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As Published http://dx.doi.org/10.1073/PNAS.1506854112
Publisher Proceedings of the National Academy of Sciences
Version Final published version
Accessed Fri Feb 01 06:47:53 EST 2019
Citable Link http://hdl.handle.net/1721.1/112107
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Reply to Grace: Role of cholinergic neurons in rapid eye movement (REM) sleep control

We thank Grace (1) for the opportunity to discuss the role of cholinergic neurons in rapid eye movement (REM) sleep further. Grace suggests that optogenetic activation of a population of neurons does not necessarily demonstrate their role in the endogenous system when interrogating complex neural circuitry. We agree that we do not prove necessity of cholinergic neurons in REM sleep generation, as we point out in our discussion, “Future studies that selectively inhibit cholinergic neurons in the PPT [pedunculopontine tegmentum] and LDT [laterodorsal tegmentum] of nonhypercholinergic mice are needed to determine if cholinergic neurons are necessary for REM sleep generation” (2). However, in our report we do demonstrate the sufficiency of PPT/LDT neurons to influence REM sleep initiation but not influence REM sleep duration, thus distinguishing the role of cholinergic neurons on these properties of REM sleep. In addition, activation of cholinergic PPT neurons during non-REM sleep induced REM sleep versus wakefulness. Our data are consistent with the role of cholinergic neurons in generating an activated brain state and many studies pointing to the role of cholinergic neurons in REM sleep regulation (reviewed in ref. 3).

Neurons change their signal strength by changing their firing rate. Optogenetics uniquely allows us to control the firing rate of a specific cell type, whereas pharmacological studies do not allow direct control of the firing rate of a subpopulation of neurons. We activated the PPT/LDT neurons using physiologically relevant firing rates, thus closely reproducing the normal properties of these neurons. Drugs can have noncell-type specific effects, diffuse to other brain regions, and do not have the temporal specificity of optogenetics to be able to activate or inhibit neurons during particular sleep states. Grace (1) suggests that cholinergic input to the subceruleus serves as positive feedback to reinforce REM sleep transitions but is not actively involved in the initial REM sleep induction (4). Single neuron recording studies from both PPT and the subceruleus simultaneously will help clarify the temporal sequence of neuronal activation necessary for REM sleep to occur. Further elucidation of the endogenous function of cholinergic PPT/LDT neurons in REM sleep regulation will come from the culmination of studies using multiple approaches.

Christa J. Van Dorta,b,1 and Emery N. Browna,b,c,d,1
aDepartment of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; bDepartment of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; ciInstitute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA 02139; and dHarvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 02139


Author contributions: C.J.V. and E.N.B. wrote the paper.
The authors declare no conflict of interest.
To whom correspondence may be addressed. Email: vandortc@mit.edu or enb@neurostat.mit.edu.