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Review

EEG microstate syntax analysis: A review of methodological challenges and advances

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ABSTRACT

Electroencephalography (EEG) microstates are "quasi-stable" periods of electrical potential distribution in multichannel EEG derived from peaks in Global Field Power. Transitions between microstates form a temporal sequence that may reflect underlying neural dynamics. Mounting evidence indicates that EEG microstate sequences have long-range, non-Markovian dependencies, suggesting a complex underlying process that drives EEG microstate syntax (i.e., the transitional dynamics between microstates). Despite growing interest in EEG microstate syntax, the field remains fragmented, with inconsistent terminologies used between studies and a lack of defined methodological categories. To advance the understanding of functional significance of microstates and to facilitate methodological comparability and finding replicability across studies, we: i) derive categories of syntax analysis methods, reviewing how each may be utilised most readily; ii) define three "time-modes" for EEG microstate sequence construction; and iii) outline general issues concerning current microstate syntax analysis methods, suggesting that the microstate models derived using these methods are cross-referenced against models of continuous EEG. We advocate for these continuous approaches as they do not assume a winner-takes-all model inherent in the microstate derivation methods and contextualise the relationship between microstate models and EEG data. They may also allow for the development of more robust associative models between microstates and functional Magnetic Resonance Imaging data.

1. Defining EEG microstates and EEG microstate syntax

Electroencephalography (EEG) microstates have become of increased interest in the field of neuroimaging. The number of papers published that have used the approach has increased substantially in recent years (Kleinert et al., 2023). Briefly, EEG microstates are defined as "quasi-stable" periods of electrical topography across the scalp in multichannel EEG (Lehmann et al., 1987), most commonly derived through clustering of topographies at Global Field Power (GFP) peaks (Khanna et al., 2014; Pascual-Marqui et al., 1995; Tibshirani and Walther, 2005) either using the data-driven approach (Kleinert et al., 2023) or matching to EEG microstate typography templates derived from previous research (Koenig et al., 2002; Milz et al., 2017; see Fig. 1 for the canonical microstate topographies, and Michel and Koenig, 2018 for a review). The microstate parameters of duration (average amount of time a microstate lasts), occurrence (average number of times a microstate class occurs in a second), and coverage (average percentage of the time series taken up by each microstate class) have been shown to differ between cognitive states (Antonova et al., 2022; Brodbeck et al., 2012; D'Croz-Baron et al., 2021; Milz et al., 2016, 2017; Seitzman et al., 2017; Tomescu et al., 2022; Zanesco et al., 2021), as well as to differentiate clinical populations from each other (e.g., Dierks et al., 1997; Nishida et al., 2013; Stevens and Kircher, 1998; Strik et al., 1997) and from healthy controls (e.g., Chu et al., 2020; Diezig et al., 2022; Férat et al.,

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2021; Kikuchi et al., 2011; Kindler et al., 2011; Schumacher et al., 2019; Serrano et al., 2018; Soni et al., 2018; Strelets et al., 2003; Tait et al., 2020; Vellante et al., 2020). These findings have sparked interest in understanding the functional significance of EEG microstates and has marked them as potential clinical biomarkers (see Michel and Koenig, 2018 for a review).

EEG microstate "syntax" analysis is a natural development of research into the functional significance of the EEG microstates using standard parameters. Here, *EEG microstate syntax* is defined as any investigation of microstate dynamics beyond the investigation of traditional EEG microstate parameters. That is, transitions in a sequence of microstates, with sequences of length 2 (pairwise) or greater. Metaphorically speaking, past microstate syntax investigations have predominantly investigated "syllables" (pairwise transitions between neighbouring microstates) or "words" (short sequences of microstates), with more recent studies beginning to investigate the underlying "grammar" (general rules of transitory dynamics).

However, the field of microstate syntax investigation remains fragmented. Different sequence types, preprocessing and analysis steps, as well as novel methodological developments have made comparison between studies difficult. To alleviate these issues, we first provide an overview of microstate derivation methods, discussing how different derivation methods impact the microstate sequence. We then define the methods for generating a microstate sequence. We then use these definitions to review previously applied methodologies for microstate syntax analysis that investigated pairwise transitions, short microstate sequences, and, more recently, complex microstate dynamics. We derive the categories of these methods for clarity, highlighting the benefits and drawbacks of each, and point to potential areas of development. Following the overview of existing methodologies, we suggest a future direction for microstate syntax analysis, which recontextualises microstates in a continuous space. Finally, we briefly discuss further considerations for future research, such as potential pitfalls in preprocessing stages, and suggest a potential approach to associating EEG microstate syntax to simultaneously recorded functional Magnetic Resonance Imaging (fMRI) data that would make the associations between them more robust.

2. The case for investigating EEG microstate syntax

Investigating pairwise transitions from one microstate to another is perhaps the most basic means of investigating microstate syntax. Transition probabilities have been shown to differentiate between cognitive processes in experimental manipulation studies (Antonova et al., 2022; Artoni et al., 2023; Ke et al., 2021; Milz et al., 2017), as well as between different clinical populations (Nishida et al., 2013), clinical and healthy populations (Lehmann et al., 2005; Lian et al., 2021; Musaeus et al., 2019; Nishida et al., 2013; Tomescu et al., 2015; Vellante et al., 2020; Zappasodi et al., 2017), and between healthy populations (Schlegel et al., 2012; Tomescu et al., 2018).

Whilst these transition probabilities may differ between populations and between cognitive processes, there is mounting evidence that microstates exhibit long-range dependencies beyond pairwise transitions, suggesting more complex dynamics than was previously thought (Gschwind et al., 2015; Van De Ville et al., 2010; von Wegner et al., 2017, 2018).

One line of support for investigating EEG microstate syntax beyond pairwise transitions comes from the analysis of short microstate sequences, which we refer to here as "*n*-grams". An *n*-gram is a microstate sequence of length *n* (see Section 4 for standard definitions). The probability of *n*-gram occurrences differ between various populations (Artoni et al., 2022, 2023; Lehmann et al., 2005; Murphy et al., 2020; Schlegel et al., 2012), with two studies (Lehmann et al., 2005; Schlegel et al., 2012), both of which investigating 4 grams (i.e., microstate sequences of length 4), showed that the order of a particular sequence is more common in one population, whilst the reverse order is more common in another (e.g., *ACDA* vs *ADCA*).

Further support for the investigation of complex EEG microstate syntax comes from studies that demonstrated that microstates exhibit scale-free dynamics (Gschwind et al., 2015; Van De Ville et al., 2010), suggesting that long-range dependencies beyond pairwise transitions were present in the EEG microstate sequences of the time series. Furthermore, von Wegner et al. (2017) applied information theoretical analysis to EEG microstate sequences and showed that much information about previous microstates was retained in the subsequent microstate sequence. Specifically, the analysis showed a non-Markovian element to resting-state microstate sequences at the zeroth, first and second orders, with devolving into a first-order Markov model occurring beyond 1000 *ms* when predicting the future microstate. Developing upon this, Sikka et al. (2020) used a Recurrent Neural Network (RNN) to model EEG microstate sequences at multiple time scales from 200 - 2000 *ms* and captured stably recurring microstate patterns. Importantly, the authors highlighted that the traditional univariate EEG microstate measures of duration, occurrence and coverage could not differentiate statistically between participants at rest vs in a stressed state. Transition probabilities were also not significantly different between rest and stress conditions. However, when training an RNN on the EEG microstate sequences of both rest and stress conditions, the model could correctly classify the sequence as occurring during each condition 63 % - 73 % of the time. The study demonstrates that microstate syntax changes with cognitive state, containing information in addition to, or at times not captured by, standard microstate parameters or pair-wise transition probabilities. Other studies lend further support to the notion that microstate syntax must be understood beyond pairwise transitions. Musaeus et al. (2019) and Tait et al. (2020) reported no significant differences in pairwise microstate transitions between Alzheimer's and mild cognitive impairment patients or between the two clinical groups and healthy controls, with Tait et al. (2020) highlighting that non-Markovian dependencies in EEG microstate syntax that cannot be captured by pairwise transitions might differentiate the groups. Additionally, Nehaniv and Antonova (2017) showed that the EEG microstate sequences reported by Lehmann et al. (2005) exhibited more complex transitional dynamics than the short sequences examined by the authors. Taken together, these findings make a compelling case that investigation

