as originally described by Britz et al. (Britz et al., 2010) and subsequently supported by EEG source localisation studies such as Custo et al. (Custo et al., 2017a). In addition, Microstate B displayed extended involvement of posterior midline and salience-related regions, including the posterior cingulate cortex and insula, as well as subcortical structures such as the thalamus and basal ganglia, showing overlap with regions commonly implicated in the default mode and salience network as described in distributed and network-based frameworks proposed by Pascual-Marqui and Yuan et al (Pascual-Marqui et al., 2014; Yuan et al., 2012).

Microstate A was predominantly associated with occipito-temporal regions, with additional involvement of limbic and subcortical structures. While earlier EEG-fMRI work by Britz et al. associated Microstate A primarily with bilateral temporal (auditory-related) networks (Britz et al., 2010), subsequent microstate source localisation studies have demonstrated a more distributed temporo-parietal organisation (Custo et al., 2017a; Musso et al., 2010). The functional synthesis by Tarailis et al. suggests that Microstate A is not exclusively linked to auditory processing but is instead associated with multimodal sensory processing and arousal-related states, with involvement of both auditory and visual paradigms depending on experimental context (Antonova et al., 2022; Milz et al., 2016; Tarailis et al., 2023). Within this framework, the present occipito-temporal extension of Microstate A may reflect the overlap between visual and temporal associative systems within distributed resting-state networks rather than deviation from canonical microstate organisation.

In our HC group, Microstate C exhibited an anteriorly dominant configuration overlapping with regions commonly engaged in the salience/cingulo-opercular network, characterised by coordinated activity within anterior insula and mid-cingulate systems. This pattern aligns with existing descriptions of Microstate C in EEG-fMRI and source localisation studies (Britz et al., 2010; Custo et al., 2017a; Musso et al., 2010), which consistently interpret this state as associated with the anterior cingulate cortex and the salience network. The additional sensorimotor and subcortical contributions observed here likely reflect the broader involvement of salience and control-related systems within resting-state networks.

Consistent with Bagdasarov et al. (Bagdasarov et al., 2022), Microstate D in the present study is best interpreted as a heterogeneous posterior configuration involving occipital and temporal regions together with posterior cingulate cortex (PCC), thalamic contributions, and limited sensorimotor involvement. This pattern only partially overlaps with earlier associations of Microstate D with the fronto-parietal attention network (Britz et al., 2010; Custo et al., 2014; Musso et al., 2010), though PCC involvement aligns with direct EEG source localisation reported by Pascual-Marqui (Pascual-Marqui et al., 2014). This reduced consistency is in line with evidence associating microstate D with variable spatial configurations (Michel & Koenig, 2018) and partial overlap with both posterior default mode regions (Pascual-Marqui et al., 2014) and fronto-parietal systems (Britz et al., 2010; Custo et al., 2017a) implicated in executive and attentional control. Under higher model orders or alternative clustering solutions, this variability may manifest as fractionation into related subcomponents, reflecting its role in coordinating distributed network interactions rather than representing a unique generator.

Although the microstates showed distinct dominant configurations, their spatial overlap suggests shared brain-wide network rather than strictly segregated sources. In particular, convergence in the posterior cingulate cortex and hippocampal regions suggests partial engagement of a posterior default mode network (DMN) core (Figure 3), consistent with previous observations (Bagdasarov et al., 2022; Custo et al., 2017a; Pascual-Marqui et al., 2014). Such brain areas have been hypothesised to represent ‘hubs’ of communication during cognitive processes, and are associated with dense structural and functional connections (Hagmann et al., 2008). The consistent contribution of brain regions to the time courses of EEG microstates, reproducible across participants, may indicate their involvement in diverse functional tasks (Custo et al., 2017a; Michel & Koenig, 2018).

