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Cognitive manipulation of brain electric microstates

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ABSTRACT

EEG studies of wakeful rest have shown that there are brief periods in which global electrical brain activity on the scalp remains semi-stable (so-called microstates). Topographical analyses of this activity have revealed that much of the variance is explained by four distinct microstates that occur in a repetitive sequence. A recent fMRI study showed that these four microstates correlated with four known functional systems, each of which is activated by specific cognitive functions and sensory inputs. The present study used high density EEG to examine the degree to which spatial and temporal properties of microstates may be altered by manipulating cognitive task (a serial subtraction task vs. wakeful rest) and the availability of visual information (eyes open vs. eyes closed conditions). The hypothesis was that parameters of microstate D would be altered during the serial subtraction task because it is correlated with regions that are part of the dorsal attention functional system. It was also expected that the sequence of microstates would preferentially transition from all other microstates to microstate D during the task as compared to rest. Finally, it was hypothesized that the eyes open condition would significantly increase one or more microstate parameters associated with microstate B, which is associated with the visual system. Topographical analyses indicated that the duration, coverage, and occurrence of microstate D were significantly higher during the cognitive task compared to wakeful rest; in addition, microstate C, which is associated with regions that are part of the default mode and cognitive control systems, was very sensitive to the task manipulation, showing significantly decreased duration, coverage, and occurrence during the task condition compared to rest. Moreover, microstate B was altered by manipulations of visual input, with increased occurrence and coverage in the eyes open condition. In addition, during the eyes open condition microstates A and D had significantly shorter durations, while C had increased occurrence. Microstate D had decreased coverage in the eyes open condition. Finally, at least 15 microstates (identified via k-means clustering) were required to explain a similar amount of variance of EEG activity as previously published values. These results support important aspects of our hypotheses and demonstrate that cognitive manipulation of microstates is possible, but the relationships between microstates and their corresponding functional systems are complex. Moreover, there may be more than four primary microstates.

1. Introduction

Conceptualizations of the brain as a complex network have initiated innovative investigations of brain organization and function (Bullmore and Sporns, 2009; Sporns, 2011). This paradigm shift towards a network-based understanding of the brain has compelled some investigators to revisit a well-established electroencephalography (EEG) technique developed to characterize the phenomenon of brain electric microstates (Lehmann and Skrandies, 1980). Microstates, observed during the recording of EEG, are defined as brief periods of time during which global electrical brain activity remains semi-stable. These transient periods of stability last between 80 and 120 ms (Lehmann and Skrandies, 1980; Lehmann et al., 1998). Each microstate is classified on the basis of its corresponding EEG scalp potential map (Pascual-Marqui et al., 1995; Wackermann et al., 1993). Previous studies revealed that just four microstates explain nearly 80% of the variance of EEG brain activity during wakeful rest, a state in which subjects are awake and alert, but not engaged in a specific task. These

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four microstates (labeled A, B, C, and D by Lehmann and colleagues) occur in a repetitive sequence within subjects and there is a typical procession of this sequence across healthy controls, regardless of gender—though there are developmental differences (Koenig et al., 2002; Lehmann and Skrandies, 1980; Lehmann et al., 2005; Van de Ville et al., 2010; Wackermann et al., 1993). Furthermore, the spatial and temporal properties of microstates differ across psychiatric and neurological disorders, including schizophrenia (Andreou et al., 2014; Kindler et al., 2011; Koenig et al., 1999; Lehmann et al., 2005; Strelets et al., 2003), panic disorder (Kikuchi et al., 2011), and Alzheimer's Disease (Strik et al., 1997). In the case of schizophrenia, several microstate abnormalities have been observed in the prodromal phase (Andreou et al., 2014) as well as in both medication-naïve (Lehmann et al., 2005) and chronic (Strelets et al., 2003) patient populations compared to healthy controls, including irregularities in duration and occurrence (Kindler et al., 2011; Strelets et al., 2003), disturbance of sequence (Lehmann et al., 2005), and abnormal topography (Koenig et al., 1999).

The foregoing findings have generated much excitement about the possibility of using microstates to further our understanding of the neurobiological bases of these various psychiatric diseases. Moreover, these results have led to speculation that microstates are fundamental building blocks of cognition, i.e. the underlying brain activity that subserves human cognitive processes (Khanna et al., 2015; Lehmann et al., 1998). This speculation that microstates are elementary cognitive components is based on two features of microstates: (1) their timescale of occurrence coincides with the sub-second range of synchronous firing of large neural networks (Bressler and Menon, 2010; Logothetis et al., 2001; Whittingstall and Logothetis, 2009); and, (2) the covariance of microstates with diseases that are characterized by profound cognitive deficits, such as schizophrenia (Andreasen et al., 1999, 1996; Schmahmann, 2004). One problem with such an assertion, however, is that EEG microstates contain scant anatomical information due to the inherent limitation in spatial resolution of this methodology—i.e., the EEG inverse problem (Grech et al., 2008). To address this issue, Britz and colleagues simultaneously recorded EEG and functional magnetic resonance imaging (fMRI) to investigate the microstate phenomenon and its relationship with functional systems of the resting human brain. Their investigation showed that the four aforementioned microstates correlated with four well-studied functional systems observed in many resting-state fMRI studies: auditory (microstate A), visual (microstate B), partially cognitive control and partially default mode (microstate C), and dorsal attention (microstate D) (Britz et al., 2010; Power et al., 2011; Yeo et al., 2011).

