Developmental plasticity of multisensory circuitry: how early experience dictates cross-modal interactions

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Sarko DK, Ghose D. Developmental plasticity of multisensory circuitry: how early experience dictates cross-modal interactions. J Neurophysiol 108: 2863–2866, 2012. First published July 11, 2012; doi:10.1152/jn.00383.2012.—Normal sensory experience is necessary for the development of multisensory processing, such that disruption through environmental manipulations eliminates or alters multisensory integration. In this Neuro Forum, we examine the recent paper by Xu et al. (J Neurosci 32: 2287–2298, 2012) which proposes that the statistics of cross-modal stimuli encountered early in life might be a driving factor for the development of normal multisensory integrative abilities in superior colliculus neurons. We present additional interpretations of their analyses as well as future directions and translational implications of this study for understanding the neural substrates and plasticity inherent to multisensory processing.

historically, it has been assumed that sensory systems operate through independent mechanisms, and that each sensory system contributes to behavior and perception independently as well. However, in the past three decades, there has been an upsurge in studies providing ample evidence that, in fact, the senses interact extensively to facilitate behavior and perception (Meredith and Stein 1983). The brain region that served as the foundation for these initial multisensory studies is the midbrain structure, the superior colliculus (SC), of the cat. Individual neurons of the SC receive converging inputs from multiple sensory modalities (Huerta and Harting 1984) and integrate those inputs such that dramatic changes in response often result when cross-modal stimuli are presented [i.e., significant increases or decreases in firing rate compared with unimodal stimulus conditions alone (Meredith and Stein 1983)]. Additionally, these changes at the neuronal level are reflected in orientation and localization behavioral gains that are critical for survival (Stein and Meredith 1993). Ineffective multisensory integration characterizes a number of clinical conditions (including autism spectrum disorder, dyslexia, and schizophrenia) in which the structure and function of multisensory brain areas appear to be compromised and alterations in both unisensory and multisensory function are typical (Zilbovicius et al. 2006). Integration across modalities depends greatly on the statistics of paired sensory stimuli. For instance, autistic individuals demonstrate a larger temporal binding window such that auditory and visual stimuli that are separated by relatively large temporal disparities are still perceived as a single event [i.e., synchronous (Foss-Feig et al. 2010)]. Thus by elucidating how the statistics of cross-modal stimulus processing drive the development of differing integrative abilities, training paradigms for autistic individuals might be tailored to specifically address such deficits and improve perceptual and behavioral capabilities.

At the neuronal level, it has been shown that neurons are not immediately multisensory at birth, but gradually acquire their multisensory character and integrative capabilities during the first few weeks of life (Wallace and Stein 1997). Prior work has shown that normal sensory experience is necessary for the development of integrative abilities such that disruption through environmental manipulations, such as dark-rearing (Wallace et al. 2004) or raising animals with abnormal cross-modal stimulus combinations (Wallace and Stein 2007), eliminates or alters multisensory integration. Thus, sensory signals have inherently complex spatiotemporal relationships, and experience with such cues might be essential for acquiring multisensory integrative abilities. In this Neuro Forum, we examine the recent paper by Xu et al. (2012) which suggests that the statistics of cross-modal stimuli encountered early in life might be a driving factor for the development of normal multisensory integrative abilities in SC neurons. To test this hypothesis, normal-reared cats (n = 4) were compared with cats that were dark-reared until postnatal day 30 and then divided into two experimental groups with either coincident (n = 2) or random (n = 2) audiovisual stimulus exposure. Stimuli delivered to the coincident exposure group involved spatiotemporally concordant audiovisual stimulus conditions such that paired visual and auditory stimuli (LEDs and speakers producing broadband noise bursts, respectively, each of 100-ms duration), always occurred spatially and temporally together, presented at 12 evenly spaced locations (30° intervals at 10-cm elevation) within a cylindrical arena in which the cats were placed for 5 h/day, 5 days/wk. In contrast, the random exposure group was presented with auditory and visual stimuli that were spatiotemporally randomized such that the timing and spatial location for stimulus presentation in each sensory modality was independent. Following an 8-mo period of exposure to these stimuli, the animals were returned to the dark for 16 mo, after which extracellular single unit electrophysiological recordings were performed in the deep layers of the SC to assess multisensory integrative abilities. Xu et al. (2012) hypothesized that if the statistical relationship between stimuli proved to be critical to the development of normal integrative abilities, then exposure to randomized multisensory stimuli would detrimentally affect the acquisition of normal integrative capacity. It was found that, indeed, animals exposed to spatio-
temporally congruent stimuli developed the capacity for multisensory integration, whereas random exposure hindered the development of integrative capacity. Moreover, exposure to spatiotemporally coincident cross-modal stimuli resulted in relatively normal development of multisensory integrative abilities as reflected by multisensory integration index (MSI) values of neuronal responses that were comparable to those of normal-reared animals (although the incidence of multisensory enhancement, i.e., the proportion of neurons demonstrating increased firing rate under multisensory conditions, was slightly lower in the coincident exposure group compared with normal controls). One important difference in the coincident exposure animals was that the temporal profile of integration more closely reflected properties of the rearing conditions, with peak integration occurring when visual and auditory stimuli were presented simultaneously (compared with normal animals for which a temporal offset of 50–100 ms, visual stimulus preceding auditory, maximizes integrative capacity) (Meredith et al. 1987). This finding further supported the fact that the “statistics” of relationships between stimuli served as the driving force guiding development of integrative abilities in SC neurons, such that the mere presence of stimulation alone across sensory modalities was not sufficient, but rather it was the relationships between spatiotemporally concordant sensory stimuli that shaped the integrative abilities of these neurons. In addition, it was shown that the integrative capacity acquired by the SC neurons of the coincident exposure group could be generalized to cross-modal stimuli with properties (e.g., size, shape, orientation, and frequency of stimuli) that were different from those of the rearing stimulus conditions. Also, SC responses in the coincident exposure group demonstrated multisensory response enhancements for stimuli that were spatially and temporally coincident, as well as weakly responsive to unisensory stimuli (i.e., low-intensity unisensory stimulus combinations produced the largest multisensory gain), as has been shown to characterize normal-reared control animals as well (Meredith et al. 1987; Meredith and Stein 1996, 1986). In contrast, a much smaller proportion of SC neurons from the random exposure group (24% compared with 64% with coincident exposure and 78% with normal rearing conditions) demonstrated multisensory response enhancements.

