

Commentary on Mather et al.: Contemplating the GANE model using an extreme case paradigm

Ronny Geva, PhD
Department of Psychology
The Gonda Brain Research Center
Bar Ilan University
Ronny.Geva@biu.ac.il;
Tel: +972-3-5318172

Abstract: Early experiences play a crucial role in programming brain function, affecting selective attention, learning and memory. Infancy literature suggests an extension of the GANE model to conditions with minimal priority-map inputs, yet suggests qualifications by noting that its efficacy is increased when tonic levels of arousal are maintained in an optimal range, in manners that are age and exposure dependent.

Mather and colleagues' intriguing GANE model underscores an important process, through which GANe changes influence the selection process, to favor high over low priority representations.

The extended literature covered in the paper concentrates mostly on experimental research with typically developing young adults, whose performance relies on an established neural network, set with implicit "know-how's" and an explicit knowledge base, which shape and set local hot spots, to be activated proactively in the prospect of newly arriving inputs (Bouret & Richmond, 2015).

One way to test this model may be with an extreme case paradigm in which top-down priorities are negligible, and the roles of global brain activation are augmented, as is the case of the newborn.

Research of infancy, early development of attention and arousal in typical and clinical samples opens the discussion of the generalizability of the GANE model, since young infants perceive stimuli with no pre-set priorities and with little previous knowledge. As such Infancy offers an interesting test-case for the GANE model.

Early-life experiences play a crucial role in programming brain function particularly with regard to selective attention, learning and memory (Geva, Eshel, Leitner, Valevski, & Harel, 2006). Newborns are busy perceiving and memorizing the environment at rates that are not surpassed thereafter, equipped with an impressionable template that does not allow yet for exerting deliberate priority operations. How might GANE function at infancy?

Models with neonates highlight four inter-dependent notions that may qualify the limits of the proposed model, with regard to development, exposure, global activity, and resilience to variance.

Dependence on development

Neonates and adults differ markedly in their ability to learn selectively (Kuhl, Williams, Lacerda, Stevens, & Lindblom, 1992). These differences were suggested to be related to in part to developmental differences in arousal response to sensory stimuli (Kuhl, 2007) as a function of differential LC-NE activity (Moriceau & Sullivan, 2004; Nakamura & Sakaguchi, 1990). Differences are such that compared with LC of the infant the adult LC gradually becomes less likely to respond to non-noxious stimuli (Kimura & Nakamura, 1985; Nakamura, Kimura, & Sakaguchi, 1987; Selden, Cole, Everitt, & Robbins, 1990), habituates earlier in response to repeated (or even single) stimulation (Vankov, Hervé-Minvielle, & Sara, 1995), and produces shortened LC responses in response to sensory stimulation (Nakamura & Sakaguchi, 1990). All these differences suggest a potential role for development in the proposed model (Moriceau & Sullivan, 2004).

Dependence on experience

Exposure at sensitive periods seems to play a significant role in the development of the LC-NE system (Nakamura et al., 1987; Rangel & Leon, 1995). – Also, experience early in development has been shown to affect PFC responsivity to LC-NE. For example, neonatal experience involving maternal contact reward was shown to affect the noradrenergic system of the rat prefrontal cortex (Kalpachidou et al., 2015). The experience was related to hypomethylation of the $\beta 1$ adrenergic receptor gene promoter

and consequently enhanced expression of its mRNA in the PFC, resulting in better discrimination and improved learning in the young pups (Kalpachidou et al., 2015).

In addition, selective recognition of maternal odors has been shown to be accompanied by increased release of glutamate and GABA from the dendrodendritic synapses and an increased efficacy of glutamate-evoked GABA release (Kendrick, Levy, & Keverne, 1992), and early-life stress related to maternal separation has been shown to alter glutamate and GABA transmission, and in particular, to alter GABA_A receptor expression (Sterley, Howells, & Russell, 2013). Taken together these findings point to the possible role of early-life exposure in the GANE model.

