Journal of the Neurological Sciences 369 (2016) 165–175

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Changes in effective connectivity of sensorimotor rhythms in thalamocortical circuits during the induction and recovery of anesthesia in mice

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ARTICLE INFO

Article history:
Received 23 July 2015
Received in revised form 7 August 2016
Accepted 13 August 2016
Available online 15 August 2016

Keywords:
Thalamocortical network
Sensorimotor rhythm
Spectral Granger causality
Anesthesia
Loss of consciousness

ABSTRACT

The thalamocortical network serves a role in both consciousness and sensorimotor processing. However, little is known regarding how changes in conscious states, via induction of and recovery from anesthesia, affect the processing of sensorimotor information in the thalamocortical network. To address this, we investigated the dynamics of causal interactions among sensorimotor rhythms (SMR; frequency range of 3–12 Hz) across the thalamocortical network during transitions into and out of ketamine-induced unconsciousness. Two local field potentials from the ventral lateral and ventrobasal thalamic nuclei, as well as two intracranial electroencephalography signals from the primary sensory and primary motor regions, were recorded in 10 mice. Spectral Granger causality analysis revealed two distinct frequency-specific patterns in sensorimotor rhythms. For the low-frequency (3–6.5 Hz) SMR, loss of consciousness evoked causal influences directed from the cortex to the thalamus. For the high-frequency (6.5–12 Hz) SMR, causal influences from the primary sensory cortex to other regions during the conscious period were abruptly altered by loss of consciousness and gradually regenerated following recovery of consciousness. The results of the present study indicate that anesthesia alters the flow of sensorimotor information in the thalamocortical network and may provide evidence of the neural basis of loss and recovery of sensorimotor function associated with anesthesia.

1. Introduction

The thalamocortical network is comprised of recurrent feedback loops between the thalamus and cerebral cortex, mainly responsible for the support of two key brain functions [1–4]: conscious awareness [5,6] and sensorimotor processing [1,7]. The recurrent feedback loops of the thalamocortical network often generate a variety of neural oscillations associated with these functions [8–11]. Specifically, changes in unidirectional or bidirectional patterns of connectivity of neural oscillations in the thalamocortical network are reflective of the integration or segregation of neural information during transitions in conscious states. Much of the evidence presented to date suggests that anesthesia-induced loss of consciousness either reduces cortical integration by decreasing feedback from frontal to parietal regions, or attenuates the capacity for cortical information processing due to loss of regional specificity [12–15]. However, descriptions of the underlying dynamics of this network associated with shifts from conscious to unconscious states have largely focused on high-frequency oscillations (~40 Hz) [13] or blood-oxygen-level dependent (BOLD) activity [16], and little is known regarding the modulation of directional connectivity associated with lower frequency oscillations by changes in conscious states. Also, sensorimotor processing often accompanies thalamocortical oscillations between 3 and 20 Hz, which are referred to as mu, alpha, theta, or sensorimotor rhythms depending on the species [2,17–19]. For instance, sensorimotor rhythms (SMRs) observed in the rodent vibrissa whisker system are related to a network comprised of the brain stem, thalamus, and barrel cortex, which coordinates the transmission of afferent and efferent information associated with specific whisking behaviors [3,20–25]. Studies have shown that sniffing and whisking in rats are under the control of interdependent SMR (4–12 Hz) generators in the thalamocortical network [26], and that there is a strong

Abbreviations: SMR, sensorimotor rhythm; MVAR, multivariate auto-regressive; DTF, direct transfer function; PDC, partial directed coherence; SGC, spectral Granger causality; S1, primary somatosensory cortex; M1, primary motor cortex; VL, ventrolateral thalamic nucleus; VB, ventrobasal thalamic nucleus; LFP, local field potential; LOC, loss of consciousness; ROC, recovery of consciousness; ADM, time of drug administration; FFT, fast Fourier transform; AIC, Akaike Information Criteria; ADF, Augmented Dickey Fuller; KPSS, Kwiatkowski–Phillips–Schmidt–Shin; iADM, interpolated time of drug administration; iLOC, interpolated loss of consciousness; iROC, interpolated recovery of consciousness; VPM, ventroposterior medial thalamus.

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http://dx.doi.org/10.1016/j.jns.2016.08.031
0022-510X/

correlation between electromyography at the vibrissa whisker and SMRs (7–14 Hz) in the primary sensory cortex [27].

Researchers have suggested that the two brain functions supported by the thalamocortical network are not mutually exclusive but rather closely tied to one other [28]. This assertion forms a hypothesis that thalamocortical network dynamics associated with SMRs would be modulated by shifts in consciousness, which to date remains undocumented. Unlike SMRs in the beta range (13–20 Hz), which are associated with high-level cognitive processes involving large-scale cortical networks, SMRs in the 3–12 Hz range are specifically associated with the processing of low-level sensory information between the thalamus and cortex [17,18,26,29]. Therefore, in the present study, we focus on variations in thalamocortical SMRs within the 3–12 Hz range due to changes in conscious states from wakefulness (conscious) into anesthesia (unconscious), and back to wakefulness. In particular, we investigate how transitions from conscious to unconscious states are associated with changes in the direction of information flows as well as the relationship between these transitions and low-frequency SMRs within the network.

A number of computational methods have been proposed to quantify the spatial and temporal characteristics of effective (bidirectional) connectivity among the areas in various brain networks. For example, the multivariate auto-regressive (MVAR) model has largely led to various potential methods for effective connectivity such as directed transfer function (DTF), partial directed coherence (PDC), and Granger causality (GC), which differ from one another according to how interactions are defined within the network (reviewed in [30]). Nonlinear effective connectivity methods such as transfer entropy have also been proposed. Unlike other methods, however, Granger causality analysis can reliably estimate bidirectional causal influences between brain areas in the spectral domain without any estimation of high-dimensional probability distribution [31]. Hence, we attempted to evaluate the hypothesis that transitions from conscious to unconscious states are associated with changes in the direction of information flow within the thalamocortical network by applying spectral Granger causality (SGC) analysis.

