Journal of Neuroscience Methods 253 (2015) 55–69

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Computational Neuroscience

Physiologically based arousal state estimation and dynamics

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HIGHLIGHTS

- Neural field theory is used to represent brain states in terms of physiology.
- Individual subject state trajectories are determined by fitting predictions to EEG.
- Traditional sleep stages are mapped to physiological model parameter ranges.
- Continuous trajectories replace unphysiological discrete transitions between stages.

ARTICLE INFO

Article history:
Received 25 February 2015
Received in revised form 13 May 2015
Accepted 3 June 2015
Available online 11 June 2015

Keywords:
EEG
Neurophysiology
Modeling
Sleep
Neural field theory

ABSTRACT

A neural field model of the brain is used to represent brain states using physiologically based parameters rather than arbitrary, discrete sleep stages. Each brain state is represented as a point in a physiologically parametrized space. Over time, changes in brain state cause these points to trace continuous trajectories, unlike the artificial discrete jumps in sleep stage that occur with traditional sleep staging. The discrete Rechtschaffen and Kales sleep stages are associated with regions in the physiological parameter space based on their electroencephalographic features, which enables interpretation of traditional sleep stages in terms of physiological trajectories. Wake states are found to be associated with strong positive corticothalamic feedback compared to sleep. The existence of physiologically valid trajectories between brain states in the model is demonstrated. Actual trajectories for an individual can be determined by fitting the model using EEG alone, and enable analysis of the physiological differences between subjects.

1. Introduction

The brain consists of a vast network of interacting elements, but exhibits large scale coordinated activity that is readily measurable. Understanding the relationship between properties of the individual components and the large scale properties of the system is crucial for understanding the operation of the brain. One readily accessible large scale measure is arousal level, which changes over the course of the sleep–wake cycle.

The arousal level of a subject is typically classified according to the Rechtschaffen and Kales (R&K) (Rechtschaffen and Kales, 1968) classification scheme, or the American Academy of Sleep Medicine (AASM) scheme (Iber et al., 2007). These schemes force the arousal level to be matched to one of a small selection of stages: wake (W); stage 1 sleep (called S1 in R&K, N1 in AASM), which corresponds to light sleep and is usually short in duration; stage 2 sleep (called S2 in R&K, N2 in AASM), which is a deeper stage of sleep marked by K-complexes (typically a large negative peak in the EEG, followed by a positive peak, similar to an evoked response) and sleep spindles (short bursts of activity at around 12–14 Hz); slow wave sleep (called S3 and S4 in R&K, N3 in AASM), which corresponds to deep sleep in which K-complexes and sleep spindles are sometimes present; and rapid eye movement (REM) sleep, which occurs during dreaming. In a typical night, sleep cycles between all the sleep stages several times.

Although the sleep stage can a provide a useful qualitative summary, it falls short in analyzing brain states, dynamics, and physiology for multiple reasons:

(i) Real brain states vary continuously (notwithstanding the transition between sleep and wake, which is rapid but continuous),

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http://dx.doi.org/10.1016/j.jneumeth.2015.06.002
0165-0270/

and therefore cannot be accurately captured by discrete stages. Discrete stages necessarily group many different brain substates into each single sleep stage, with somewhat arbitrary boundaries.

(ii) The traditional sleep stages are motivated by the external appearance of the subject, which are then matched to a number of different markers for these stages including EEG. Because stages were not designed around the physiology that underlies brain states and associated EEG, there is no unique correspondence of EEG and other features with specific sleep stages.

(iii) Sleep stages are usually assigned to 30 s epochs based on the presence or absence of EEG features in that epoch; e.g., S1 epochs cannot contain sleep spindles or K-complexes, and S3 and S4 are distinguished by amount of time slow wave activity is present (Rechtschaffen and Kales, 1968). Therefore, the sleep stage that is assigned to the epoch can be quite sensitive to the precise timing of the epoch boundaries. Shifting the epochs forward or backward by only a few seconds can change the sleep stage assigned to otherwise identical data, by including or excluding features in the epoch, or by causing the percentage of slow wave activity in the epoch to be split between two epochs, or vice versa. This issue is particularly significant for short-lived stages like S1 that can last for less than a minute, and may therefore be significantly affected by the epoch timings.

(iv) Interobserver agreement with AASM staging is only 83% (Rosenberg and Van Hout, 2013), and even lower levels of agreement have been reported for R&K staging; e.g., interobserver agreement of just 73% was reported by Norman et al. (2000). These low levels of agreement arise because the classical sleep stages are defined via many criteria that are based partly on subjective classification.

(v) Classical sleep scoring forces a discretization of a continuum of brain states into a phenomenological classification scheme that provides a qualitative measure of the responsiveness of the subject but contributes little toward understanding the physiological differences between the states, and hinders the estimation and tracking of the continuous dynamics of arousal.