The comparison of microstate-source coupling maps revealed a high degree of spatial stability across both HC subgroups (n=61) and between ALS (n=121) and controls (n=122), with strong significant

diagonal correlations for all corresponding microstates ($r \geq 0.90$; $q < 0.05$) and no significant off-diagonal associations, indicating high reproducibility of spatial topographies across (sub)groups. These similarities remained robust after correction for spatial autocorrelation using Moran spectral randomisation, suggesting that they are not driven by spatial smoothness.

Given this stable microstate-source coupling in HC, a key question is whether it withstands the structural and functional changes known to occur in ALS. Multimodal MRI studies in ALS report a well-characterised pattern of progressive structural involvement, with cortical thinning concentrated in motor and frontotemporal regions and progressive loss of white-matter integrity along corticospinal and callosal pathways (Bede et al., 2023; Bede & Hardiman, 2018; Burgh et al., 2020). Resting-state electrophysiology studies have similarly demonstrated ALS-specific functional reorganisation, including reduced beta-band power over temporo-posterior regions, increased theta-band co-modulation over centro-posterior regions that persists on longitudinal follow-up, and a longitudinally stable reduction in beta-band synchrony over sensorimotor cortex (Dukic et al., 2019; Metzger, Dukic, McMackin, Giglia, Mitchell, Bista, Costello, Peelo, Tadjine, Sirenko, McManus, et al., 2024b; Trubshaw et al., 2024). Against these concurrent structural and functional alterations across motor and extra-motor regions, the absence of a detectable group difference in microstate-source coupling is notable. Microstate topography and its coupling to underlying sources appear stable in ALS, while disease effects instead appeared in temporal dynamics such as occurrence, duration, and transition probabilities (Metzger, Dukic, McMackin, Giglia, Mitchell, Bista, Costello, Peelo, Tadjine, Sirenko, Plaitano, et al., 2024; Notturmo et al., 2022).

While microstates A, B, and D are mostly coupled with posterior DMN, limbic, and occipito-temporal regions largely distinct from primary ALS-affected territory, microstate C couples with sources including sensorimotor regions that sit within the networks most classically altered in ALS. The persistence of stable coupling even for this microstate suggests that anatomical distance from disease-affected region cannot be the sole explanation for the absence of difference between ALS and HC groups.

A plausible basis for this stability lies in the overlapping ‘hub’ regions shared across multiple microstates, centred on a posterior DMN core (Figure 4) (Custo et al., 2017b). Regions engaged by more than one microstate class are consistent with the signature of degeneracy: a small set of hubs capable of contributing to several, structurally distinct large-scale networks rather than being dedicated to a single one (Edelman & Gally, 2001). This is consistent with recent computational modelling showing that a region's degeneracy, its tolerance to perturbation before switching state, is shaped by its structural connectivity, suggesting that highly interconnected hubs are also dynamically more resilient (Gudibanda et al., 2026). Partially independent pathways converge, allowing output to be sustained even when one or more inputs are degraded; coupling contributed by overlapping regions should therefore be more resilient to moderate, spatially uneven atrophy.

A second, non-exclusive explanation could be local compensatory mechanisms: the same functional output can, in principle, be sustained through adjusted local neural changes rather than through degenerate structural routing. On this account, a region experiencing some disruption could preserve its microstate contribution through local mechanistic adjustment alone, without requiring multiple structurally distinct pathways.

Together, these hypotheses suggest the ‘where’ of microstate generation is buffered by degeneracy and local compensation, while the ‘when’ and ‘how often’ of microstate engagement are not, explaining why microstate topography stays stable while temporal engagement shows subtler ALS-related change.

4.1. Limitations

A key limitation of this work is the inherent uncertainty in EEG source estimates, particularly in subcortical regions. Consistent with the high variability of microstate sources reported across studies, this reflects the ongoing challenge of localising stable and specific microstate generators (Michel & Koenig, 2018). Although microstates exhibit distinct topographical prototypes, they are not temporally independent processes (Britz et al., 2010; Yuan et al., 2012), and may be better understood as part of a continuous dynamical sequence with canonical forms emerging primarily at peaks of global field power (Mishra et al., 2020). This temporal overlap could contribute to the high overlap observed between microstate sources (Bagdasarov et al., 2022; Custo et al., 2017a; Pascual-Marqui et al., 2014) and the difficulty of dissociating between such sources.