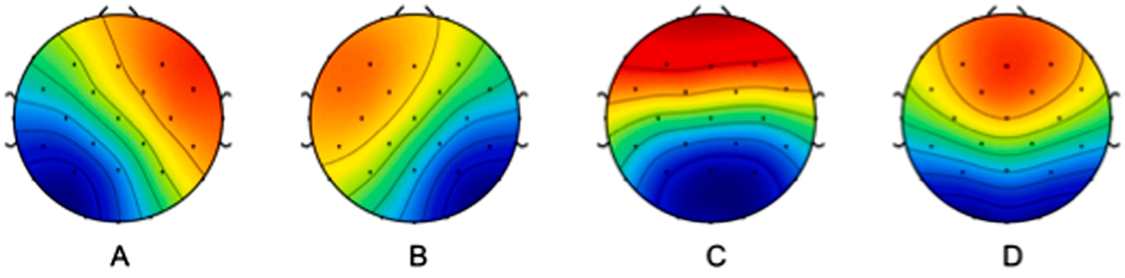

Fig. 1. The "canonical" microstate classes *A* to *D* left to right adopted from Milz et al. (2017). EEG microstate classes are defined by the topographical distribution of electrical activity across the scalp. Note that the location of the poles defines a microstate class, with the polarity considered irrelevant.

of longer microstate sequences is required to better understand EEG microstate syntax and its relationship to cognitive and mental processes.

To better understand complex non-Markovian dynamics of EEG microstate sequences, appropriate methodologies for syntax analysis must be used. However, in many cases standardised methods used for deriving microstates may "disturb" the original syntactic structure of the time series, but previous studies have not considered this. In the following section, we identify analysis steps that change the microstate sequence, discussing the implications for EEG microstate syntax.

3. The impact of EEG microstate derivation on EEG microstate syntax investigation

The approach used for EEG microstate derivation defines the temporal boundaries of each microstate. This not only affects the microstates' duration, but more importantly for syntax investigation, the transitional sequence of microstates in the time series. The most popular means of deriving microstate boundaries is back-fitting (Murray et al., 2008; Nagabhushan Kalburgi et al., 2024; Poulsen et al., 2018). After microstates are derived as topographies that best (or adequately) explain variance across GFP peaks, be it through common clustering methods (Brunet et al., 2011; Pascual-Marqui et al., 1995; Tibshirani and Walther, 2005) or other more uncommon means such as Independent Component Analysis (ICA; Yuan et al., 2012), the topography of each microstate map is correlated with each time point in the time series at the subject-level, effectively resulting in a correlation time series for each microstate (Fig. 2A, top). Each time point is then labelled with the microstate that shows the highest correlation in a winner-takes-all fashion (see Section 6 for a discussion of winner-takes-all), resulting in a discrete sequence of microstates with a microstate label assigned to each time point (Koenig et al., 1999). This process results in periods where consecutive time points are labelled with the same microstate.

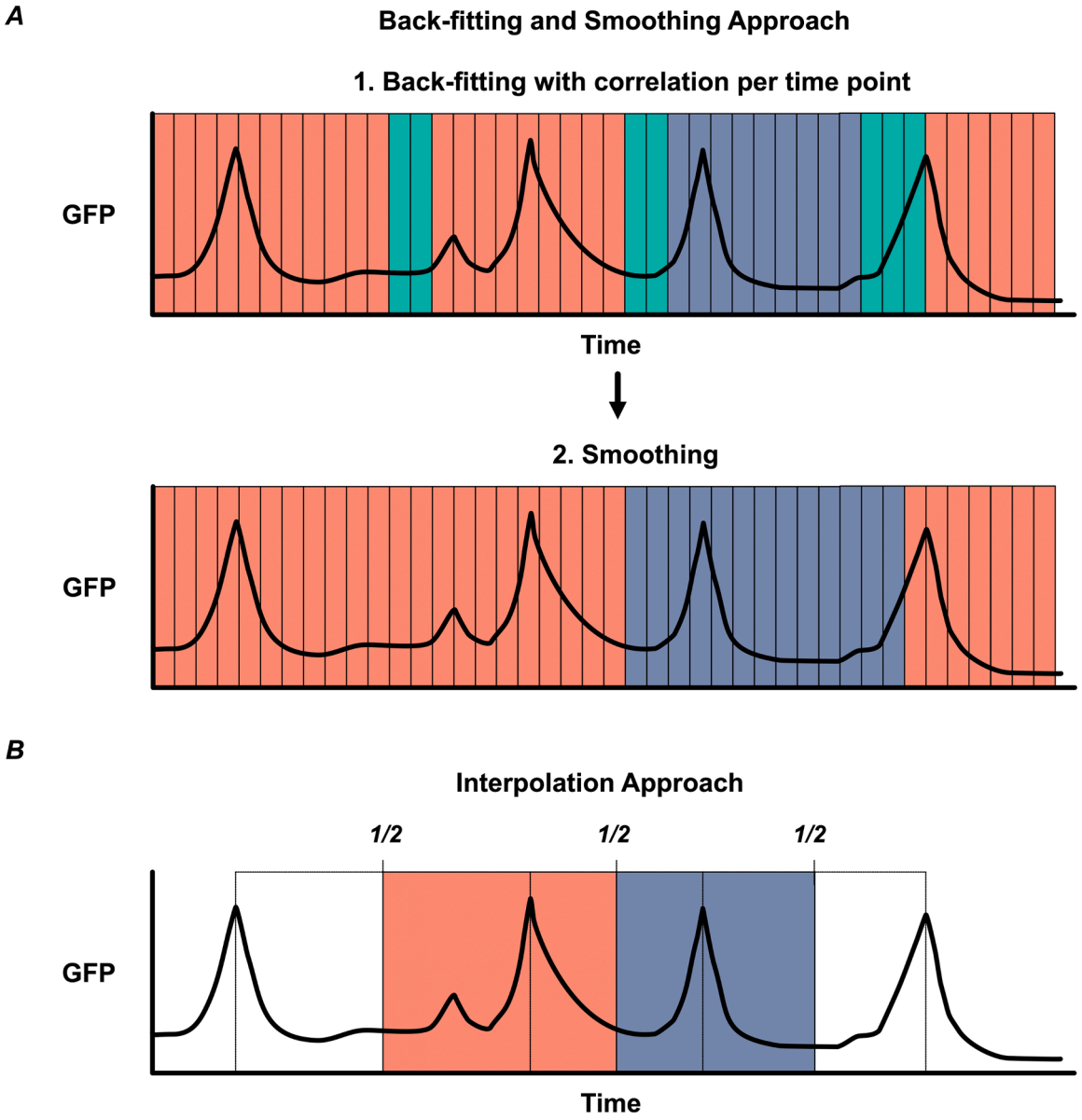

Fig. 2. Comparison of the back-fitting plus smoothing approach with the interpolation approach. Colours are representative of different microstates. *A.* Top panel (1) shows the back-fitting method, where each time point is correlated with each microstate, and is then labelled with the microstate it is most similar to (note labels are not to scale temporally). Bottom panel (2) then shows the smoothing process. Where the number of consecutive time points for a microstate is under the user-defined number of time points, the short microstate is assimilated into neighbouring microstates. *B.* shows the interpolation method. GFP peaks (top) are subject to clustering and hence are already labelled with microstates (bottom). The durations are defined by the mid-points between microstates.

The number of consecutive labels of a single microstate is an estimation of that microstate instances duration.

Due to the conception that a microstate generally lasts approximately 60 - 120 *ms* on average (Koenig et al., 2002; Lehmann et al., 1987), it is common for a smoothing step to be carried out to remove microstate instances that are considered too short (Kleinert et al., 2023; Murray et al., 2008). This smoothing step removes microstates that last less than a predefined duration (which varies between studies) through relabelling. The microstates that occur before and after a short microstate are identified, and the short microstate is reassigned to whichever of the two neighbouring microstate classes it is most similar to (Fig. 2A, bottom).

