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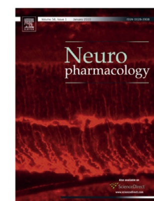

Differential effects of cholinergic and noradrenergic neuromodulation on spontaneous cortical network dynamics

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A B S T R A C T

Cholinergic and noradrenergic neuromodulation play a key role in determining overall behavioral state by shaping the underlying cortical network dynamics. The effects of these systems on synaptic and intrinsic cellular targets are quite diverse and a comprehensive understanding of how these neuromodulators regulate (spontaneous) cortical network activity has remained elusive. Here, we used multielectrode electrophysiology *in vitro* to investigate the effect of these neuromodulators on spontaneous network dynamics in acute slices of mouse visual cortex. We found that application of Carbachol (CCh) and Norepinephrine (NE) both enhanced the spontaneous network dynamics by increasing (1) the activity levels, (2) the temporal complexity of the network activity, and (3) the spatial complexity by decorrelating the network activity over a wide range of neuromodulator concentrations (1 μM, 10 μM, 50 μM, and 100 μM). Interestingly, we found that cholinergic neuromodulation was limited to the presence of CCh in the bath whereas the effects of NE, in particular for higher concentrations, induced plasticity that caused outlasting effects most prominently in the deep cortical layers. Together, these results provide a comprehensive network-level understanding of the similarities and differences of cholinergic and noradrenergic modulation of spontaneous network dynamics.

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1. Introduction

Cortical networks exhibit a broad range of different activity states that range from slow, rhythmic discharges during slow-wave sleep to fully desynchronized activity patterns during periods of behavioral arousal and focused attention (Steriade and Amzica, 1998; Steriade et al., 2001). The neuromodulators acetylcholine (ACh) and norepinephrine (NE) play a key role in controlling this activation which leads to desynchronization of cortical network dynamics (Armitage et al., 1969; Celesia and Jasper, 1966; Constantinople and Bruno, 2011; Jouvet, 1969; Kalmbach et al., 2012). However, phasic release of these neuromodulators also occurs in the awake state in response to different behavioral triggers. ACh appears to be tightly linked to attentional processing and learning whereas NE is released under circumstances of substantial changes in the environment that need overall behavioral adjustment (Baxter and Chiba, 1999; Dalley et al., 2001; Vankov et al., 1995; Yu and Dayan, 2005). Both neuromodulators target a wide range of cellular targets that affect intrinsic and synaptic excitability in a complex way (Armstrong-James and Fox, 1983; Giocomo and Hasselmo, 2005; Hasselmo et al., 1997; Sato et al., 1989; Sillito and Kemp, 1983). Furthermore, both ACh and NE have the potential to introduce long-term circuit modification due to their ability to alter the rules by which synaptic weights are altered during experimentally-induced long-term potentiation (LTP) and long-term depression (LTD) (Huerta and Lisman, 1995; Kirkwood et al., 1999; Seol et al., 2007; Thomas et al., 1996). Despite this growing understanding of context-dependent release of ACh and NE and the

Abbreviations: ACh, Acetylcholine; aCSF, artificial Cerebral Spinal Fluid; ApEn, Approximate Entropy; CCh, Carbachol; FR, Firing Rate; LTD, Long Term Depression; LTP, Long Term Potentiation; NE, Norepinephrine; PCA, Principal Component Analysis; PSD, Power Spectral Density; V1, Primary Visual Cortex.

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corresponding cellular targets, very little is known about the direct effect of these neuromodulators on cortical network dynamics. We here examined what the net effects of neuromodulation on cortical networks are in absence of experimental and potentially unphysiological stimulation paradigms. To this purpose, we studied how spontaneous, desynchronized cortical network dynamics are modulated by using multichannel electrophysiology in acute cortical slices combined with quantitative strategies from information theory (Pincus and Goldberger, 1994) and network science (Tononi and Sporns, 2003) to elucidate the effects on the spatiotemporal network dynamics.