Dependence on tonic levels of activity

LC is thought to play a central role in regulating arousal states in addition to its role in attention and memory (Howells, Stein, & Russell, 2010; Rajkowski, Kubiak, & Aston-Jones, 1994). Initial leads from human infancy research point to the notion that in the case of the newborn, **arousal homeostasis possibly plays a significant role in attention and in recognition** (Geva, Gardner, & Karmel, 1999), with brainstem pathways playing a central role in gating arousal self-regulation (Geva & Feldman, 2008). Feeding-dependent arousal differences were shown to affect newborn preferences for cognitively demanding stimuli (Geva et al., 1999; Geva, Yaron, & Kuint, 2013), the interaction is such that more aroused neonates tend to orient towards less intense familiar stimuli; yet when less aroused, newborns prefer more intense stimuli (Gardner & Karmel, 1983; Gardner & Karmel, 1984) and orient towards novel stimuli as compared with familiar ones in visual recognition memory tasks (Geva et al., 1999).

Sleep-wake arousal states also seem to play a similar role. Recent work with intra-cellular recordings has shown an interaction of LC activity in monkeys as a function of fatigue, an effect attributed to the LC possibly providing the impetus to act when the predicted outcome value is low (Bouret & Richmond, 2015). Indeed arousal states were shown to affect attention in young human infants. Neonatal sleep fragmentation was shown to be associated with infant's focused attention to specific stimuli early on in development

(Geva et al., 2013). Compared with good sleepers, infants who were poor sleepers as neonates had difficulties focusing on target stimuli in the presence of complex distracters, but managed focusing in the presence of simpler distracters. Integration of the findings on arousal state effects on attention and memory emphasizes the need to consider tonic arousal changes in the GANE model.

Finally, the validity of the model may gain from testing of its limits in neuropsychiatric disorders, such as attention-deficit-hyperactivity-disorder (Sterley et al., 2013), which involve poor adaptation to change (Sara, 2009). Such an exploration may suggest the notion that GANE efficacy is increased when tonic levels of arousal are maintained in an optimal range.

Taken together these data may suggest an extension of the GANE model to infancy, however, an integration of the above findings with the framework presented suggests a qualification to the GANE model, by noting that its efficacy is increased when tonic levels of arousal are maintained in an optimal range, in manners that are age and exposure dependent.

References

- Bouret, S., & Richmond, B. J. (2015). Sensitivity of Locus Ceruleus Neurons to Reward Value for Goal-Directed Actions. *The Journal of Neuroscience*, 35(9), 4005-4014. doi: 10.1523/jneurosci.4553-14.2015
- Gardner, J. M., & Karmel, B. Z. (1983). Attention and arousal in preterm and full-term neonates. *Infants born at risk: Behavior and development*, 69-98.
- Gardner, J. M., & Karmel, B. Z. (1984). Arousal effects on visual preferences in neonates. *Developmental Psychology*, 20(3), 374-377. doi: 10.1037/0012-1649.20.3.374
- Geva, R., Eshel, R., Leitner, Y., Valevski, A. F., & Harel, S. (2006). Neuropsychological Outcome of Children With Intrauterine Growth Restriction: A 9-Year Prospective Study. *Pediatrics*, 118(1), 91-100. doi: 10.1542/peds.2005-2343
- Geva, R., & Feldman, R. (2008). A neurobiological model for the effects of early brainstem functioning on the development of behavior and emotion regulation in infants: Implications for prenatal and perinatal risk. *Journal of Child Psychology and Psychiatry*, 49(10), 1031-1041. doi: 10.1111/j.1469-7610.2008.01918.x
- Geva, R., Gardner, J. M., & Karmel, B. Z. (1999). Feeding-based arousal effects on visual recognition memory in early infancy. *Developmental Psychology*, 35(3), 640-650.