While this homogenises the duration of microstates, both within and across the microstate classes, the smoothing step introduces potentially arbitrary distortions into the microstate sequence. For example, if a section of the time series shows a short period that is most similar to microstate *D*, but is then relabelled with *C*, the microstate sequence is altered to a form that explains less variance in the EEG signal than before smoothing took place. Smoothing may also potentially further impact the syntactic structure of the sequence, at least theoretically. Microstates are most commonly generated using the topographies at GFP peaks with clustering methods (Khanna et al., 2014; Michel and Koenig, 2018). The back-fitting process then uses these cluster centres, which are only generated using the GFP peaks, to label the whole time series. The approach intends to identify a precise transition point between GFP peaks where the microstate label switches. It is possible, however, that smoothing could occur across a GFP peak if the back-fitting process found the duration of the microstate around the GFP peak to be under the experimenter-defined threshold. This possibility highlights the flaw inherent in smoothing, given that retaining a microstate sequence that maximises the explained variance of the underlying EEG signal (without overfitting) is a priority in EEG microstate syntax research. The impact of back-fitting and smoothing on EEG microstate syntax has been highlighted elsewhere previously (von Wegner et al., 2017), with the solution being to simply not apply smoothing. Whilst this does avoid alteration of syntactic structure, it does not account for the noise that smoothing intends to remove. A previously applied approach is back-fitting that only includes EEG time points with a correlation value greater than some user defined threshold (Artoni et al., 2022; Férat et al., 2021, 2022). Whilst this may have been applied due to the specific analysis method used (see Section 5.2), the approach warrants consideration. On the one hand, it ensures that the time points considered in the microstate model are always time points with the highest correlation with said model. On the other hand, the approach assumes that periods of the EEG time series that do not highly correlate with the microstates, and therefore do not fit into the model, are not functionally significant data, which might not be the case (see Section 6).

An alternative to correlating each time point with each microstate is the interpolation approach (Poulsen et al., 2018; Tait and Zhang, 2022), where the centre points between GFP peaks are assumed as the transition point (Fig. 2B). Unlike the back-fitting approach, this approach preserves the original transitional structure of the EEG microstate sequence in the time series, as the GFP peaks that were used to derive the microstates in the first place are assumed to create the sequence structure. Additionally, this approach allows for the analysis of interactions between consecutive GFP peaks that have been assigned to the same microstate class, which is not possible using back- fitting. Two neighbouring microstates in a back-fitting derived sequence would likely be made up of different numbers of peaks in a row. This simplifies the complexity of the relationship between microstate sequences and the underlying EEG signal and limits the investigation of within-class dynamics. However, the interpolation approach does assume that there are no meaningful transitional dynamics between GFP peaks. Studies of EEG microstate syntax (Hermann et al., 2024) as well as EEG signal (Shaw et al., 2019) have challenged this assumption by showing structure between GFP peaks. For these reasons, it is recommended that future research examines the impact of backfitting, smoothing (or any other temporal post-processing) and interpolation on microstate syntax analysis.

3.1. Canonical versus data-driven EEG microstates in the context of syntax investigations

The four discrete topographies that are most commonly observed and are highly replicable across studies in both healthy and clinical populations, accounting for about 80 % of variance in eyes-closed resting-state EEG signal (Michel and Koenig, 2018), have been referred to as "canonical" EEG microstates and are labelled *A*, *B*, *C* and *D*. Using the canonical set of microstates ensures comparability across studies, which is a benefit that extends to microstate syntax analysis (Koenig et al., 2023; Michel and Koenig, 2018). However, fitting the observed data to topographic maps that were not derived from that data may result in a poor fit, impacting the ability to detect syntax specific to the time series.

Future researchers should also consider the number of generated microstates. Data-driven methods may require more microstate topographies than the canonical four to sufficiently explain the variance of underlying data, which would in turn require consideration more complex microstate sequences (see Section 5.1). However, a data-driven microstate sequence and its modelled syntax will likely be a more accurate reflection of the observed EEG signal than the canonical set, ultimately increasing our ability to understand the functional significance of microstates from syntax analysis. Hence, future research should use data-driven microstates in syntax analysis methods, whilst ensuring a balance between explained variance and the number of microstates (which also avoids overfitting; Michel and Koenig, 2018).

4. EEG microstate *n*-grams

Initial investigations into microstate syntax beyond one-to-one transitions have come from investigations of EEG microstate *n*-grams. We define a sub-sequence of microstates as a microstate *n*- gram, where *n* is the number of consecutive microstate labels in the sub-sequence. The term "*n*-gram" is borrowed from language models in machine-learning (Jurafsky and Martin, 2000). Synonyms in the microstate analysis field include "microstate words" (e.g., Artoni et al., 2023) and "k-history" (e.g., von Wegner, 2018). Here, the definition of an *n*-gram does not have a limit on length *n*, as any limit would be arbitrary without some functionally meaningful reason. An illustration of *n*-grams of different lengths is shown in Fig. 3. The *n*-gram approach can be considered a sliding window of length *n* that moves along the microstate sequence one microstate at a time.

In the following subsection, we define the types of microstate sequence that *n*-grams can be defined within.

4.1. Defining EEG microstate sequence types

The EEG microstate sequence can be constructed using different "time-modes", which may affect syntactic sequence analysis. Nehaniv and Antonova (2017) used two time-modes: clock- and event-based. In our more recent research, we have also been using the peak-based time-mode. EEG microstate syntax research is yet to adopt these distinctions more broadly, but doing so would be beneficial since the utility of these three time-modes might differ when investigating EEG microstate syntax in different contexts and/or populations. We define each time-mode of microstate sequence construction below and provide illustrative examples in Fig. 4.

Fig. 4A (top) shows the most conventional means by which *n*-grams are defined, referred to here as "event-mode" (Nehaniv and Antonova, 2017). The term "event" refers to a transition from one microstate to another, different microstate. That is, this mode does not have repeating microstates in a sequence (i.e., *AAB* is impossible in event-mode). Note