Thus, Xu et al. (2012) demonstrate that integration of cross-modal cues is not an innate capacity of multisensory neurons, but rather it is acquired in early life and is dependent on (and adjusts according to) the statistical relationship of cross-modal stimuli in the natural environment. This finding is in accordance with, but goes a step beyond, previous studies demonstrating plasticity of integrative abilities through environmental manipulations such as dark-rearing and spatial disparity-rearing (Wallace et al. 2004; Wallace and Stein 2007). It was shown that dark-rearing resulted in SC neurons that were capable of responding to, but not integrating, information from multiple sensory modalities (Wallace et al. 2004), whereas early experience with only spatially disparate (but temporally coupled) audiovisual cues shifted multisensory responses in SC neurons such that enhancements were generated by spatially disparate rather than colocalized audiovisual cues (Wallace and Stein 2007). Through combining manipulations of early sensory experience (dark-rearing and coincident vs. random spatiotemporal exposure) and examining the generalizability of multisensory enhancements to stimuli beyond the rearing conditions, Xu et al. have provided further evidence that the statistical relationship of cross-modal stimuli plays a pivotal role in the development of multisensory integration, dictating how the senses interact in SC neurons. Moreover, it is particularly encouraging that even after termination of exposure to experimental stimulus conditions (and a return to dark-rearing) for a period of 16 mo, integrative abilities were retained, as this suggests that even with sensory deficits early in life, timely intervention has the potential to restore some degree of normal multisensory function in adulthood. As the authors point out, existing literature indicates that early correction of sensory deficits in human patients is unable to restore normal perception. However, the present study suggests that timely exposure to appropriate cross-modal stimuli might aid in restoration of integrative abilities of multisensory neurons that may in turn yield behavioral and perceptual benefits (although these remain to be empirically tested).

These findings raise a number of interesting issues that may serve as important research questions for future studies. For instance, given that Xu et al. (2012) focused on multisensory enhancements as a measure of integrative ability, how would the proportion of responses that demonstrate a different type of integrative process, response depression, have changed according to manipulation of stimulus statistics? Given that random exposure to audiovisual stimuli precludes establishing relationships between stimuli that should or should not be bound together, and that response depressions generally occur for stimuli encoded as separate events [e.g., auditory and visual stimuli presented from distinct spatial locations and therefore likely belonging to independent sources (Meredith and Stein 1996)], it is possible that the incidence of response depressions would also decrease in the random exposure group due to increased inexperience with statistically meaningful relationships between audiovisual events. Recent studies have also shown that the receptive fields of multisensory SC neurons are heterogeneous (Krueger et al. 2009) and that neuronal responsiveness and integrative abilities of the same neuron change with the spatial location being tested within the receptive field. Thus, it would be interesting to present stimuli at different, but controlled, receptive field locations (such as within or outside of “hotspots”; see Fig. 1) to examine how integrative properties of SC neurons might change following exposure to discordant vs. coincident audiovisual stimulation. Furthermore, it would be interesting to test how the present findings extend to other aspects of the neuronal response beyond firing rate measures, such as response variability. It seems likely that with exposure to unreliable stimuli (e.g., see Burge et al. 2010), the random exposure group might demonstrate greater levels of response variability along with decreased integrative capacity, given that rearing conditions involved unpredictable stimulus combinations that would make reliable encoding difficult at the neuronal level. Also, how much exposure to sensory cues is necessary and sufficient for development of normal integrative abilities, and would the present findings extend to alert animals using more complex, behaviorally relevant stimuli? Performing extracellular recordings from multisensory neurons at different time points during development throughout the period of exposure to experimental stimuli (rather than only after the exposure period) might help to pinpoint the emergence of integrative abilities. Longitudinal recordings would help to decipher whether sustained exposure throughout development
until adulthood is necessary to retain integrative abilities (i.e., establishing a multisensory critical period), or whether shorter exposure times would suffice in generating normal integrative abilities. Such a timeline would help to standardize training paradigms for human patients whose early sensory deficits can be corrected over time and would provide them a template for establishing behavioral training using cross-modal stimuli that would facilitate regaining normal perceptual and behavioral function.

In summary, by disrupting the spatiotemporal relationship between audiovisual stimuli, Xu et al. (2012) effectively disrupted the development of normal multisensory processing. These impairments were not present if statistical relationships between multisensory stimuli were preserved through spatial and temporal coincidence, even in animals that were otherwise sensory deprived (i.e., dark-reared). Thus, the study by Xu et al. represents an important step towards addressing a series of questions critical to sensory processing, including what sensory experience is necessary to produce normal multisensory integration, how changes in early experience alter effective multisensory processing, and how lasting such changes might be (i.e., the degree of plasticity inherent to cross-modal processing).

**DISCLOSURES**

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AUTHOR CONTRIBUTIONS

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