Despite the evidence implicating each microstate with a specific functional brain system and the association between these systems and specific cognitive functions, to our knowledge only one study to date has attempted to alter microstate features through behavioral manipulation. Recently, Milz and colleagues showed that several microstate parameters are affected by visualization and verbalization tasks compared to both wakeful rest and to each other (Milz et al., 2016). Moreover, there is some evidence that microstates affect the perception of sensory stimuli. A recent study demonstrated that awareness of visual stimuli near the perceptual threshold is influenced by the topography of the microstate that occurs just before stimulus presentation (Britz et al., 2014). However, if microstates are true markers of cognitive and psychological function, then they should be modulated by both task demands and sensory inputs. In this study, the goal is to examine the degree to which specific microstates are influenced by cognitive task, in this case serial sevens subtraction, and by altering sensory input to the visual system (i.e., eyes-open vs. eyes-closed conditions). Another goal of the study is to examine the effect of performing a cognitive task on the sequence of microstate transitions, as alterations in microstate sequence have been observed in patients with schizophrenia (Lehmann et al., 2005).

Serial sevens subtraction was selected for the task condition for several reasons. First, there is evidence demonstrating that serial subtraction activates the dorsal attention system (Kazui et al., 2000). The dorsal attention system is thought to be involved in the voluntary control of attention (Klingberg et al., 1997; Mantini et al., 2007; Ozaki, 2011; Posner and Petersen, 1990; Posner et al., 1988). Moreover, serial sevens is used to measure attention in the Mini Mental State Exam (Moore et al., 1980; Smith, 1967), although some have argued that the task is primarily an index of arithmetic skill and not attention (Karzmark, 2000). Finally, such a task can be performed with both eyes-open and eyes-closed, which allowed for the examination of the effects of alterations in visual input.

It was predicted that (1) a task requiring the voluntary control of attention would significantly increase one or more microstate parameters (duration, occurrence, and coverage) for microstate D, which is associated with the dorsal attention system, as compared to wakeful rest; (2) the sequence of microstates would preferentially transition from all other microstates to microstate D during the task condition as compared to rest; and, (3) the eyes-open condition would significantly increase one or more microstate parameters for microstate B, which is associated with the visual system, as compared to eyes-closed rest.

2. Materials and method

2.1. Participants

Twenty-four healthy young adults were recruited to participate in the study from fliers posted around the campus of Indiana University and the city of Bloomington for payment, as well as from a subject pool of undergraduate students for course credit. All participants provided written informed consent and the study was approved by the Indiana University Institutional Review Board (protocol #0903000109). Exclusion criteria included a history of neurological or psychiatric disorders, a history of chronic substance use, learning disabilities, and head injuries resulting in a loss of consciousness. More than 24 young adults were recruited, but these excluded participants had an insufficient amount of clean data after application of stringent artifact rejection methods (detailed below). The 24 included participants ranged between the ages of 18–35 (9 male, 15 female; mean age=21.1; SD=4.5 years).

2.2. Electroencephalogram

EEG was recorded from 61 cortical Ag-AgCl electrodes (International 10–20 cap system; Falk Minow Services/EasyCap, Munich, Germany) at a sampling rate of 1,000 Hz and gain of 10,000. The specific electrodes sites are Fp1/2, Fpz, AF7/8, AF3/4, AFz, F7/8, F5/6, F3/4, F1/2, Fz, FT7/8, FC5/6, FC3/4, FC1/2, FCz, T7/8, C5/6, C3/4, C1/2, Cz, TP7/8, CP5/6, CP3/4, CP1/2, CPz, P7/8, P5/6, P3/4, P1/2, Pz, PO7/8, PO3/4, POz, O1/2, and Oz. During acquisition EEG data were high pass filtered at 0.02 Hz (12 dB/octave), low pass filtered at 300 Hz (8th order elliptic), and amplified with an EPA Sensorsium (Charlotte, NC) bioamplification system. The horizontal electrooculogram (EOG) data were recorded from electrode sites F9 and F10, and vertical EOG data were recorded from electrodes placed on the left superior and inferior orbits. All EEG electrodes were referenced to a single electrode placed on the tip of the nose. EEG data were recorded continuously using NeuroScan Acquire 4.1 software package and impedances were established below 10 kΩ for all electrode sites. Participants were seated in a comfortable chair in an acoustically attenuated and electrically shielded room.

2.3. Procedures

Participants completed a total of four tasks during the experiment: eyes-open wakeful rest (EOR), eyes-closed wakeful rest (ECR), eyes-open serial subtraction (EOSS), and eyes-closed serial subtraction