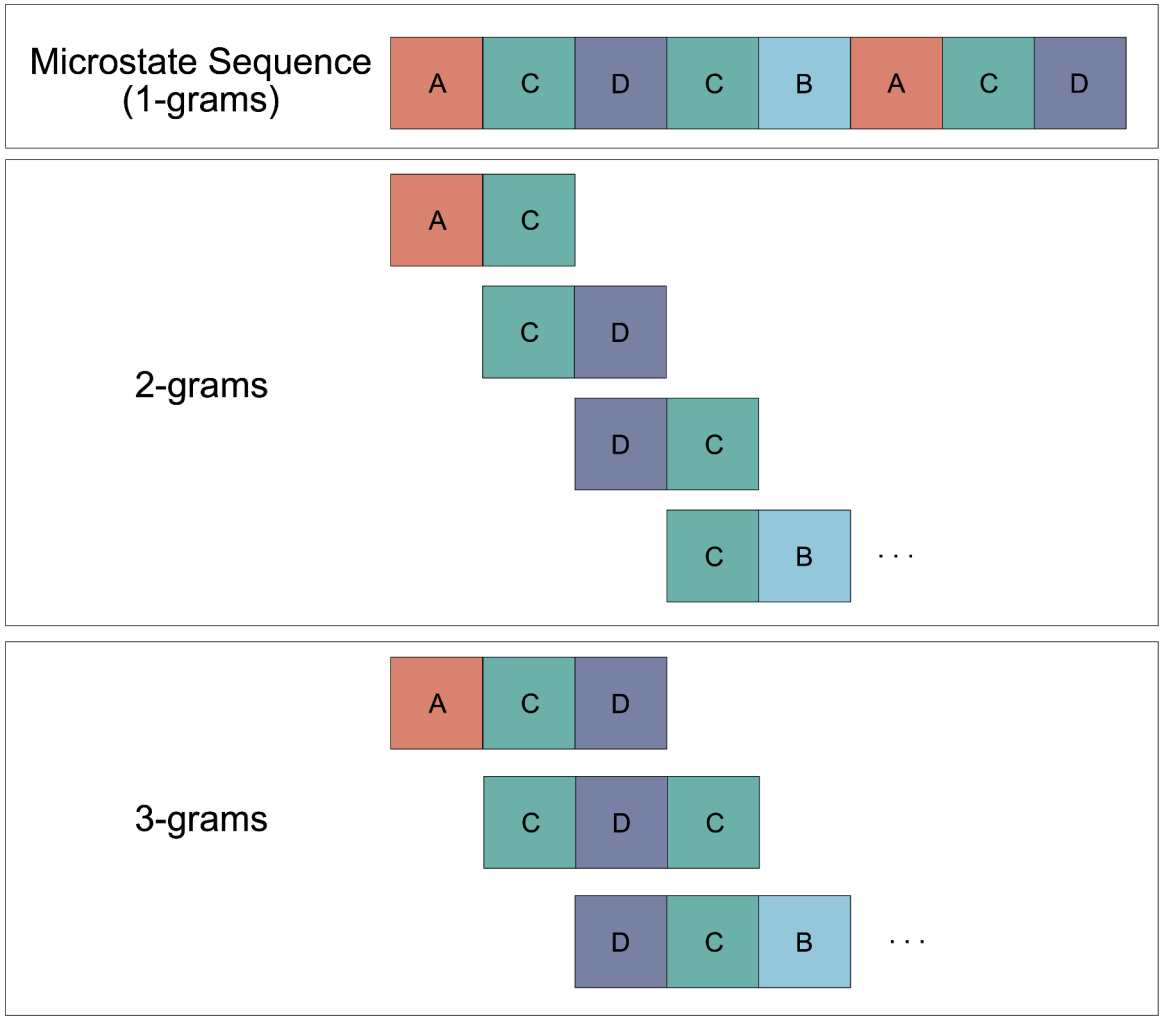

Fig. 3. Illustration of microstate *n*-grams. Top panel shows sequence of microstates from observed EEG time-series, equivalent to 1 grams. Second panel shows 2 grams; third panel shows 3 grams in event-mode (see Section 4.1 for a definition of sequence time-modes). *n*-grams are derived using a sliding window of size *n* with step size 1.

that Fig. 3 showed event-mode *n*-grams of various lengths. In the example given in Fig. 4A, the 3 gram $A \rightarrow C \rightarrow D$, has *A* lasting 100 *ms*, *C* 80 *ms*, and *D* 120*ms*, with the observed EEG signal at a sampling frequency of 250*Hz* (i.e., each time point lasting 4*ms*). The estimation of the pairwise transition probabilities performed in most studies to date (see Section 1 for an overview) as well as of transition probabilities of *n*-grams longer than length 2 (e.g., Lehmann et al., 2005; Schlegel et al., 2012) use event-mode EEG microstate sequence analysis. Event-mode may be beneficial in circumstances where the duration of a microstate is not important, or where abrupt changes in topography are of more interest than microstate duration.

The second approach to constructing the EEG microstate sequence is the "clock-mode" (Nehaniv and Antonova, 2017). Clock-mode refers to a sequence where each label represents a clock tick on the time series. An example sequence is presented in Fig. 4A (bottom). A sample frequency of 250*Hz* would give 250 microstate labels per second: one label for each time point. Hence, the event-mode sequence *ACD* would be represented as a 75 gram in clock-mode: 25 *A*s (100$ms/4ms = 25$ time points), 20 *C*s (80$ms/4ms = 20$ time points) and 30 *D*s (120$ms/4ms = 30$ time points). Clock-mode is dependent on sampling frequency and therefore could be of utility in contexts requiring high microstate sequence granularity and/or the retaining of temporal information. Some past studies have utilised clock-mode (e.g., von Wegner et al., 2017) or what is coined "permanence" by Artoni et al. (2022), but it has been used less frequently than event-mode.

The third approach to microstate sequence construction is referred to as "peak-mode". Peak-mode only considers the microstate labels of GFP peaks that were assigned during microstate derivation. Fig. 4B depicts the GFP time series that was used to define the microstates. In this example, microstate *D* is comprised of two GFP peaks. The event-mode sequence of *ACD* would be represented in the peak-mode as *ACDD*. Despite not retaining temporal information like clock-mode, peak-mode allows for repeating microstate labels in a sequence, which event-mode does not. Note also that peak-mode cannot be derived using the back-fitting plus smoothing approach (see Section 3) since the process of back-fitting assigns microstate labels based on similarity of the EEG time series to each microstate class, so the "transition" point from one GFP peak to another of the same class cannot be identified (see Fig. 2). A shortcoming of peak-mode is that it assumes that GFP peaks are the only relevant time points for generating the microstate sequence, which is likely not the case (see Section 6).

A key difference between time-modes is recoverability of microstate parameters. Clock-mode is the only time-mode of the three defined here that can be used to recover the standard EEG microstate parameters. Event- and peak-mode on the other hand do not allow for this recoverability, meaning transform to either of these time-modes removes microstate parameter information from the sequence.

As evident from the examples of *n*-grams given above to illustrate

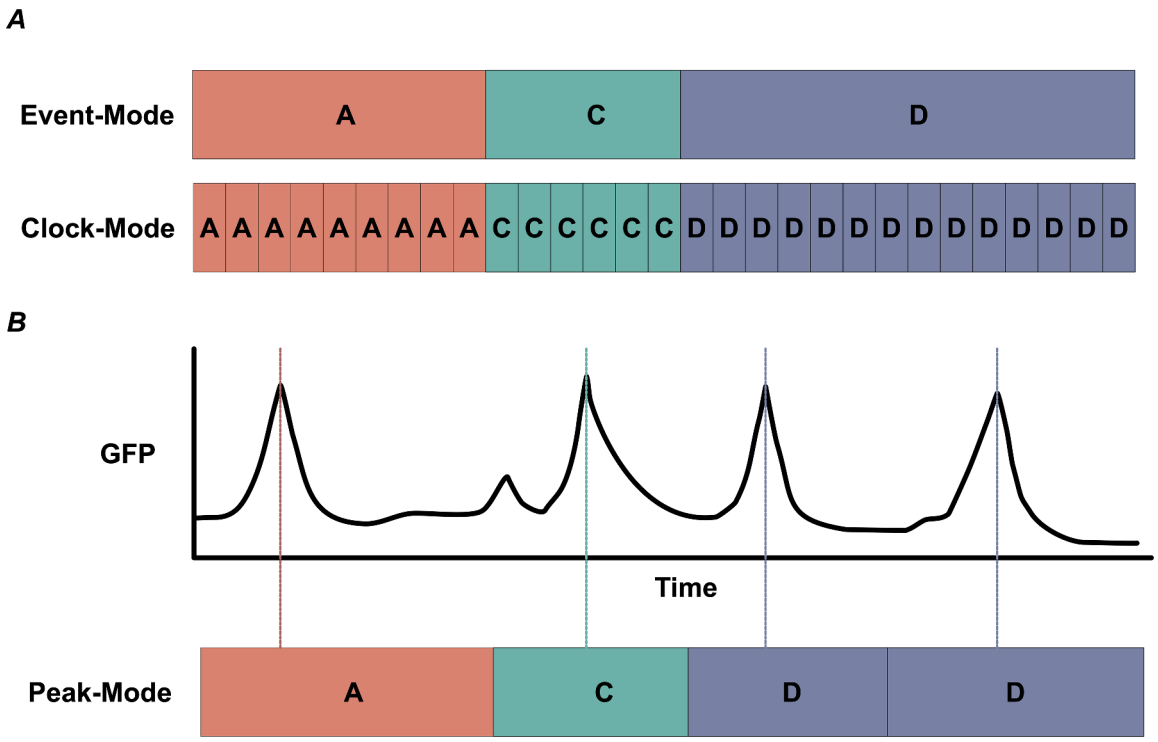

Fig. 4. Illustration of three EEG microstate sequence derivation modes: event, clock and peak. *A.* Top panel shows the event-mode microstate sequence, in which transitions between microstates defined by microstates' boundaries. Bottom panel shows the clock-mode sequence, where each clock tick is regarded as a separate state in the sequence (note that illustration is not to scale temporally). *B.* Top panel shows the GFP time-series used to generate the microstate sequence. Two GFP peaks in a row labelled with microstate *D* would constitute a single occurrence of *D* in the event-mode. Bottom panel shows the peak-mode sequence derived from the GFP time-series. Note how there is a single microstate label for each GFP peak. Duration of each peak-mode microstate is represented here by use of interpolation for visualisation, but peak-mode duration is unnecessary (see Section 4.1).

each time-mode, the *n*-grams constituting the EEG microstate sequence vary drastically depending on the time-mode, potentially affecting syntax analysis. Future research should compare the three time-modes with each other in the same dataset to better understand differences between syntactic rules, as well as the contexts in which each time-mode may be preferable.