2. Materials and methods

2.1. Ethical statement

All animal procedures were approved by the Institute of Animal Use and Care of the University of North Carolina – Chapel Hill and were in compliance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978). All efforts were made to minimize animal suffering, to reduce the number of animals used, and to utilize alternative approaches where available.

2.2. Solutions

All chemicals were purchased from Sigma (St. Louis, MO). Sucrose solution: 83.0 mM NaCl, 2.5 mM KCl, 0.5 mM $CaCl_2$, 3.3 mM $MgSO_4$, 1.0 mM NaH_2PO_4, 26.2 mM $NaHCO_3$, 22.0 mM Dextrose Anhydrose, 72.0 mM Sucrose. Artificial cerebral spinal fluid (aCSF): 119.0 mM NaCl, 2.5 mM KCl, 1.0 mM NaH_2PO_4, 26.2 mM $NaHCO_3$, 22.0 mM glucose, 1.0 mM $MgSO_4$, and 1.0 mM $CaCl_2$. Incubation solution: aCSF modified to contain 2.0 mM $MgsSO_4$ and 2.0 mM $CaCl_2$. Control aCSF: aCSF with added KCl to a final concentration of 3.5 mM KCl. Nicotine aCSF: control aCSF with 10 μM nicotine added. Pirenzipine aCSF: control aCSF with 50 μM pirenzepine added. L-Phenylephrine aCSF: control aCSF with 50 μM L-Phenylephrine. Clonidine aCSF: control aCSF with 50 μM clonidine. Isoproterenol aCSF: control aCSF with 40 μM isoproterenol added. Prazosin aCSF: control aCSF with 20 μM prazosin added. Yohimbine aCSF: control aCSF with 40 μM yohimbine. Propranolol aCSF: control aCSF with 40 μM propranolol added.

2.3. Slice preparation

Adolescent (p15-p36) C57BL/6J mice were deeply anesthetized with Euthasol and decapitated. Brains were removed and quickly placed in ice-cold sucrose solution bubbled with carbogen (95% O_2, 5% CO_2) and 200 μm coronal slices were then cut from the primary visual cortex (V1) using a VT1000S (Leica Microsystems, Wetzlar, Germany). Slices recovered in incubation solution bubbled with carbogen for at least 45 min at 34 °C before placement on the array.

2.4. Drug application and experiment design

Slices were placed on a MEA 2100 (Multichannel Systems, Reutlingen, Germany) with perforated arrays of 59 electrodes of 30 μm diameter and 200 μm × 200 μm spacing. The array was perfused from both sides with control aCSF bubbled with carbogen at 36 °C (Fig. 1A). After a 1800s control epoch the perfusion was switched to control aCSF with 1 μM, 10 μM, 50 μM, or 100 μM of carbachol (CCh) or NE which was then followed by a 1800s washout epoch with control aCSF. Providing oxygenated aCSF to both sides of the slice together with a high perfusion flow rate (>4 mL/min) in a relatively small chamber around the array enabled the occurrence of spontaneous activity without any pharmacological manipulations in control conditions. Control aCSF differed from the aCSF commonly used in slice experiments by containing only 1 mM Mg^{2+} and 1 mM Ca^{2+}. Reduced Mg^{2+} and Ca^{2+} concentrations more closely resemble the values of CSF *in vivo* (Sanchez-Vives and McCormick, 2000). We found that switching to the higher, standard

