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What BANE can offer GANE: Individual differences in function of hotspot mechanisms

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Abstract: In this commentary we focus on individual differences in proposed mechanisms underlying arousal-based enhancement of prioritized stimuli. We discuss the potential of genotyping studies for examining effects of noradrenergic processes on stimulus prioritization in humans, and stress the importance of potential individual differences in the activity of specific receptor subtypes in hotspot processes proposed by the GANE model.

We believe that the GANE model makes a novel and vital contribution to understanding emotional modulation of attention and memory — specifically via its detailed description of the influence of glutamate on noradrenergic processes mediating the impact of emotional arousal on the fate of neutral items. However, the target paper does not address potential individual differences in such mechanisms, which may be linked to mood disorders and addiction.

In our BANE model we described effects of the LC-NE system in enhancing attention and memory for stimuli that are salient because of associations with arousal (Markovic et al., 2014). However, a key focus of the BANE model was on individual differences in prioritization of affectively salient stimuli (Todd et al., 2012, Markovic et al., 2014). This

emphasis on individual differences has been based in part on observations of human carriers of a common deletion variant in the *ADRA2b* gene, which codes for noradrenergic α2b autoreceptors (Small et al., 2001). The GANE model makes a valuable contribution in extending beyond the BANE model to incorporate the role of glutamatergic activity in enhancing effects of arousal on processing stimuli that are already high priority. However, the authors are somewhat dismissive of studies examining polymorphisms in genes coding for noradrenergic receptors, and specifically of the notion that findings concerning the role of *ADRA2b* can be discussed in relation to the GANE model's hot spot mechanisms. They do so based partly on evidence that α2b receptors are unlikely to play an important role in GANE hotspots because the inhibitory role of α2b receptors is not as well established as for α2a receptors, and because α2b receptors are poorly expressed in key regions mediating affective salience. We argue that the study of genetic influences on affective prioritization of salient stimuli can provide data relevant to some of the GANE Model's claims, and that evidence against an inhibitory role of α2b receptors in key brain regions is not entirely straightforward.

First, we argue that genotyping studies have value in general for understanding mechanisms of stimulus prioritization because, along with a pharmacological manipulations [e.g., (Strange et al., 2003, De Martino et al., 2008), they are among the few vehicles for examining effects of inhibitory vs. excitatory noradrenergic processes in humans. Because the specificity of ligands for receptor subtypes is limited (Jasper et al., 1998), genotyping studies can help specify the role of each subtype in patterns of brain activation and behavior. Of course, we acknowledge that it is important to use other methods, such as PET and examination of mRNA activity, to help confirm the role of specific *ADRA2a* and *ADRA2b* polymorphisms in α2 activity.

Second, it is important to consider potential individual differences in the activity of specific receptor subtypes in proposed hotspot processes, and what the behavioral consequences might be. Genetic differences influencing such receptor function are one source of such differences, and can provide a valuable window into how GANE mechanisms can vary normally and go awry. For example, common variants in genes

coding for both *ADRA2b* and *ADRA2a* receptors have been associated with neural and behavioral indices of enhanced attention and memory for affectively salient stimuli that characterize affective disorders as well as cognitive biases associated with addictive behaviors (de Quervain et al., 2007, Todd et al., 2013, Havranek et al., in press). Using genotyping to infer the role of each receptor subtype on such endophenotypes can help elucidate how patterns of inhibitory/excitatory activity proposed by GANE may contribute to variation in healthy populations and in psychopathology.

Studies of the *ADRA2b* deletion variant can serve precisely that function. Convergent evidence is highly consistent with the view that *ADRA2b* deletion carriers have reduced inhibitory autoreceptor function. In vivo, consequences of carrying the *ADRA2b* deletion variant (found in ~50% of the populations we have studied) are similar to those of α2 antagonist yohimbine (de Quervain et al., 2007). This claim is supported by the reliability and robustness of effects of enhanced emotional biases in attention and memory, increased amygdala and ventromedial prefrontal activation for arousing stimuli, and differences in amygdala grey matter volume associated with carrying the deletion variant (de Quervain et al., 2007, Rasch et al., 2009, Todd et al., 2013, Todd et al., 2014, Ehlers et al., 2015, Todd et al., 2015). According to the GANE model, affectively salient stimuli are one category of prioritized stimulus whose encoding is enhanced by arousal. Here, the enhanced affective prioritization we have observed in deletion carriers could lead to intensified positive feedback loops at hotspots – although possibly only when stimuli are prioritized because of their pre-existing associations with arousal. Further, since outside of the lab there are likely to be a range of motivationally relevant goals, behavior of deletion carriers may be driven by affective or visual salience over more 'top-down' goals relative to non-carriers.

Finally, with regard to the authors' claims that it is α2a autoreceptors that carry the full burden of inhibitory function in the brain, we suggest that the picture is somewhat more complicated. There is evidence that, in addition to its pre-synaptic inhibitory function, α2a is the most commonly observed *post-synaptic* receptor in the PFC (U'Prichard et al., 1979, Arnsten et al., 1996). Indeed, some evidence suggests that increased post-synaptic

α2a activity in the PFC may be associated with enhanced rather than reduced noradrenergic transmission (Ramos, Stark, Verduzco, van Dyck, & Arnsten, 2006). Moreover, brain regions mediating heightened emotional sensitivity in deletion carriers show relatively high levels *of ADRA2b* expression [Allen Human Brain Atlas, 2015; (Hawrylycz et al., 2012)]. Animal research points further towards the importance of α2b receptors in emotional processing (Moriceau and Sullivan, 2004). This challenges the notion of a straightforward role for α2a receptors as the only mediators of inhibitory activity suggested by the GANE model.

In summary, while we acknowledge that effects of the deletion variant may be mediated by factors other than proposed GANE hotspot mechanisms, the growing body of research on polymorphisms influencing both a α2a and α2b receptors poses both questions and challenges for the GANE model.

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