GABAergic circuits underpin valuative processing

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Affect is the fundamental neuropsychological state combining value- and arousal-related processes underpinning emotion and mood. A major goal of the emerging field of affective science is to explain the mechanisms of valuation within the brain. A core network of brain activity is seen across mammals in response to appetitive or aversive stimuli, and appears to be largely independent of stimulus modality (Bissonette et al., 2014; Hayes et al., 2014a). However, the underlying mechanisms of valuation (i.e., appetitive- and aversive-related brain activity) are unclear, and there is particularly little information about how these two valuative networks interact. One candidate which is likely central to the activity of both networks is the neurotransmitter γ-aminobutyric acid (GABA). Here, I briefly discuss some of the evidence pointing to GABA as a central player in mediating appetitive and aversive activity throughout the brain. The broader implication is that the role of GABA in valuative processing may be at the heart of affective regulation, and thus also important for a wide variety of psychological phenomena, from emotion (Stan et al., 2014) and impulsivity (Hayes et al., 2014b) to sense of self (Wiebking et al., 2014a,b).

Keys to Understanding GABA Circuitry

An exploration of GABA in appetitive and aversive behavior began following its identification in the mammalian brain (Roberts and Frankel, 1950). Although central dopamine was discovered seven years later, many barriers to GABA-related research—including its relative ubiquity throughout the brain, the robust effects of GABAergic drugs administered systemically (e.g., which can easily lead to seizures or immobility), and little knowledge about GABAergic neurocircuitry—has led to a much greater understanding of dopamine in this context (Iversen and Iversen, 2007). Early advances in rodents were nonetheless made delineating key roles for GABA in consummatory behavior, stress, and anxiety (Kelly et al., 1977; Biggio et al., 1990). Studies such as these revealed that beyond dopamine, GABA was involved in mediating motivated behaviors in widespread, but regionally-selective ways (Kelly et al., 1977), and that dynamic cortical and subcortical changes to GABAergic microcircuits were involved (Biggio et al., 1990).

Improved mapping of the extensive brain GABAergic circuits (illustrated in Figure 1), coupled with technological advances in detection and manipulation, have partly driven the recent focus of the role of GABA, and its sister excitatory neurotransmitter glutamate, in value-related processing. Moreover, structural advances have continued steadily, from the identification of key GABAergic hubs, such as the basal ganglia and nucleus accumbens (Groenewegen and Russchen, 1984), to more

Abbreviations: Ctx, cortex; DA, dopamine; Amyg, amygdala; GABA, gamma-aminobutyric acid; GP, globus pallidus; LHb, Lateral habenula; Motor ctx, motor cortices including premotor, supplementary motor, and frontal eye fields; NAcC, nucleus accumbens septi core; NAcS, nucleus accumbens septi shell; PFC, prefrontal cortex; SN substantia nigra; Thal, thalamus; VP, ventral pallidum; VTA, ventral tegmental area.
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FIGURE 1 | Simplified schematic diagram of GABAergic circuitry underlying valuative processing. Inhibitory connections, mainly GABAergic, are indicated by black arrows; excitatory connections, which are glutamatergic unless otherwise indicated, are indicated by green arrows. Brain regions are grouped by neocortex (blue), basal ganglia (brown), thalamus (orange), midbrain/mesencephalon (gray), amygdala (purple) and brainstem (green) for illustrative purposes. Adapted from Dalley et al. (2011), Squire et al. (2012), and Nieh et al. (2013).

recent elaborations on the nature of inter- and intra-regional short and long-range GABAergic connections (Caputi et al., 2013). GABA circuits are uniquely situated as both local communicators and whole-brain integrators, given their dynamic control over excitatory and inhibitory signal conduction through axo-dendritic and astrocytic synapses (Frola et al., 2013) and their role in broader oscillatory and synchronistic activities (Melzer et al., 2012).

GABAergic interneurons, particularly parvalbumin-containing, are fundamental drivers of cortical oscillations, which emerging research suggests may be a fundamental context-dependent mechanism for intra- and inter-regional communication (Sohal, 2012; Jadi and Sejnowski, 2015). For instance, beyond the hippocampus and select regions of the neocortex, where these oscillations are better studied, there is also evidence for GABA-driven oscillatory synchronization within the striatum (Sharott et al., 2009)—a hub region connecting the cortex to the basal ganglia and heavily involved in motivation and valuative processing. Moreover, there is evidence that GABA cells are necessary for sustained reward-related signaling, as noted in a study of reversal learning in mice with decreased levels of prefrontal cortical GABAergic interneurons (Bissonette et al., 2015). Going forward, I briefly discuss a sample of recent studies which support the fundamental role of GABA in valuative processing and highlight future directions which will likely contribute to advances in this area.