5. Distinguishing microstate syntax methodologies

To facilitate comparison between studies and make a clear distinction between microstate syntax analysis methods that would otherwise be difficult to compare, we define the categories of "Within-*n*" and "Between-*n*" methodologies. Within-*n* methodologies refer to syntax analysis methods which can only investigate microstate *n*-grams of a single length at a time. By contrast, Between-*n* methodologies employ an approach which allows analysis across *n*-gram lengths, i.e., they are "*n*-agnostic".

5.1. Within-n methodologies

Within-*n* methodologies, which do not consider the relationship between microstate sequences of different lengths, are the category of method which have been most commonly applied. The investigation of pairwise transitions in event-mode sequences (*n*-gram length 2) have been the most common (e.g., Antonova et al., 2022; Milz et al., 2016), with some studies having investigated the probabilities of transitions in a sequence of 4 microstates (e.g., 4 grams; Lehmann et al., 2005; Schlegel et al., 2012). These methods are concerned with occurrence ratios of microstate *n*-grams and have been shown to differentiate between cognitive states/processes (e.g., Milz et al., 2016), different clinical populations (e.g., Musaeus et al., 2019; Zappasodi et al., 2017) as well as between clinical and healthy populations (e.g., Lehmann et al., 2005; Vellante et al., 2020). It is important to consider however, that a mapping of the occurrence ratios of all possible *n*-grams between different groups and cognitive states/processes becomes a combinatorial problem that may make interpretation untenable. This is highlighted in what has been referred to as "dictionary size" by Artoni et al. (2023). If considering a hypothetical event-mode (see Section 4.1) sequence where the four canonical microstates (Fig. 1) are the possible states at each time point, the number of all possible 4 grams (its dictionary size) that could be generated would be 108 (e.g., *ABAB*, *ABAC*, *ABAD*, *ABCA*, *ABCB*… *DCDC*). We formally define the dictionary size of each time-mode as follows:

For event-mode:

$$E_k(n) = k \cdot (k-1)^{n-1}, \tag{1}$$

where $E_k(n)$ is the number of *n*-grams that can be generated in event-mode of length n with k microstates.

For clock- and peak-modes:

$$P_k(n) = k^n, \tag{2}$$

where $P_k(n)$ is the number *n*-grams that can be generated in peak- or clock-mode. Note that the temporal length of a peak- or clock mode *n*-gram of the same length n will differ. Additionally, very few of the possible clock-mode *n*-grams will be observed in practice, due to the repetition of microstate labels.

When applying data-driven approaches to microstate class derivation rather than using the canonical set of four (see Section 3.1), the size of k may increase, which in turn will increase the number of possible *n*-grams to consider. This increased dictionary size makes interpretation of results more difficult, especially when attempting to understand how *n*-grams interact within and across lengths of *n*. Some Within-*n* methodologies have developed approaches which aim to circumvent the

dictionary size problem by categorising *n*-grams. Thus, *Microsynt* (Artoni et al., 2023) extracts an optimal "vocabulary" of *n*-grams based on the length and complexity of the full microstate sequence; *n*-grams are then sorted into "entropy classes", which are then statistically compared between participant groups or conditions within groups. As an example, the 6 gram *ABDCBA* shows microstate-to-microstate transitions that are "more random" within the *n*-gram, meaning higher entropy. In contrast, the 6 gram *ABABAB* shows a transition back and forth between two microstates within the *n*-gram, indicating lower entropy. Artoni et al. (2023) extracted event- and clock-mode 6 grams from the time series and categorised them into entropy classes, which were then compared within-subjects during states of full alertness and deep anaesthesia as well as against surrogate data. High entropy classes had greater representation in surrogate data and during the fully alert state, whilst low entropy classes had greater representation during deep general anaesthesia. These findings suggest the complexity of EEG microstate syntax is subject to the levels of waking consciousness.

Another method that reduces dictionary size is epsilon-machine construction (Nehaniv and Antonova, 2017), which utilises concepts of computational mechanics (Crutchfield and Young, 1989) and its precursors (Grassberger, 1986). An epsilon-machine is a predictive and generative dynamics model which can be conceptualised as a unifiliar (the mapping from observations to states is deterministic rather than probabilistic) Hidden Markov Model (HMM), where the observation that occurs from a given state is probabilistic.

A single microstate can be thought of as a 1 gram. The first utility of the epsilon-machine is it can calculate transition probabilities of *n*-grams where $n > 1$. For example, consider the 4 gram *ABCD*. In event-mode,

