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.

Early Social Experience and Brain Development

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Review of Card et al. (http://www.jneurosci.org/cgi/content/full/25/40/9102)

Early postnatal experience can alter behavioral and/or physiological responses to stress and produce lasting changes in neural development (Meaney, 2001). In a recent issue of *The Journal of Neuroscience*, Card et al. (2005) examined the effects of rearing conditions on the assembly of autonomic emotional motor circuits in the developing rat. Integral components of this system include hypothalamic and limbic forebrain neurons that regulate visceral responses to stressful and/or emotionally arousing stimuli. In rodents, these circuits undergo a progressive increase in synaptic connectivity early in postnatal development (Rinaman et al., 2000), potentially allowing environmental influences to alter neural development.

Card et al. (2005) compared the development of autonomic motor circuits between rat pups from two rearing paradigms: control pups who remained with their dam continuously and handled/separated pups who were briefly handled daily when separated from their dam during 15 min or 3 h periods. Pseudorabies virus inoculation, which requires synapse formation for retrograde transport and subsequent infection of neural circuits, was used to assay neural development [Card et al. (2005), their Fig. 1 (http://www.jneurosci.org/cgi/content/full/25/40/9102/FIG1)]. After peripheral inoculation of the stomach wall, transynaptically infected cells were immunolabeled and quantified in regions of interest, including the paraventricular hypothalamic nucleus (PVN), the bed nucleus of the stria terminalis (BNST), the central nucleus of the amygdala (CeA) and visceral cortices (infralimbic, prelimbic, and insular cortices).

Control pups inoculated on postnatal day 8 (P8) and killed on P10 had more infected cells in the PVN, BNST, and CeA, compared with control pups inoculated on P6 and killed on P8, indicating substantial synaptic development during a brief postnatal period [Card et al. (2005), their Fig. 4 (http://www.jneurosci.org/cgi/content/full/25/40/9102/FIG4)]. Although the number of infected cells in the PVN of the handled/separated pups was comparable with age-matched controls, significantly fewer labeled neurons were found in the BNST and both medial and lateral subdivisions of the CeA of the handled/separated pups at this same developmental time point [Card et al. (2005), their Fig. 8 (http://www.jneurosci.org/cgi/content/full/25/40/9102/FIG8)]. Interestingly, the reduction of infected cells in the BNST and CeA was similar for the pups regardless of the separation duration (i.e., 15 min or 3 h daily). Analysis of infected cells in visceral cortices revealed a similar, although less consistent pattern of reduced transneuronal infection in the handled/separated pups. These findings suggest that early social experiences, particularly removal from the mother and/or human handling, can alter the formation of neural circuits that provide control over autonomic emotional motor responses.

Although the study by Card et al. (2005) provides quantitative evidence of altered neural circuit development following handling/separation, it does leave several important questions unanswered. First and foremost, are the changes in neural circuitry permanent? The handled/separated pups were inoculated on P8 and killed on P10. Given that circuitry formation was only assessed at one developmental time point, it is possible that the changes in neural circuitry may represent a delay in maturation of the circuits, rather than permanent alteration. The authors also point out that the neuroanatomical basis of the decreased number of labeled cells in the handled/separated pups is not known (i.e., fewer limbic and cortical neurons in synaptic contact with autonomic neurons vs reduced synapses and/or activity formed by each descending neuron). Future research is also needed to determine whether the changes in neural circuitry are causally linked to the maternal separation, human handling, or both factors. Indeed, separation from the mother results in the loss of a complex system (i.e., nutrient, sensorimotor, and thermal influences), which has discrete regulatory effects on behavior, physiology, and presumably neural development (Hofer, 1994). It would be of great interest to determine whether the neural effects of handling/separation reported by Card et al. (2005) could be reversed, possibly through increased maternal contact at later developmental time points. Finally, given that these circuits

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contribute to autonomic responses to emotional stimuli, what are the behavioral consequences of the altered circuitry? In rodents, daily handling during brief periods of separation has been associated with decreased anxiety and stress reactivity later in development, in contrast to longer periods of separation that lead to increased anxiety and stress (Meaney, 2001). Given that the neural organization of pups handled for 15 min did not significantly differ from pups handled for 3 h, future experiments are needed to simultaneously evaluate both the behavioral phenotype and neuroanatomical assembly to determine the functional significance of the altered circuitry.

The study by Card et al. (2005) provides a detailed description of the progressive age-dependent assembly of central autonomic circuits early in the postnatal period, indicating that these circuits may be modified by early experience. More importantly, this study indicates that as little as 15 min of separation and handling a day is sufficient to alter neuronal circuitry development. This finding has broad implications for the field of neuroscience research. It is well accepted that differences in environmental enrichment (i.e., enriched vs impoverished housing) have a profound effect on brain development (Benefiel et al., 2005). However, the early social rearing environment (i.e., the presence or absence of the mother and/or other conspecifics) also plays a critical role in neural organization (Winslow, 2005). The results presented by Card et al. (2005) illustrate the profound effects that small changes in social rearing conditions may have on the developing neural system. Much of our knowledge of basic neuroscience is based on research from animals that are separated from their mothers and/or handled daily. Thus, we must consider the possibility that the neural circuit development may have been delayed or permanently altered by current laboratory research practices. The findings by Card et al. (2005) provide compelling evidence that social rearing conditions, in particular maternal separation and human handling, should be taken into consideration for studies that evaluate behavior, endocrine, or neural functions of an organism.

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