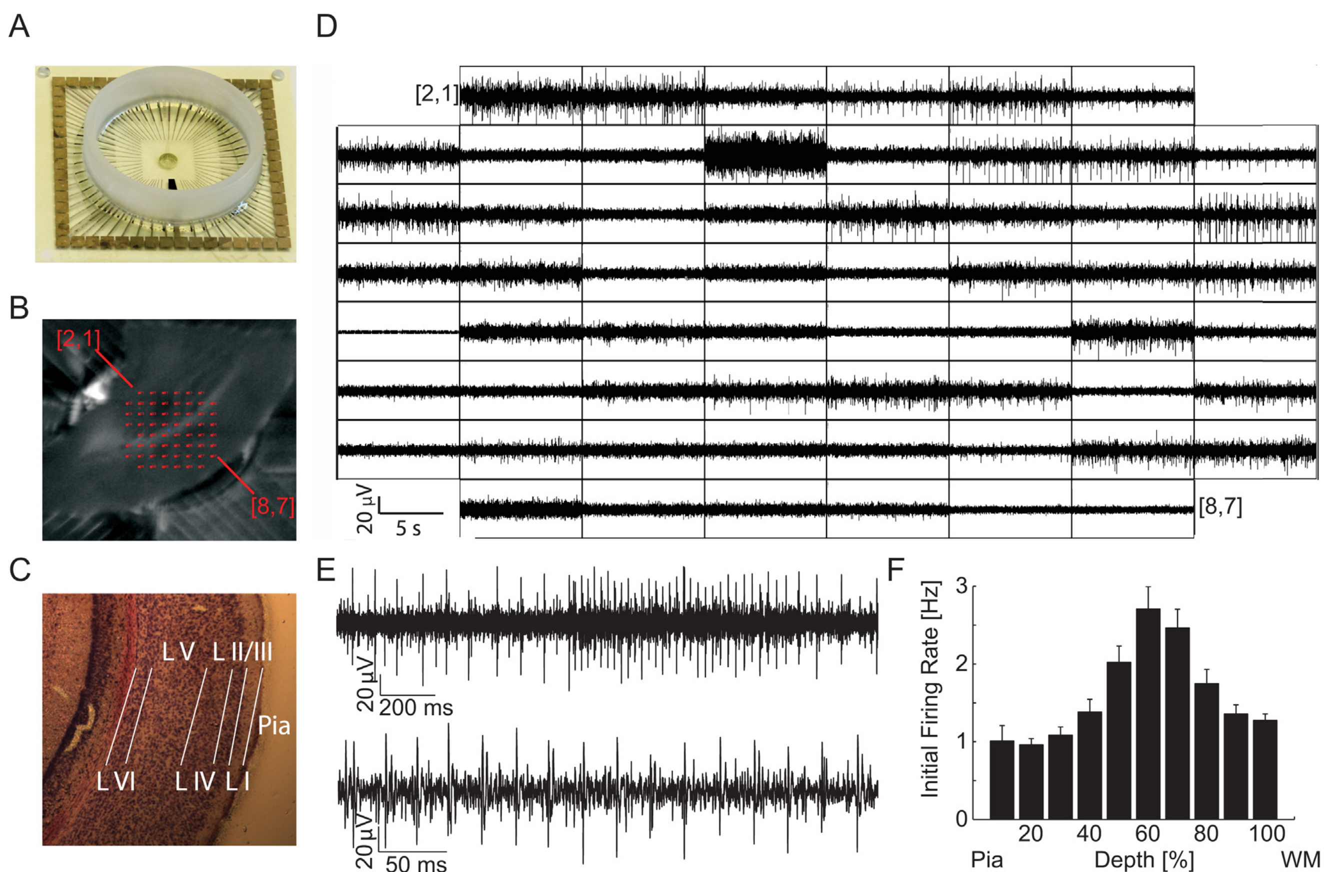

Fig. 1. Use of a multielectrode array (MEA) allows simultaneous readings of neuronal activity on 59 channels. A. 200 μm × 200 μm MEA. B. Cortical slice on the MEA with electrode locations superimposed (red); electrodes [2, 1] (top, leftmost) and [8, 7] (bottom, rightmost) indicated. C. Nissl stained slice of mouse primary visual cortex with cortical layers and pia indicated. D. A 10 s trace of all channels simultaneously recorded (top left: electrode [2, 1]; bottom right electrode [8, 7]). E. Expanded traces from a single channel of panel (D) with many action potentials visible (Top: 1 s; Bottom: 250 ms). F. Spontaneous activity (spikes per second) by cortical depth exhibited laminar profile with deeper layers more active than superficial layers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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