Here, we implement an experimental protocol that effectively measures the exact timing of the loss and recovery of consciousness. SMRs were measured in four different mouse brain regions, including the primary somatosensory cortex (S1), the primary motor cortex (M1), the ventral lateral thalamic nucleus (VL), and the ventrobasal thalamic nucleus (VB). VB drives somatosensory cortical activity [7,32,33] and VL delivers motor control information [34]. These four regions are known to be directly or indirectly interconnected with each other and to be essential for sensorimotor processing (e.g. in the whisker system) during conscious states [1,21,26]. However, it remains elusive how transitions from consciousness to unconsciousness change the connections between these four regions. Causal interactions between SMRs measured at these four sites were evaluated using SGC analysis [35–38], which has been employed to assess the characteristics of effective connectivity associated with consciousness [39–42]. Specifically, we traced temporal variations in causal interactions among SMRs during normal sensorimotor behavior as well as during the loss and recovery of consciousness. We then compared these variations with that state of consciousness as estimated by the anesthetic concentration level and order parameter models [43].

2. Materials and methods

2.1. Ethics statement

All experimental procedures were conducted in accordance with the guideline for the Institutional Animal Care and Use Committee, following Act 1992 of the Korea Lab Animal Care Regulations and associated guidelines. The protocol was approved by the Committee on the Ethics of Animal Experiments of the Korea Institute of Science and Technology (Permit Number: AP-201001047). Surgery for electrode implantation and anesthetic experiments were performed under ketamine-xylazine anesthesia, and all efforts were made to minimize suffering.

2.2. Experimental procedure

For the investigation of causal interactions in the thalamocortical network, we recorded local field potentials (LFPs) from two thalamic sites and EEG signals from two cortical sites in ten male hybrid mice (C57BL/6 × 129 F1; 8–10 weeks; body weight 19–25 g). The mice were trained in a forced walking task [44], which was designed to measure the exact timing of loss of consciousness (LOC) and, presumably, recovery of consciousness (ROC). By using the matched motor activities on the treadmill that are obtained from an accelerometer sensor, the exact transition between conscious states can be obtained. It is noteworthy that the mice were continuously moving the whiskers while walking on the treadmill. Although the mice occasionally lagged behind the rotation speed of the treadmill, they immediately sped up to keep up with the speed of the treadmill while rhythmically sweeping their whiskers.

The experiment began with 5 min of suspended conditioning that allowed animals to habituate to a treadmill (LE 8708, Panlab, Spain). Mice were then forced to walk on the treadmill, at which time the recording of electrophysiological signals began. Following the 10-min walking period, an anesthetic drug was administered (ADM). More specifically, mice were anesthetized with a ketamine-xylazine cocktail (120 and 6 mg/kg for ketamine and xylazine, respectively), which was administered through polyethylene tubing (10 cm in length, 1520/86 μm in outer/inner diameter; PE 100, Clay Adams, Sparks, MD, USA) surgically inserted into the abdominal cavity and firmly fixed in the lateral abdomen using dental cement. The other side of the tube was connected to the EEG connector. The length of the exposed tube was approximately 3 cm. The detailed experimental procedure is described in our previous study [44]. When the mice lost consciousness following injection of the anesthetic, they were automatically moved by the rotation of the treadmill into a residual holding space behind the treadmill, which had been prepared to keep an anesthetized mouse free from injury due to the motion of the treadmill while being unconscious. LOC occurred shortly after ADM (the duration from ADM to LOC varied across mice). After a certain amount of time, mice began to exhibit a gradual ROC. Again, the duration from LOC to ROC varied across mice. Electrophysiological recording ceased approximately 30 min after ROC.

A three-axis accelerometer sensor (MMA 7260Q, Freescale Semiconductor Inc., Austin, TX, USA) was attached to the headstage of each mouse to trace head motion. Peak physical activity and head posture angles were obtained from these signals, which were then used to identify the precise timing of ADM, LOC, and ROC [44]. The time of behavioral events was determined using the magnitude of physical activity and the angle of the head, which was recorded by the three-axis accelerometer. The analysis of motion was conducted in accordance with procedures detailed in our previous studies [43–45].

LFPs were measured using two electrodes (Teflon-insulated tungsten wire, 76.2/114.3 μm in bare/coated diameter, A-M System, Sequim, WA, USA) implanted in the ventral lateral (VL; anterior-posterior, −1.06; mediolateral, 1.1; dorsoventral, 3.5 mm) and ventrobasal (VB; anterior-posterior, −1.82; mediolateral, 1.5; dorsoventral, 3.7 mm) thalamic nuclei. EEG signals were simultaneously recording using two microscrew-type electrodes (Chrome-plated stainless steel, 3 mm in length and 1 mm in diameter, Asia Bolt, Seoul, Korea) implanted on the surface of the primary motor (M1; anterior-posterior, 0.74; mediolateral, 1.5 mm) and primary somatosensory (S1; anterior-posterior −1.82; mediolateral, 3.0; dorsoventral, 0 mm) cortical regions. A screw electrode for the ground and reference was fixed in the interparietal bone. All electrode positions were determined following the mouse brain atlas [46] and stereotaxically implanted under ketamine-xylazine anesthesia. During the entire experimental period, electrophysiological signals were