Journal Club

Editor's Note: These short reviews of a recent paper in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to mimic the journal clubs that exist in your own departments or institutions. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Is Neuroplasticity of the Hypothalamic–Pituitary–Adrenal Axis Maternally Mediated?

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Review of Fenoglio et al. (<http://www.jneurosci.org/content/full/26/9/2434>)

Neonatal handling, a type of early life experience, has long-lasting impact on neural development in the rat leading to changes in physiological and behavioral reactivity to stress (Weaver et al., 2004). Specifically, repeated neonatal handling decreases hypothalamic–pituitary–adrenal (HPA) hormonal response to stressors at multiple levels, including release of corticotropin releasing hormone (CRH) from the hypothalamic paraventricular nucleus (PVN), adrenocorticotrophic hormone (ACTH) from the pituitary gland, and corticosterone (CORT) from the adrenal glands. These changes arise sequentially, with attenuated PVN–CRH expression observed by postnatal day 9 (P9) and decreased levels of stress-evoked ACTH and CORT observed by P23 (Avishai-Eliner et al., 2001). In a recent article in *The Journal of Neuroscience*, Fenoglio et al. (2006) expand on this previous research by (1) examining whether early changes in PVN–CRH expression depend on the recurrence of handling and (2) investigating whether maternal care mediates this neuroplasticity.

The authors compared differences in PVN–CRH expression on P9 among three groups of pups: (1) handled 15 min daily from P2 to P8, (2) handled once on P5 or P8, and (3) left undisturbed from P2 to

P8. CRH mRNA levels were significantly lower in pups handled daily than pups handled only once or left undisturbed [Fenoglio et al., their Fig. 1 (<http://www.jneurosci.org/cgi/content/full/26/9/2434/F1>)], indicating that recurrent handling is necessary for downregulation of PVN–CRH expression. The authors also examined handling-induced changes in expression of Fos protein, a marker for neural activity, in three brain regions that project to the PVN: the central amygdala (ACe), bed nucleus of the stria terminalis (BnST), and thalamic paraventricular nucleus (PVT). Pups handled daily from P2–P9 showed significant increases in Fos expression in all three brain regions 30 min after posthandling return to the dam on P9. Almost no Fos expression was observed on P9 in undisturbed pups or pups that were separated from the dam for 3 h and not returned to the home cage [Fenoglio et al., their Fig. 3 (<http://www.jneurosci.org/cgi/content/full/26/9/2434/F3>)]. In contrast to the repeatedly handled pups, pups handled only once on P9 showed significant elevations in Fos expression in the ACe and BnST but not in the PVT [Fenoglio et al., their Fig. 5 (<http://www.jneurosci.org/cgi/content/full/26/9/2434/F5>)]. These results suggest that recurrent handling is necessary to induce changes in PVT Fos expression and the PVT may transmit information regarding these experiences to the PVN that could in turn serve to reduce PVN–CRH gene transcription in response to stress.

Fenoglio et al. (2006) further demonstrate that maternal care may mediate handling-induced neuroplasticity. Dams of handled pups showed a significantly greater duration of maternal licking and grooming during the first 30 min after pups were returned to the cage than dams of undisturbed pups [Fenoglio et al., their Fig. 2 (<http://www.jneurosci.org/cgi/content/full/26/9/2434/F2>)]. Fos expression in the PVT and BnST of recurrently handled pups was near baseline levels 5 min after the pup–dam reunion and peaked 30–60 min after the reunion [Fenoglio et al., their Fig. 4 (<http://www.jneurosci.org/cgi/content/full/26/9/2434/F4>)]. Such a time course of Fos expression suggests that sensory stimulation given by the dam, rather than the handling itself, was responsible for the neural changes leading to downregulation of PVN–CRH expression. ACe Fos expression, however, peaked 5 min after return of pups to the dam, suggesting that this increase in neural activity was induced by the handling episode itself.

The results of Fenoglio et al. (2006) support the hypothesis that handling-induced HPA neuroplasticity is mediated by increases in maternal care. Other studies, however, suggest that effects of early experience on the HPA axis do not depend entirely on maternal care. For example, Macrí et al. (2004) reported that 15 min daily handling and 4 h daily maternal separation produce similar increases in active nursing (licking/grooming and

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arched-back nursing) compared with undisturbed litters. Handled rats, however, displayed lower peak elevations in ACTH and CORT in response to restraint stress during adulthood than maternally separated rats. This study therefore points toward a dissociation between maternal care and offsprings' hormonal response to stress.

Considering both the Fenoglio et al. (2006) and Macrí et al. (2004) findings, there may also be a dissociation between maternal care and offsprings' PVN-CRH expression. Fenoglio et al. (2006) found no significant elevation in Fos expression in pups separated from the dam for 3 h on P9 and not returned to the home cage. Given that Macrí et al. (2004) reported that a burst in maternal care occurs immediately after returning pups to the dam after maternal separation, it is likely that the maternally separated pups, if reunited with the dam, would have a similar elevation in Fos expression as that observed in handled pups. If recurrent handling-induced increases in maternal care lead to an elevation of Fos expression in the PVT, then recurrent separation-induced increases in maternal care may also result in increased PVT Fos expression. Therefore,

maternally separated pups, similar to handled pups, might also display decreased PVN-CRH expression as a consequence of PVT input to the PVN. Plotsky et al. (2005), however, reported that maternally separated rats display a significant increase in PVN-CRH mRNA compared with handled rats. Together, these findings suggest another possible dissociation between maternal care and HPA neuroplasticity, because handled and maternally separated pups experience similar increases in maternal care but display different directions of change in PVN-CRH expression.

The study by Fenoglio et al. (2006) provides a detailed sequence of events by which recurrent neonatal handling culminates in enduring neuroplasticity of the HPA axis. Although maternal care certainly plays a role, more studies are needed to determine whether maternal care exclusively mediates the effects of early experience or whether other developmental factors also contribute. The findings of Fenoglio et al. (2006), together with other studies of neonatal experience, demonstrate the critical influence of early life experience in shaping brain develop-

ment, which has broad implications for human development.

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