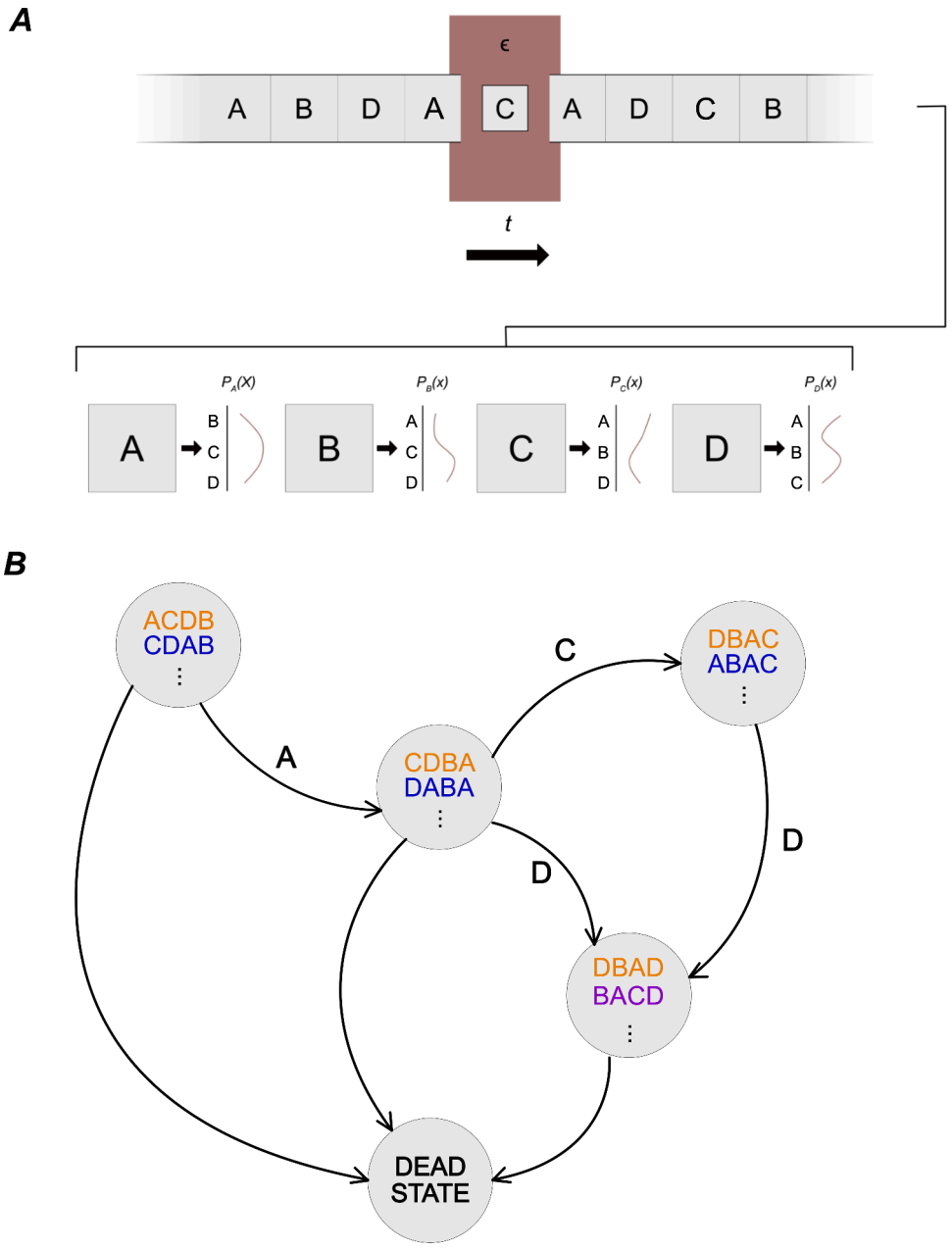

Fig. 5. Illustration of epsilon machine and an example of a resulting minimised automata. *A.* Illustration of an epsilon-machine. The epsilon-machine takes the observed microstate sequence (top) and calculates transition probabilities from each *n*-gram to each possible following *n*-gram (bottom). The transitions shown here use 1 grams for simplicity. *P* is probability, with each lettered *P* representing probability of transition from the given microstate. *B.* Example of minimised automata using 4 grams. Causal states are represented as grey nodes with the binned 4 grams included in each node. "Dead state" works as a catch all at the end of the observed sequence.

the next possible microstate in this sequence can be *A*, *B*, or *C*, making the next 4 gram in the sequence either *BCDA*, *BCDB*, or *BCDC*, respectively. The epsilon-machine can be built using these 4 grams (or any length *n* from the observed sequence; Fig. 5A), taking transitions between *n*-grams of the same length as input rather than the transition being between pairs of neighbouring microstates. The second utility of the epsilon-machine approach is the process of "minimisation". The *n*-grams are grouped into a "causal-state", where all *n*-grams within the causal-state have sufficiently similar probability of transition to the next *n*-gram (over a defined similarity threshold). Fig. 5B shows an example of the resulting automata using 4 grams where each node is a causal state, with its constituent 4 grams. The number of possible event-mode 4 grams with the canonical set of microstates (108) is reduced to a set of probabilistic states that can be further scrutinised. A methodological study by Nehaniv and Antonova (2017) used epsilon-machines to demonstrate that the data in the Lehmann et al. (2005) study require a richer model to sufficiently capture microstate syntax complexity than the findings based on 4 gram transitions reported by the authors. Nehaniv and Antonova (2017) also applied the epsilon-machine approach to two single-case studies of an experienced meditator and a meditation-naïve control during mind-wandering and found a higher complexity in causal-state transition patterns in the meditator than in the non-meditator.

Despite these methods simplifying the complexity of *n*-gram dictionary sizes and highlighting group/state differences, the specific functional significance of the *n*-grams investigated remains elusive. Additionally, transitions between microstates within an *n*-gram are assumed to hold the same weight in these approaches. To understand the dynamics of *n*-grams of higher lengths, the dynamics within the *n*-gram must also be understood; that is, each *n*-gram of length *n* is dependent on all *n*-grams of shorter length. For example, to understand the dynamics of the 4 gram *ABAB*, its constituting *n*-grams *A*, *B*, *AB*, *BA*, *ABA* and *BAB* must also be understood. It may be the case that specific constituting *n*-grams are driving the occurrence of the measured *n*-gram, but current methods do not account for this. Additionally, there may also be interactions between *n*-grams of different lengths that are not accounted for using these approaches. Fixing *n*-gram length to investigate microstate syntax is unlikely to uncover the natural varied syntactical structure of the sequence and the underlying neural dynamics.

It is also worth highlighting that short *n*-grams fall within the period where information is retained in the sequence, with the average duration of a microstate being 80–120*ms* (Koenig et al., 2002), a length 4 sub-sequence can be reasonably expected to last between 320 *and* 480*ms*. Given that von Wegner et al. (2017) importantly highlighted that the non-Markovian element of microstate sequences lasts up to 1000*ms*, we can extrapolate that the average microstate duration means *n*-grams up to length 10 or higher, and every length below that, would have to be exhaustively investigated in a brute-force fashion using the *n*-gram approach. This would effectively create an inexhaustible dictionary of *n*-grams that itself would require further cross-referencing between lengths to uncover how each of the *n*-grams interacted. Therefore, we suggest that future methods aim to understand the rules that dictate syntactic structure of EEG microstate sequences generally and in different contexts specifically, rather than using methods that require characterising every *n*-gram at every viable length in every context. To facilitate this, utilising methods which compare between *n*-gram lengths may alleviate problems regarding dictionary size. Rather than a few differences between specific *n*-grams being compared between groups or cognitive states, meaningful relationships between functional states and metrics that summarise microstate sequence dynamics could be established.

5.2. Between-n methodologies

Between-*n* methodologies allow for the investigation of microstate sequences across lengths. They are "*n*-agnostic", in that relationships can be established along the microstate sequence regardless of length *n*. An example is an approach developed by Murphy et al. (2020), which applied sample entropy as a measure to investigate *n*-grams from $n = 2$ to $n = 10$ between early-course psychosis patients and controls. Sample entropy is a measure of conditional probability that two patterns that are identical for length *n* remain identical at length $n + 1$. Murphy et al. (2020) demonstrated that sample entropy decreased for longer microstate patterns in healthy controls, but the decrease was not observed in patients, suggesting that complexity of microstate sequencing (or perhaps a randomness of transitions) is more common in psychosis patients versus controls. Whilst this approach does allow for comparison between *n*-gram lengths, and has identified a meaningful biomarker of psychosis, a shortcoming of the approach is it only allows comparison between two *n*-gram lengths at a time.

Studies have also utilised the Auto-information Function (AIF) (von Wegner et al., 2017, 2018), which is a generalised 2-point correlation that directly accepts nominal variables (microstate class labels), avoiding the need for arbitrary numerical mapping. Like autocorrelation, AIF measures the dependence between different time points in the observed microstate sequences by calculating Shannon entropy of all microstates across time points and comparing those measures between time points. Expected AIF measures of zeroth, first and second order Markov chains were computed using surrogate data. The AIF of the observed microstate sequence showed periodicities that were not apparent in surrogate data, suggesting a microstate sequence structure with long-range dependences, that cannot be accounted for by analysis methods which consider short sequences.

Lempel-Ziv complexity (LZC), which counts the number of unique sub-sequences within a sequence and uses that as a measure of complexity, has also been applied (Artoni et al., 2022, 2023; Tait et al., 2020). The Within-*n* method applied by Artoni et al. (2023) (which is discussed in Section 5.1) utilised this measure, but chose an "optimal" *n*, to limit investigation to a single length of *n*-gram. The measure was used in a general sense across *n*-gram lengths by Tait et al. (2020) on 20 s epochs of data collected from Alzheimer's patients and healthy controls, showing that LZC was lower in Alzheimer's patients than in controls. Whilst this approach does show a relevant and useful biomarker by investigating a measure across *n*'s, LZC is limited by the epoch across which it can be applied. Since LZC counts *n*-grams of all lengths *n* within the epoch considered, the approach becomes more computationally expensive as the length of the considered epoch increases. Application of the approach may therefore be difficult in contexts where a longer epoch needs to be recorded.

Whilst studies that applied Between-*n* methodologies have identified meaningful relationships between underlying signals and microstates, as well as many biomarkers, each method identified has shortcomings. LZC only allows comparison across *n*-grams by isolating epochs of time to reduce the lengths of *n* to consider. Additionally, AIF application requires converting the discretised sequence of microstates into a continuous parameter that can be subject to further investigation. Whilst this is not inherently problematic, there have been relatively few studies that have instead attempted to compare microstates to the underlying continuous EEG signal *used to derive them.*

6. Reframing microstates in a continuous space

Previous investigations primarily used parameters to characterise microstates in various contexts, with the measures of duration, occurrence and coverage being the most prominent (Michel and Koenig, 2018). Parameters are defined based on the winner-takes-all approach to microstate derivation, where each time point is labelled by a single microstate. It has been highlighted that the winner-takes-all approach to defining microstates may affect our ability to understand the functional significance of EEG microstates and their sequences, as it assumes the presence of well-delineated discrete microstate classes, ignoring the variability of topography present in the EEG time series (Mishra et al.,

2020; Shaw et al., 2019).

