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The brainstem perspective on cortical functional connectivity

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The brainstem is a crucial yet understudied structure of the human brain. Due to the technical difficulties of imaging deep brain structures, the cerebral cortex has long been the focus of in-vivo human imaging studies. Functional magnetic resonance imaging (fMRI) in particular has deepened our understanding of the cortex, including the presence of functionally specialized brain regions, intrinsic functional networks, and our understanding of higher-order cognitive processes. The brainstem's role in what is now considered primarily cortical organization and function remains an open question. Here we employ a recently acquired 7T fMRI brainstem dataset, which underwent rigorous physiological noise correction and was delineated according to 58 brainstem nuclei, to study how functional activity in the brainstem aligns with cortical function. We identify a set of brainstem hubs that are maximally connected to the cortex, including the periaqueductal grey, the dorsal raphe, and the laterodorsal tegmental nucleus. Likewise, cortical regions that are maximally connected with the brainstem appear in anterior regions. We demonstrate that these brainstem and cortical hubs reflect both slow (fMRI) and fast (MEG) dynamics, including lag-1 temporal autocorrelation, signal variability, and MEG alpha power. Next, we cluster brainstem regions with respect to how they connect to the cortex and identify modules of brainstem nuclei that subserve familiar cortical functional activation patterns related to memory, social cognition, movement and sensation, and emotion. Using PET-derived cortical profiles for 19 neurotransmitter receptors and transporters we show that neuromodulatory systems are likely mediating the relationship between brainstem and cortical functional activity. Finally, we demonstrate that unimodal and transmodal cortical regions have distinct patterns of connectivity to the brainstem. Altogether, this study extends our perspective of cortical function—including dynamics, cognitive function, and the functional hierarchy—to the brainstem, demonstrating the importance of brainstem activity to cortical function.

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