A further limitation is that both microstate activation time series and ROI-based source signals are derived from the same EEG data through different linear transformations. However, while the microstate templates and the leadfield are shared across all participants, the beamformer weights are participant-specific. The ridge regression coefficients are invariant to a uniform rescaling of source activity, but not to a change in its covariance structure (such as a regional change in spectral power or functional connectivity) (Supplementary Note 5). Accordingly, the regression analyses do not reflect independence between variables, but rather shared variance between two complementary decompositions of the same signal. Although the use of temporally and spatially constrained permutation models controls for the effects of temporal autocorrelation and spatial dependence, the results should be interpreted as associations between EEG-derived representations rather than evidence of directed or causal interactions between microstate dynamics and regional or subcortical activity.

4.2. Conclusion

This study provides the first assessment of microstate-source coupling in ALS. Across groups, microstates retain distinct spatial configurations, supporting the robustness of their whole-brain organisation. This coupling was stable and reproducible in both ALS and HC groups, including for Microstate C, whose sources overlap with the sensorimotor cortex directly implicated in ALS. Anatomical separation from pathology cannot fully explain this stability of microstate-source coupling in ALS. Unlike this stability, previously reported alterations in microstate temporal dynamics (Metzger, Dukic, McMackin, Giglia, Mitchell, Bista, Costello, Peelo, Tadjine, Sirenko, Plaitano, et al., 2024; Notturmo et al., 2022) showed that temporal measures can register ALS-related change that the coupling measure used here did not detect. Degeneracy and local compensatory mechanisms offer plausible explanations for this microstate-source coupling stability. These findings suggest that spatial coupling, at least as implemented here, remains preserved even for disease-relevant networks, may be less able to capture network dysfunction in ALS and would benefit from being complemented by temporal measures.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author on reasonable request from qualified investigators. Data sharing is subject to the participant's consent and approvals by the Data Protection Officer and the Office of Corporate Partnership and Knowledge Exchange in Trinity College Dublin.

CODE AVAILABILITY

The code for the microstate-source coupling analysis and subsequent statistics will be made available

AUTHORS CONTRIBUTIONS

Marjorie Metzger, Bahman Nasserroleslami, Orla Hardiman, Niall Pender, Muthuraman Muthuraman, Peter Bede: Conceptualisation. Marjorie Metzger, Stefan Dukic, Roisin McMackin, Eileen Giglia, Matthew Mitchell, Saroj Bista, Emmet Costello, Colm Peelo, Yasmine Tadjine, Vladyslav Sirenko, Serena Plaitano, Amina Coffey, Prabhav Mehra, Narin Suleyman, Eva Woods: Investigation (Data acquisition). Marjorie Metzger, Bahman Nasserroleslami: Methodology. Marjorie Metzger: Formal Analysis. Marjorie Metzger, Adelais Farnell Sharp, Mark Heverin, Bahman Nasserroleslami, Orla Hardiman: Project Administration. Bahman Nasserroleslami, Orla Hardiman: Resources. Marjorie Metzger, Bahman Nasserroleslami, Orla Hardiman, Niall Pender, Muthuraman Muthuraman, Peter Bede: Funding Acquisition. Marjorie Metzger, Gabriel Costa, Stefan Dukic, Bahman Nasserroleslami: Software. Bahman Nasserroleslami, Orla Hardiman: Supervision. Marjorie Metzger: Validation. Marjorie Metzger: Visualisation. Marjorie Metzger: Writing-original draft. Marjorie Metzger, Bahman Nasserroleslami, Orla Hardiman: Writing-review and editing.

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DECLARATION OF COMPETING INTERESTS

No conflict of interest to disclose.

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