Microstates could instead be conceptualised as attractor points in a multidimensional space (Milz et al., 2017). Whenever a microstate occurs on the time series, that is, whenever a point on the EEG time series *is more similar to* that microstate than any other microstate (the back-fitting approach; see Section 3), that time point is assigned a given microstate label. Fig. 6 presents three animations of a simulated signal represented as a multidimensional trajectory in three different contexts over a period of 2 s. In this illustrative example, all three axes represent a dimensionally reduced time series as a trajectory (in black) moving through a three-dimensional space as time progresses. The coloured and labelled data points are representative of canonical microstate topographies embedded in the space. The left axis shows how the microstate sequence represents the observed simulated signal, the middle axis shows the observed GFP peaks (peaks in standard deviation of the simulated signal) that were used to generate the microstate sequence, and the right axis shows the whole simulated time series.

Supplementary material associated with this article can be found, in the online version, at: doi:10.1016/j.neuroimage.2025.121090.

Although it is undoubtedly the case that microstates explain a high percentage of variance of GFP peaks and have clearly distinguished functionally significant features between groups (Michel and Koenig, 2018), the use of a continuous space explicitly shows the difference between the observed GFP peaks, observed EEG signal, and the microstate model. In the existing winner-takes-all approach to microstate labelling (Fig. 6, left), each time point is assigned a single label. This simplifies the topography at each GFP peak to a handful of cluster centres, which are averages of a set of topographies. In reality, each GFP peak shows a different topography (Fig. 6, middle), which contains complexity that cannot be accounted for with microstate syntax models. Further, the use of GFP peaks assumes that there are no complex dynamics in the observed signal between peaks, which is not the case (Fig. 6, right; Shaw et al., 2019).

Embedding microstates in the context of a continuous space allows for an investigation of these assumptions and may also elucidate open questions about the nature of microstates in general (Mishra et al., 2020). For example, differences between time-modes (see Section 4.1) are readily investigable in this context, as all sequences can be placed in the same space, subject to the same measures. Standard microstate parameters of duration, occurrence and coverage can be reconceptualised in an attractor space: duration is how long the EEG time series is "under the influence of" the microstate as an attractor point; occurrence is how many times the trajectory returns to the influence of a given attractor within a second; and coverage is how much of the overall EEG spatial trajectory is spent under the influence of each attractor point. A pairwise transition is the EEG time series moving from the influence of one attractor point to another. Microstate syntax would then be the rules that dictate the movement of the EEG signal between these attractor points. Information about the observed EEG signal that would usually be lost when investigating microstates as a sequence alone is readily available when using a continuous model and could be utilised to understand the syntactic rules of EEG microstate sequences.

Whilst these points regarding the underlying continuous EEG signal may be obvious, relatively few existing methodologies have attempted to model the relationship between microstate classes and the underlying continuous signal (Mishra et al., 2020; Shaw et al., 2019).

The continuous space may highlight issues inherent in the microstate approach in general, but it also provides potential solutions to issues that existing syntax methodologies are unable to address. For example, whilst microstate duration in this context does show how long the EEG signal is under the influence of a microstate, investigation of event-mode microstate syntax assumes that each microstate instance is of equal weight. It may be the case that individual instances of a microstate are of different durations, but neither Within-*n* nor Between-*n* methodologies (see Section 5) could address this. Cross-referencing of microstate labels and continuous EEG signal allows for consideration of this through the comparison of various sub-trajectories. Additionally, it may be the case that the specifics of observed EEG topographies impact transitional dynamics between microstates, which are readily investigated in a continuous space, but are lost in the microstate sequence. Therefore, the functional significance of microstates and microstate transitions could be elucidated when cross-referenced with the underlying EEG signal. For these reasons it is strongly recommended that future investigations of microstate syntax consider dynamics in the context of a continuous signal, potentially comparing them to the dynamical systems models of EEG signal that have been proposed in the past (e.g., Stam, 2005).

7. Towards a methodological standard for EEG microstate syntax analysis

Following the discussion of existing methodologies for microstate derivation and microstate syntax investigation, a discussion of what should constitute standard practice with regards to preprocessing and analysis in future investigations of microstate syntax is needed. It is also necessary to consider how future investigators may best attempt to associate microstates with simultaneously recorded fMRI data. The following section outlines potential pitfalls in both areas and suggests a best practice.

7.1. EEG preprocessing steps

The standard EEG data preprocessing steps applied prior to

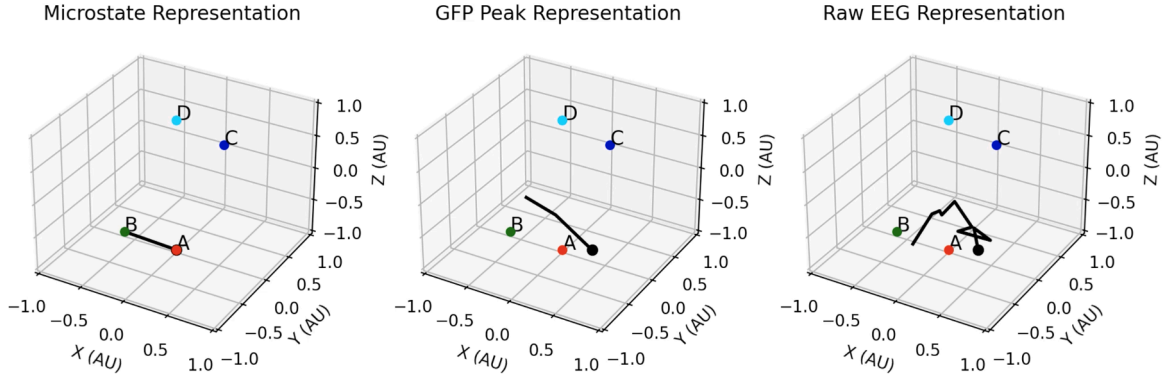

Fig. 6. Visualisation of simulated microstates, GFP peaks, and the signal represented in a multidimensional, continuous space. Coloured points in each axis represent the four canonically labelled microstates, *A*, *B*, *C*, and *D*. The black trail of each axis represents the trajectory of the signal over time in each of the three spaces. All trajectories are of the same 2 s snippet of simulated data represented in three ways. Representative of, left to right, the difference between the microstate sequence, the GFP peaks used to derive the microstates, and the observed simulated signal.

microstate derivation include re-referencing, band-pass filtering, down-sampling from the recorded frequency, artefact correction if applicable, removal of noisy epochs and channels, and ICA followed by rejection of noise components (Kleinert et al., 2023; Michel and Koenig, 2018; Poulsen et al., 2018; Tait and Zhang, 2022). These steps are intended to remove any signal in the EEG data that may be from sources other than the brain, such as eye and head movement, heartbeat and muscles of the scalp, or from issues during the recording process. In the case of simultaneous EEG-fMRI recordings, algorithms for Magnetic Resonance (MR) noise removal are also employed (e.g., Allen et al., 2000).

While these methods adequately clean the EEG for microstate derivation, researchers must be aware of how each of these steps affect the microstate sequence. As all steps are intended to improve the signal-to-noise ratio (SNR) of the EEG signal, a microstate sequence derived from this signal are in turn more likely to have a high SNR. Researchers must be cautious when applying epoch removal, however. Whilst this may improve the SNR of the data (Peng, 2019), the removed noisy period creates a "cut" in the microstate sequence, meaning that the time series' before and after the cut must be considered as individual and separate sequences during analysis (Artoni et al., 2022). Any form of concatenation would result in identification of false syntactic structures. An alternative is to minimise epoch removal, but including periods of noise in the time series for later microstate analysis would add noise to microstate cluster centres, also reducing SNR in the microstate sequence. Application of noise removal methods such as Fourier transforms on a sliding window (e.g., Mitra and Bokil, 2007), bad channel identification algorithms using different forms of interpolation (e.g., Bigdely-Shamlo et al., 2015), or other windowed noise correction algorithms (e.g., Mullen et al., 2013) may reduce the need for epoch removal. But in cases where epoch removal is still required to remove noisy components from the signal, it is emphasised that concatenation of microstate sequences before and after the problem epoch should not take place.