GABAergic Microcircuits Regulate Valuative Networks

The present focus on GABA is not intended to ignore the important role played by other neurotransmitters. GABA-glutamatergic dynamics are fundamentally important for a complete understanding of circuit dynamics, as has been underscored by findings of neuronal co-release in value-related regions (Root et al., 2014) and multimodal neuroimaging studies in humans (Duncan et al., 2014). Nonetheless, GABA likely plays a unique role in neural control as, for instance, local and long-range GABAergic projections are highly diffuse and GABAergic synapses can precisely target the dendritic shafts of pyramidal cells, allowing for earlier neuronal signal gating in comparison to glutamatergic synapses (Chiu et al., 2013). Moreover, some GABAergic projections are noted to bypass the typical brainstem-thalamo-cortical and cortico-basal ganglia-thalamo-cortical connections, including for instance the direct meso-cortico, meso-limbic, and pallidal-cortical pathways (Cohen et al., 2012; Nieh et al.,...
Interestingly, a recent study suggested that increases in feeding following intra-pallidal, but not intra-accumbens, GABA<sub>A</sub> receptor antagonism corresponded to a specific “fat craving” signal instead of general increases in appetitive activity (Covelo et al., 2014). Aversion-related activity may also involve GABAergic inhibition of infralimbic cortex in rats, a homolog to the primate medial prefrontal cortex, as has been demonstrated by showing that pain-related GABAergic inhibitions in the prefrontal cortex are reversed following the local injection of GABA<sub>A</sub> receptor antagonists (Ji and Neugebauer, 2011)—though infralimbic activation in the absence of pain may also be anxiogenic (Bi et al., 2013). Moreover, GABA<sub>A</sub> receptor activation in the infralimbic cortex increases impulsive responding (Murphy et al., 2012), while activation in the prelimbic cortex reduces aversive behaviors such as fear-potentiated startle and freezing (Almada et al., 2015).

Beyond the regions of the extended amygdala noted above (e.g., nucleus accumbens shell, habenula), the amygdala itself is one region that deserves a brief note. Although its role in processing aversive stimuli is well-established, our understanding of its role in appetitive encoding is relatively recent—it is also considered mainly as a singular structure in human studies, though it is known to be made up of a number of uniquely-connected nuclei (e.g., central, basolateral, and lateral) comprised of differing cell types (Phelps and LeDoux, 2005; Janak and Tye, 2015). Few studies have looked at how this region processes both appetitive and aversive stimuli and none have focused on GABAergic cells. Studies in primates and rodents using single cell basolateral and central area recordings showed that at least half of the cells sampled were value-responsive, sensory modality-independent, consisted of general responders and those with preferences for either appetitive or aversive stimuli, and that there was no clear anatomical distribution for such cells across each subregion (Paton et al., 2006; Belova et al., 2007, 2008; Shabel and Janak, 2009). At least one study has also shown the importance of safety signaling for cells throughout the basal amygdala, identifying subpopulations of cells that respond to combinations of value and safety cues (Sangha et al., 2013). Of further interest, recent reports have described long-range GABAergic hippocampal- and intra-amygdalar projections likely involved in valuation processing (Bienvenu et al., 2015; McDonald and Zaric, 2015).

Taken together, and as underscored by Figure 1, these studies support the hypothesis that interconnected GABAergic microcircuits are a binding feature of valuative processing. Indeed, these circuits may be at the heart of whole-brain reinforcement or valuative networks (English et al., 2011; Vickery et al., 2011). Moreover, they likely also contribute to the intraregional integration and differentiation of appetitive and aversive signals (Hayes et al., 2014a).
Future Considerations

A corollary of the hypothesis above is the emphasis on undiscovered intra- and inter-regional value-related GABAergic signaling throughout the brain. In this vein, our group showed in a human multimodal neuroimaging study that GABA_A receptors in medial prefrontal cortex are negatively correlated to aversive signals in both the medial prefrontal region itself as well as distant sensorimotor clusters, but that GABA_A receptors within different clusters of sensorimotor cortex respond differentially to the context of aversive stimuli (Hayes et al., 2013). Moreover, we reviewed the human and rodent literature on impulsivity and GABA, and concluded that GABAergic networks throughout at least cortico-basal ganglia regions acted as a common substrate of impulsive behaviors (Hayes et al., 2014b).

We believe that affective/valuative networks are at the core of many psychological phenomena, from emotion (Stan et al., 2014) and impulsivity to sense of self (Wiebking et al., 2014a,b), and may even be fundamental to the initial recruitment of cognitive control (Inzlcht et al., 2015). Indeed, some neuroimaging studies have identified a common wide-spread network of regions which may be common to these processes (Northoff and Hayes, 2011; Amft et al., 2015). Future studies using complex multimodal neuroimaging approaches will be necessary to elaborate and connect the present neural and biochemical findings in humans (Duncan et al., 2014). These should also include in vivo neuroanatomical explorations of affective circuitry white matter, by for instance using recent advancements in multitenor tractography (Chen et al., 2014).

