This Week in The Journal

Visual Working Memory Representations in Cerebellum

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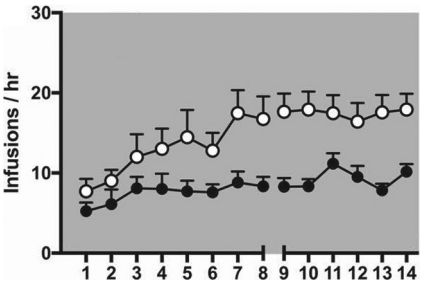
(see pages 1033–1045)

The cerebellum is active in a wide variety of sensorimotor, affective, autonomic, and cognitive tasks. Different cerebellar lobules appear to have distinct roles, paralleling the regional specialization of the cerebral cortex. Indeed, functional imaging studies have suggested that specific cerebellar lobules are interconnected selectively with cortical areas that serve the same function. For example, human cerebellar lobule VIIb/VIIIa is active during spatial working memory tasks, and subregions that are more sensitive to memory load or spatial components of the task are functionally connected to occipito-parietal cortical regions that have similar functional specificity in the task (Brissenden and Somers, 2019, Curr Opin Psychol 29:239).

How the cerebellum contributes to cognitive functions is unclear. In working memory tasks, for example, cerebellar activity might help to maintain representations of items to be remembered, or it might have a more general role in maintaining attention or planning a response. To distinguish these possibilities, Brissenden et al. used functional imaging to assess cerebellar activity during the delay period of a working memory task. Participants were shown two stimuli consisting of coherently moving dots, and after the stimuli disappeared, were instructed to remember either the left or the right. A few seconds later, participants rotated a line to indicate the direction of movement of the remembered stimulus. The authors then asked whether the remembered stimulus could be decoded from brain activity during the delay period, when no stimulus was present and no response could be planned. As expected, the movement direction of the remembered stimulus could be decoded from activity in parietal and frontal cortical areas previously tied to working memory. More importantly, the direction could be decoded from the pattern of voxel activity in cerebellar lobule VIIb/VIIIa. Moreover, for each subject, the decoding probability from lobule VIIb/VIIIa was correlated with the decoding probability from specific cortical areas across trials. No other cerebellar lobules contained representations of the remembered stimulus during the delay period.

These results suggest that cerebellar lobule VIIb/VIIIa contains representations of specific visual stimuli held in working memory, and they support the hypothesis that interactions between the cerebellum and parietal cortex are important for working memory. How the cortex and cerebellum work together to maintain stimulus representations in working memory remains to be determined.



Female mice with inactive Npas2 (open circles) self-administer more doses of cocaine during the dark period than wild-type females (filled circles). See DePoy et al. for details.

Sex-Specific Role of Circadian Clock Gene in Drug Seeking

Lauren M. DePoy, Darius D. Becker-Krail, Wei Zong, Kaitlyn Petersen, Neha M. Shah, et al.

(see pages 1046–1058)

Most forms of animal activity, from metabolism to behavior, exhibit circadian rhythmicity. These rhythms are governed by a master clock, located in the suprachiasmatic nucleus in mammals, which coordinates molecular clocks that are present in nearly all cells of the body. Molecular clocks are driven by transcription factor dimers composed of BMAL1 and either CLOCK or its homolog NPAS2. These dimers regulate transcription of thousands of genes, and disruption of this regulation has wide-ranging effects on brain function. For example, a single-nucleotide polymorphism in the human *Clock* gene has been linked to schizophrenia, bipolar disorder, and alcohol use (Barko et al., 2019, doi:10.1016/B978-0-12-812202-0.00013-0). Similarly, *Clock* mutations promote consumption of alcohol and cocaine in mice. Surprisingly, however, mutation of *Npas2*, which is highly expressed in the striatum, reduced cocaine place preference in male mice. This counterintuitive result prompted DePoy et al. to ask whether the effects of *Npas2* mutation on cocaine seeking depend on sex and time of day.

Mice were trained to press a lever to receive cocaine infusions. During the light (normally inactive) period, both male and female *Npas2*-mutant mice self-administered more cocaine doses than wild-type mice. During the dark period, however, only female *Npas2* mutants administered more cocaine than wild type. Consistent with previous work, when mice received cocaine infusions in a particular chamber of a cage, *Npas2*-mutant males showed less preference for that chamber than wild type. In contrast, mutant and wild-type females developed similar preference for the cocaine-paired chamber. Gene-expression analysis indicated that the effects of *Npas2* mutation on cocaine seeking in female mice may have stemmed partly from altered expression of potassium channels in the striatum. Finally, studies on ovariectomized mice suggested that sex differences in behavior were driven partly by circulating estrogen.

These results indicate that circadian clock proteins can have sex-dependent effects on cocaine seeking in mice. Notably, these effects emerged during the dark period, when mice are most active and striatal *Npas2* levels are at their highest. Future work should determine how estrogen, *Npas2*, and downstream genes work together to regulate striatal activity and cocaine seeking in female mice.

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