It is also emphasised here that any future studies of microstate syntax should report full details of the implemented preprocessing and analysis steps. This crucially includes documentation of the microstate derivation method used, along with the parameters used for derivation such as minimum window length for smoothing. Doing so will improve comparability and, potentially, replicability between studies.

7.2. *Associating simultaneously recorded EEG-fMRI data*

Many studies have attempted to understand the functional significance of EEG microstates by associating them with functional brain networks, be it using EEG source localisation (e.g., Custo et al., 2017; Milz et al., 2017) or simultaneously acquired fMRI data (Abreu et al., 2021; Britz et al., 2010; Case et al., 2017; Xu et al., 2020; Yuan et al., 2012). Whilst it is the case that some meaningful associations have been made using these approaches, it is important to highlight the potential pitfalls of associating microstates with fMRI data.

The most common means by which EEG data have been associated with simultaneously acquired fMRI data is the use of a voxel-wise General Linear Model (GLM). The GLM allows for the application of EEG microstates as regressors to the fMRI Blood-Oxygenation Level Dependent (BOLD) signal. The EEG microstate sequence (Fig. 7, top) is correlated with each time point of EEG topography to generate a continuous signal of "microstate strength" (Fig. 7, middle). Each microstate class time series is then down-sampled to the sampling frequency of the simultaneously acquired fMRI data (an example TR of 2 s would be 0.5*Hz*) and is then convolved with the Hemodynamic

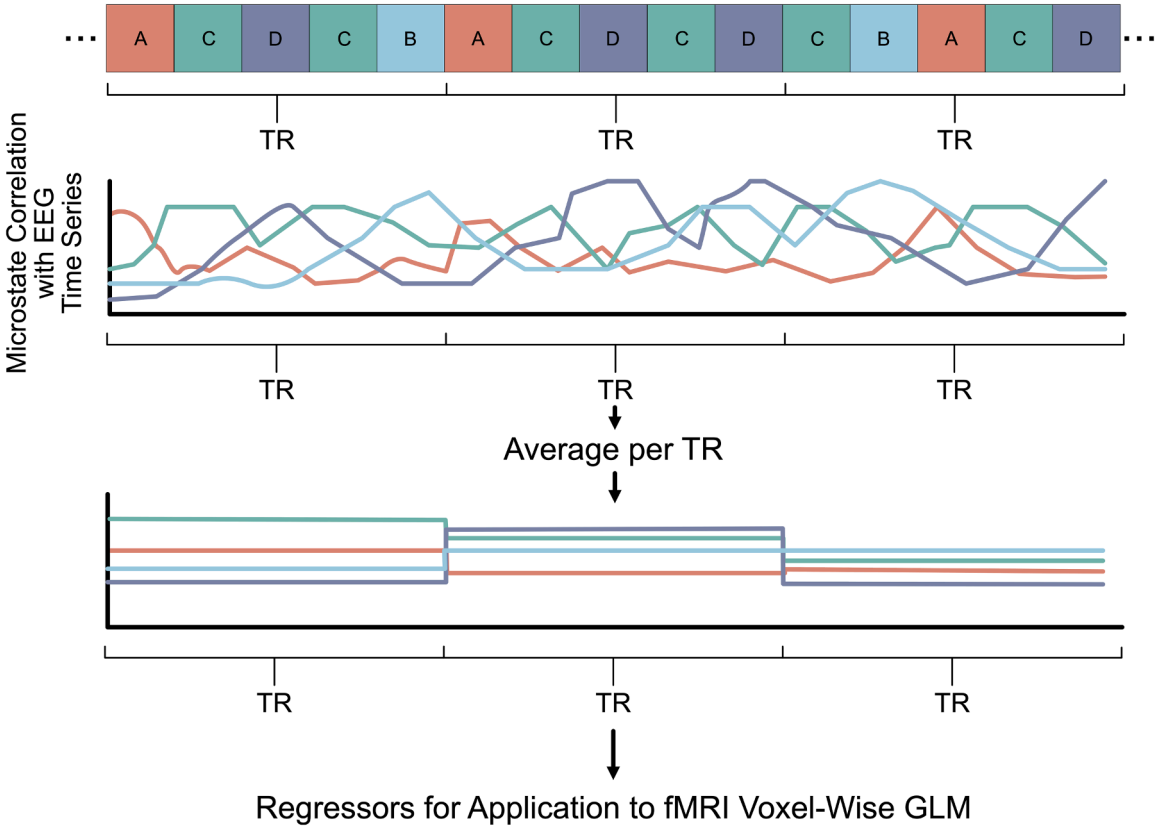

Fig. 7. Illustration of the standard process of generating regressors for application to fMRI BOLD signal from EEG microstate sequences. First, the microstate sequence is derived on the EEG time-series (top panel). The microstate topographies are then correlated with each EEG time-point (middle panel), which are then down-sampled to the (fMRI data acquisition repetition time or TR) of the simultaneously recorded fMRI data (bottom panel). This down-sampled signal is used in the voxel-wise General Linear Model (GLM) analysis. Note that the duration of microstates as illustrated is not true to that of observed data.

Response Function (HRF) before being applied as a regressor to a voxel-wise GLM, meaning that each TR is effectively given an "average dominance" value for each microstate (Fig. 7, bottom).

The main issue with this approach is down-sampling. Reducing each microstate time series to the relatively low sample frequency of fMRI removes any syntactic information that is contained within the microstate sequence, instead providing a summary of EEG signal for each fMRI volume. Comparison of fMRI BOLD signal and an EEG signal which retains the EEG sampling frequency will likely assist in understanding the functional significance of EEG microstate syntax.

To this end, use of a continuous EEG signal may be beneficial. In Section 6 we discussed conceptualising microstates in a continuous space, highlighting that the data microstates are generated from is a continuous EEG signal that could be utilised to understand microstate function. Methods which use the microstate time series (or any other continuous EEG signal) without summarising the EEG signal per TR are yet to be developed, but development in this area would yield meaningful insight into the functional significance of EEG microstate syntax.

8. Concluding remarks

Microstate analysis offers a structured framework for segmenting brain activity. Investigating EEG microstate syntax could potentially advance our understanding of the neural dynamics underlying EEG signal and its associated cognitive processes. However, there is a risk that pre-emptively imposing discrete sequences upon the EEG signal may obscure vital information embedded in the ongoing neural signal. We, thus, affirm here that microstate syntax analysis must be grounded in a deeper understanding of its relationship with a continuous EEG signal. Future research should prioritise methodologies that retain and integrate continuous EEG dynamics, ensuring that microstate syntax analysis enhances, rather than restricts, our understanding of brain function.

Developing analysis frameworks that balance methodological rigour with practical feasibility is a key challenge. Within-n approaches have been shown to identify useful biomarkers in multiple contexts, but their application must be carefully considered to avoid oversimplification. Between-n methodologies in particular hold promise for uncovering broader patterns in microstate syntax that may not conform to individual n-gram lengths. Additionally, further development is needed in integrative methods that associate simultaneously recorded EEG-fMRI data, as current methods remove the temporal complexity of the EEG signal.

The field should shift towards a more dynamic perspective that embraces the interplay between continuous EEG signals and microstate syntax. The development of methodological approaches that address the issues outlined in this review may deepen our understanding of how microstates emerge from underlying neural processes, ultimately enhancing their utility as biomarkers and windows into brain function.

CRediT authorship contribution statement

David Haydock: Writing – original draft, Methodology, Conceptualization. **Shabnam Kadir:** Writing – review & editing, Supervision. **Robert Leech:** Writing – review & editing, Supervision. **Chrystopher L. Nehaniv:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Elena Antonova:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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