- Geva, R., Yaron, H., & Kuint, J. (2013). Neonatal Sleep predicts attention orienting and distractibility. *Journal of Attention disorders*.
- Howells, F. M., Stein, D. J., & Russell, V. A. (2010). Perceived mental effort correlates with changes in tonic arousal during attentional tasks. *Behav Brain Funct*, 6, 39. doi: 10.1186/1744-9081-6-39
- Kalpachidou, T., Raftogianni, A., Melissa, P., Kollia, A.-M., Stylianopoulou, F., & Stamatakis, A. (2015). Effects of a Neonatal Experience Involving Reward Through Maternal Contact on the Noradrenergic System of the Rat Prefrontal Cortex. *Cerebral Cortex*. doi: 10.1093/cercor/bhv192
- Kendrick, K. M., Levy, F., & Keverne, E. B. (1992). Changes in the sensory processing of olfactory signals induced by birth in sheep. *Science*, 256(5058), 833-836.
- Kimura, F., & Nakamura, S. (1985). Locus coeruleus neurons in the neonatal rat: Electrical activity and responses to sensory stimulation. *Developmental Brain Research*, 23(2), 301-305. doi: [http://dx.doi.org/10.1016/0165-3806\(85\)90055-0](http://dx.doi.org/10.1016/0165-3806(85)90055-0)
- Kuhl, P., Williams, K., Lacerda, F., Stevens, K., & Lindblom, B. (1992). Linguistic experience alters phonetic perception in infants by 6 months of age. *Science*, 255(5044), 606-608. doi: 10.1126/science.1736364
- Kuhl, P. K. (2007). Is speech learning 'gated' by the social brain? *Developmental Science*, 10(1), 110-120. doi: 10.1111/j.1467-7687.2007.00572.x
- Moriceau, S., & Sullivan, R. M. (2004). Unique Neural Circuitry for Neonatal Olfactory Learning. *The Journal of Neuroscience*, 24(5), 1182-1189. doi: 10.1523/jneurosci.4578-03.2004
- Nakamura, S., Kimura, F., & Sakaguchi, T. (1987). Postnatal development of electrical activity in the locus ceruleus. *Journal of Neurophysiology*, 58(3), 510-524.
- Nakamura, S., & Sakaguchi, T. (1990). Development and plasticity of the locus coeruleus: A review of recent physiological and pharmacological experimentation. *Progress in Neurobiology*, 34(6), 505-526. doi: [http://dx.doi.org/10.1016/0301-0082\(90\)90018-C](http://dx.doi.org/10.1016/0301-0082(90)90018-C)
- Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1994). Locus coeruleus activity in monkey: Phasic and tonic changes are associated with altered vigilance. *Brain Research Bulletin*, 35(5-6), 607-616. doi: [http://dx.doi.org/10.1016/0361-9230\(94\)90175-9](http://dx.doi.org/10.1016/0361-9230(94)90175-9)
- Rangel, S., & Leon, M. (1995). Early odor preference training increases olfactory bulb norepinephrine. *Developmental Brain Research*, 85(2), 187-191. doi: [http://dx.doi.org/10.1016/0165-3806\(94\)00211-H](http://dx.doi.org/10.1016/0165-3806(94)00211-H)
- Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nat Rev Neurosci*, 10(3), 211-223.
- Selden, N. R. W., Cole, B. J., Everitt, B. J., & Robbins, T. W. (1990). Damage to ceruleo-cortical noradrenergic projections impairs locally cued but enhances spatially cued water maze acquisition. *Behavioural Brain Research*, 39(1), 29-51. doi: [http://dx.doi.org/10.1016/0166-4328\(90\)90119-Y](http://dx.doi.org/10.1016/0166-4328(90)90119-Y)
- Sterley, T. L., Howells, F. M., & Russell, V. A. (2013). Maternal separation increases GABA(A) receptor-mediated modulation of norepinephrine release in the hippocampus of a rat model of ADHD, the spontaneously hypertensive rat. *Brain Res*, 1497, 23-31. doi: 10.1016/j.brainres.2012.12.029

Vankov, A., Hervé-Minvielle, A., & Sara, S. J. (1995). Response to Novelty and its Rapid Habituation in Locus Coeruleus Neurons of the Freely Exploring Rat. *European Journal of Neuroscience*, 7(6), 1180-1187. doi: 10.1111/j.1460-9568.1995.tb01108.x