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CEREBELLAR CIRCUIT MECHANISMS WHICH ACCOMPANY COORDINATED LIMB TRAJECTORY PATTERNS IN THE RAT: USE OF A MODEL OF SPONTANEOUS CHANGES

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This project was designed to evaluate the effect of estrous hormones on function of the olivo-cerebellar circuitry in association with improved motor performance. Towards this end rats were chronically implanted with arrays of microwires to record from the dorsal accessory olive (rDAO) and its target, Purkinje cells in the paravermal cerebellum. In many cases, simultaneous recordings were carried out from as many as 48 neurons in both areas during tredmill locomotion tasks used to evaluate concomitant sensorimotor performance. The justification for these studies comes from the findings that elevations in endogenous estrous hormones across the estrous cycle are associated with marked improvements in limb trajectory. Our fundings suggest that the ability of a rat to maintain treadmill position on a variable speed treadmill paradigm is improved on the night of behavioral estrus, following elevations in both estrous hormones, estradiol and progesterone.

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Genevieve M. Haddad, Ph.D.
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Dear Dr. Haddad,

I am submitting 9 manuscripts as partial fulfillment of the final technical report for grant # F49620-93-1-0136 CEREBELLAR CIRCUIT MECHANISMS WHICH ACCOMPANY COORDINATED LIMB TRAJECTORY PATTERNS IN THE RAT: USE OF A MODEL OF SPONTANEOUS CHANGES IN LIMB COORDINATION. In addition, I presented data at two national meetings for 1996-97 (one an invited symposium): total presentations over the budget period=10. The project summary follows:

SUMMARY: This project was designed to evaluate the effect of estrous hormones on function of the olivo-cerebellar circuitry in association with improved motor performance. Towards this end rats were chronically implanted with arrays of microwires to record from the dorsal accessory olive (rDAO) and its target, Purkinje cells in the paravermal cerebellum. In many cases, simultaneous recordings were carried out from as many as 48 neurons in both areas during treadmill locomotion tasks used to evaluate concomitant sensorimotor performance. The justification for these studies comes from the findings that elevations in endogenous estrous hormones across the estrous cycle are associated with marked improvements in limb trajectory. Our findings suggest that the ability of a rat to maintain treadmill position on a variable speed treadmill paradigm is improved on the night of behavioral estrus, following elevations in both estrous hormones, estradiol and progesterone. To determine this, both spatial and temporal indices of shoulder displacement were lowest, and thus motor performance was optimal, when

assessed during the dark on the night of behavioral estrus. At this time displacement of the shoulder averaged 1.5 ± 0.2 over a 0.5 ± 0.05 sec period during random changes in treadmill acceleration/deceleration. Both parameters were significantly lower during the dark on estrus compared with the light phase of estrus ($P<0.05$), as well as other days of the cycle when hormone levels are low.

Hormone effects on the cerebellar circuitry: In the first study, simultaneous recording of both DAO and paravermal cerebellum during a variable speed treadmill paradigm revealed: 1. Over 90% of Purkinje (Pnj) cells recorded exhibited significant increases (80%) or decreases (10%) in activity correlated with the stance phase of locomotion.2. In contrast, cells from the rDAO increased activity during speed changes or when the rat failed to maintain the treadmill speed (position slip). On the night of behavioral estrus, during peak elevations of circulating levels of both estradiol and progesterone, the magnitude of both increases and decreases in stance-correlated Pnj cell activity increased by 85-115%. These results are consistent with our previous findings that 17β-estradiol and progesterone enhance excitatory and inhibitory responses of single Pnj cells to locally applied glutamate and GABA, respectively. This dual enhancement of both excitatory and inhibitory effects, apparently paradoxical at the cellular level, produced a marked heightening of the contrast of the neural population "signal" at the neuronal ensemble level. Furthermore, the stance-correlated discharge of Pnj cell during estrus preceded that during diestrus by ~120 msec. Frame-by-frame video analysis also suggested that the swing phase of the step cycle was shortened on estrus compared with diestrus.Thus, estrus was associated with changes in both the amplitude and timing of Pnj cell discharge correlated with specific behavioral events. Together, these findings suggest that the increases in the contrast of stance-correlated Pnj cell discharge observed following peak circulating levels of sex steroid hormones are associated with improved motor performance on a task requiring a corrective gait response to random changes in treadmill speed. .

Selective sensory gating of the rDAO across hormone state: rDAO discharge was correlated with speed change or position slip during the variable speed treadmill paradigm. This parameter was also significantly increased ($P<0.05$) during high estradiol periods. This increase in the "error signal" of the rDAO may be associated with an enhanced selective sensory gating response.

Responses of rDAO neurons to electrical stimulation of peripheral afferents were determined during active movement or non-movement conditions. Elevations in circulating estrous hormones produced greater excitatory responses of rDAO neurons to stimulation during non-movement, and conversely, enhanced inhibition of rDAO activity during active movement of the stimulated peripheral area compared with control diestrous conditions. These results are similar to those above in that they demonstrated an increase in the contrast of response associated with improved performance on a challenging treadmill task, and suggest that error signals are signficantly enhanced on estrus.

Synchronized, rhythmic olivary activity: A second function of the rDAO is as a timer of rapid movement. Intrinsic sub-threshold membrane oscillations of this structure occur which are dependent upon a low-threshold Ca++ spike. When assessed in vivo, rhythmic, synchronized activity of the rDAO is correlated with rapid limb movement, but not observed during rest, suggesting a tight coupling between rDAO activity and limb

movement. Because these two parameters can be uncoupled over transient episodes, it suggests that oscillatory activity of the inferior olive may be due to both an intrinsic rhythm as well as ongoing sensorimotor input. Local administration of estradiol, in combination with systemic progesterone, enhanced rhythmic olivary oscillations recorded during rhythmic limb movement. Similar facilitating effects of synchronized, rhythmic olivary discharge is observed on estrus or following systemic injection of both estrous hormones. The synchronized oscillatory discharge of neurons with the inferior olive is a putative timing mechanism which may underlie hormone-associated facilitation of rapid limb movements. The results from the present study provide evidence that both hormonal and circadian factors can enhance olivary rhythmicity in association with behavioral rhythmicity.

Comment: These results are especially significant for the Air Force, as they suggest a potential mechanism for improved performance. The hormone model suggests at the network level a strategy that may enable CNS circuits to operate optimally. Synchronized oscillations within a motor "timer" could be implemented as a performance enhancer for either human or robotics applications. Further research is needed to more clearly define the ways in which such mechanisms could be triggered.

Please find enclosed 9 manuscripts resulting from this funding.

Thank you for your support.

Yours sincerely,

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