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PERSPECTIVES

Ready, set, go: the bridging of attention to action by acetylcholine in prefrontal cortex

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Each time we watch for a green light or wait for a safe opportunity to cross the street, we pay attention, often maintaining awareness of multiple cars, cyclists and pedestrians. While most of us are able to do this effortlessly every day, it is a phenomenal feat of the brain to be able to navigate through such a complex world. While you may find yourself lost in thought during your daily commute, if that light suddenly turns green, or a motorist swerves into your lane, you can be sure that your attentional system will kick into gear. In the brain, the neuromodulator acetylcholine helps convey the message: Hey! You need to pay attention to this! When a salient stimulus is detected, acetylcholine is released rapidly in the prefrontal cortex, a brain structure involved in executive function. How this signal mobilizes the circuits essential to appropriate action, however, remains an open question.

In this issue of *The Journal of Physiology*, Baker *et al.* (2018) suggest that acetylcholine may convert attention to action by preferentially activating corticopontine over commissural/callosal neurons. The authors report the rapid and powerful ability of optogenetically released endogenous acetylcholine to activate corticopontine neurons within layer 5 of prefrontal cortex. They found that even a single flash of light evokes sufficient acetylcholine release to enhance excitation of these neurons. By contrast, the other major class of layer 5 pyramidal neurons (known as commissural/callosal cells) appears less sensitive to endogenous acetylcholine. This research probes deeply into the cellular mechanisms underlying the M_1 muscarinic acetylcholine receptor activation of corticopontine neurons. The findings are complex, and include the suppression of a Kv7 'M' current together with the activation of two distinct non-selective cation conductances that are differentially modulated by Ca^{2+} ions. This work gives new insight into the circuit specificity and underlying cellular mechanisms of acetylcholine-evoked persistent activity within prefrontal cortex, extending earlier phenotypic characterizations of the electrophysiological and modulatory properties of cortical layer 5 neurons classified by projection target (reviewed in Dembrow & Johnston, 2014).

The corticopontine class of layer 5 neurons innervates a rich collection of movement-relevant targets, including the pons, The striatum and the spinal cord (Kawaguchi, 2017), and also forms recurrent excitatory interconnections within cortex. The action command exerted by endogenous acetylcholine on these neurons thus activates a powerful circuit capable of coordinating motor planning and action. As illustrated in Fig. 1, a corticopontine 'Go!' command will not occur in isolation. A growing body of work demonstrates that optogenetic release of endogenous acetylcholine quickly excites corticothalamic neurons of prefrontal layer 6 (Hedrick & Waters, 2015;

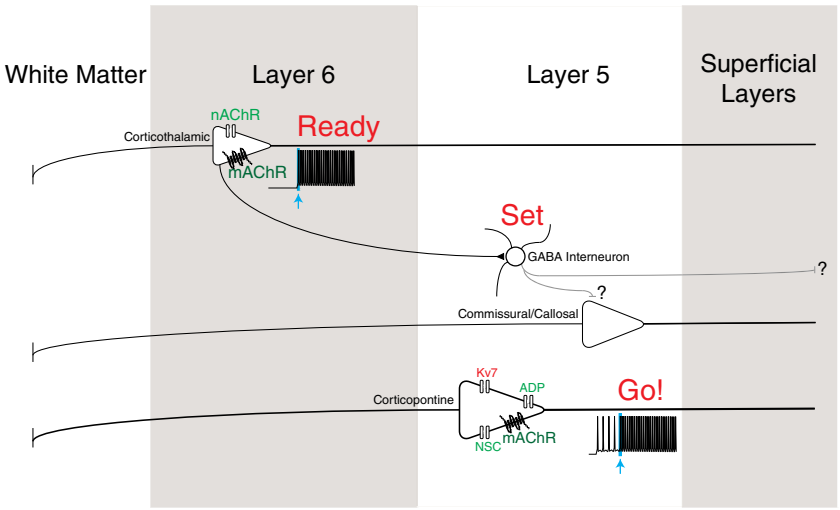

Figure 1. Schematic illustration of the modulation of prefrontal circuitry for attention and action by optogenetic release of endogenous acetylcholine
ADP, afterdepolarization; mAChR, muscarinic acetylcholine receptor; nAChR, nicotinic acetylcholine receptor; NSC, non-selective cation.

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Sparks *et al.* 2018), which are strongly implicated in attention (Proulx *et al.* 2014). The attentional state appears to be triggered via rapid activation of ionotropic nicotinic receptors and amplified and prolonged via muscarinic receptors (Proulx *et al.* 2014; Hedrick & Waters, 2015; Sparks *et al.* 2018). Layer 6 pyramidal neurons not only send massive feedback projections to the thalamus that are important for top-down attention, but also exert cortical gain control through feed-forward projections to inhibitory local circuit interneurons (Tian *et al.* 2016). Many questions remain about the interactions and timing of the cholinergic control over deep cortical neurons and the inhibitory circuitry that lies between them.

Likewise, much is still unknown about the cellular mechanisms necessary to move from active monitoring to action. Studies in awake, behaving organisms are increasingly feasible, including the mapping and interrogation of cholinergic signalling with *in vivo* multiphoton imaging or light-sheet microscopy in zebrafish – where a conserved role for acetylcholine in mediating arousal has recently been shown (Lovett-Barron *et al.* 2017) – or with fibre photometry in rodents. Such experiments permit the identification of behaviourally relevant circuits and the sequence of their activation.

Genetically encoded calcium indicators make such work possible; however, the work of Baker and colleagues underscores the importance of Ca^{2+} ions in fine-tuning postsynaptic cholinergic signalling, and highlights the potential for unwitting disruption of channel mechanisms essential for normal circuit performance. It is fitting to emphasize that investigations of cholinergic signalling will continue to benefit from elegant physiological approaches in brain slices, such as those employed here. Baker and colleagues have enhanced our understanding of the cellular mechanisms by which corticopontine neurons translate cholinergic signals into a prolonged excitable state that may be a call to action ... and that just may allow you to cross the street safely.

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Additional information

Competing interests

None of the authors has any conflicting interests.

Author contributions

All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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