The above issues are illustrated schematically in Fig. 1. Note that throughout this study we use the term 'state' to refer to the physiological state of the brain at an instant in time, and the term 'stage' to refer to R&K or AASM classifications. We relate each state to a single set of underlying physiological parameters in our model. Discrete 'transitions' occur when the classified sleep stage changes, whereas brain states evolve continuously and are linked by 'trajectories'.

In Fig. 1(a), brain states are represented in terms of their underlying physiology, and continuous trajectories link one brain state to the next. Differences between individual subjects are reflected in the different trajectories taken. In Fig. 1(b), arousal stages have been identified by some criteria that correspond to the definitions of these stages provided in a scoring scheme, which are not expressed in terms of neural physiology. There is significant overlap between the assigned stages because each individual has different physiology, and a single combination of measurable or physiological parameters may correspond to more than one arousal stage. The ambiguity of the stages also requires scorers to make qualitative, subjective judgements that further contribute to the overlap in assignment of stages.

In Fig. 1(c), the arousal stages have been decoupled from the underlying physiology, and although overlap between the assigned stages is permitted, it can only be quantified by interobserver disagreement. Finally, Fig. 1(d) shows the current common usage of sleep staging, where each epoch of EEG is classified as belonging to one of the sleep stages, and the possibility of overlap between multiple stages is not considered because the classification schemes require that a single sleep stage be selected. Thus the end result is

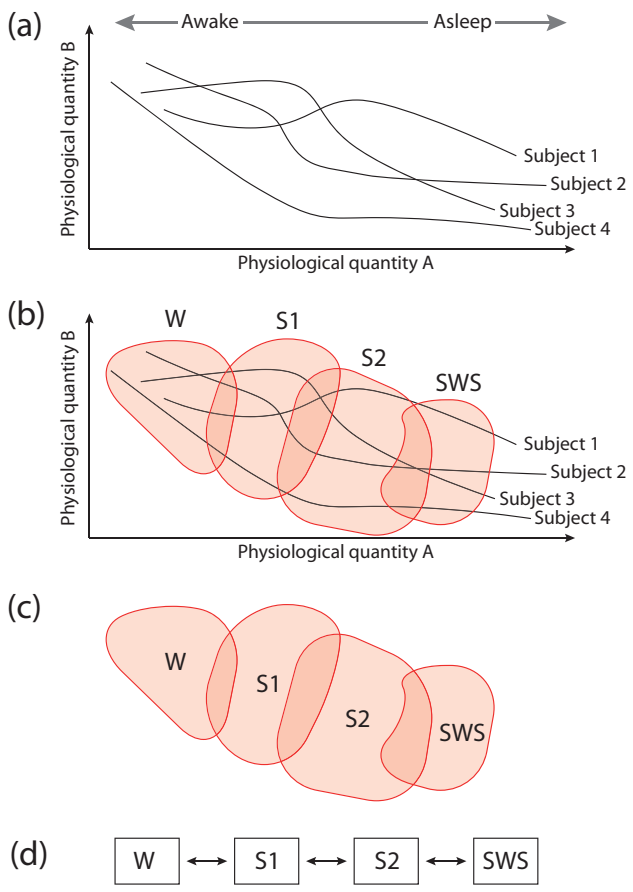

Fig. 1. (Color online) Schematic illustration comparing physiological brain states to classical sleep stages. (a) Brain states are differentiated by their physiology. Two quantities are shown here for clarity. Over time, brain states follow continuous trajectories. Both the states and the shape of the trajectories are individualized. (b) Classical sleep stages are superimposed on the trajectories, showing their association with the underlying physiology. The overlap between stages can be quantified in terms of physiology. (c) Removing the physiological axes and trajectories shows only the sleep stages, without reference to the underlying physiology, but still acknowledging the overlap between stage assignments. (d) Common use of classical sleep stages, with discrete classifications where no overlap is permitted. The arrows between the stages correspond to discrete jumps, that are the discrete analogs of the trajectories in (a).

that the true continuous trajectories in Fig. 1(a) have been replaced by discrete jumps between artificially defined stages, thereby losing information about the physical processes underlying the change in brain state and resulting in inconsistency in assignment of stages.

The aim of this study is to find a continuous representation of brain states that reflects underlying physiology and can be observed simply and easily. We use EEG in this study as it is a readily accessible, noninvasive measure, although this does not preclude including other aspects of polysomnograms such as actigraphy, eye movement, or muscle tone, that might later expand the range of physiology that can be inferred.

Neural field modeling is a powerful technique for constructing relatively simple, physiologically based models of the brain that can predict large-scale measures of brain activity (Deco et al., 2008; Pinotsis et al., 2012). We have developed a neural field corticothalamic model (Robinson et al., 2001, 2002, 2004, 2005; Rowe et al., 2004) that we have previously used to investigate the alpha rhythm (O'Connor and Robinson, 2004; Robinson et al., 2003b), age-related changes to the physiology of the brain (van Albada et al., 2010), evoked response potentials (Rennie et al., 2002), and many other phenomena. Among other measurable signals, the model accurately predicts EEG activity from physiologically based parameters