Conceptually, it is important to note that when discussing a “system” of any sort in neuroscience (e.g., GABAergic, valuative) one is often taking a broad sum-of-parts operational definition. Because the entirety, and mechanic underpinnings, of such systems are incomplete, and cannot be fully understood in isolation, these terms become placeholders for our dynamic knowledge (see LeDoux, 2012; Gross and Barrett, 2013; Hayes et al., 2014a for related discussions). For example, future research will have to continue to identify clusters of GABAergic cells which make up value-processing microcircuits as well as their connections to other value- and non-value related clusters, including other cell types, such that a better understanding of their true function becomes clearer (and probably resulting in clearer delineations between multiple “systems”). Analogous advances in network neuroscience have been made to identify many major nodes/hubs (i.e., clusters), edges (i.e., connections), and the interactions within and between such brain networks (Behrens and Sporns, 2012)—while most of this work is being done in humans, progress on the vast animal literature has also been made (Ikemoto, 2010). At this point, the greatest advances at the molecular-cellular level of understanding are likely being made through the identification and spatiotemporal electrochemical characterization of value-related microcircuits, for instance in the traditional mesocorticolimbic circuit (e.g., Nieh et al., 2013; Lamml et al., 2014). Indeed, the bulk of information connecting behavior to underlying mechanisms is confined to this value-related circuit, with disparate results for other areas. Moreover, behavioral-cellular/neurochemical connections related to GABA have been mainly restricted to single regions, such as the VTA, nucleus accumbens, and areas of the prefrontal cortex, although recent experiments have focused increasingly on inter-regional interactions (Lamml et al., 2012; Shabel et al., 2012; Hayes et al., 2013; Wang et al., 2014).

Going forward, future studies will also need to clearly answer the question of how brain areas within similar affective networks parse aversion- and appetitive-related neural signals, while also providing mechanisms for fast intraregional communication. Recent reviews of the human and animal literature have provided some insight to this question (Bissonette et al., 2014; Hayes et al., 2014a; Lindquist et al., 2015), but more work is needed. For instance, the significance, if any, of structures which show asymmetrical activity is unclear, e.g., appetitive and aversive stimuli may result in more dopamine in the right and left accumbens, respectively (Besson and Louilot, 1995). Moreover, how these neural processes are translated at the behavioral or “cognitive” level is of equal importance. Can appetitive and aversive stimuli be subjectively, consciously, experienced simultaneously (Barrett et al., 2007)? Why do some people experience painful experiences as pleasurable, and is there any connection to those who prefer to self-administer aversive stimuli rather than be alone with their own thoughts (Wilson et al., 2014)?

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References

Almada, R. C., Coimbra, N. C., and Brandão, M. L. (2015). Medial prefrontal cortex serotonergic and GABAergic mechanisms modulate the expression of contextual fear: intratelencephalic pathways and differential involvement of cortical subregions. Neuroscience 284, 988–997. doi: 10.1016/j.neuroscience.2014.11.001

Amft, M., Bzdok, D., Laird, A. R., Fox, P. T., Schilbach, L., and Eichhoff, S. B. (2015). Definition and characterization of an extended social-affective default network. Brain Struct. Funct. 220, 1031–1049. doi: 10.1007/s00429-013-0698-0

Barrett, L. F., Mesquita, B., Ochsner, K. N., and Gross, J. J. (2007). The experience of emotion. Annu. Rev. Psychol. 58, 373–403. doi: 10.1146/annurev.psych.58.110405.085709

Behrens, T. E. J., and Sporns, O. (2012). Human connectomics. Curr. Opin. Neurobiol. 22, 144–153. doi: 10.1016/j.conb.2011.08.005

Belova, M. A., Paton, J. J., and Salzman, C. D. (2007). Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala. Neuron 55, 970–984. doi: 10.1016/j.neuron.2007.08.004

Belova, M. A., Paton, J. J., and Salzman, C. D. (2008). Moment-to-moment tracking of state value in the amygdala. J. Neurosci. 28, 10023–10030. doi: 10.1523/JNEUROSCI.1408-08.2008
Murphy, E. R., Fernando, A. B. P., Urcelay, G. P., Robinson, E. S. J., Mar, A. C., Theobald, D. E. H., et al. (2012). Impulsive behaviour induced by both NMDA receptor antagonism and GABAergic receptor activation in rat ventromedial prefrontal cortex. *Psychopharmacology (Berl)*. 219, 401–410. doi: 10.1007/s00213-011-2572-1

Nieh, E. H., Kim, S.-Y., Namburi, P., and Tye, K. M. (2013). Optogenetic dissection of neural circuits underlying emotional valence and motivated behaviors. *Brain Res*. 1511, 73–92. doi: 10.1016/j.brainres.2012.11.001

Northoff, G., and Hayes, D. J. (2011). Is our self nothing but reward? *Biol. Psychiatry* 69, 1019–1025. doi: 10.1016/j.biopsych.2010.12.014

Paton, J. J., Belova, M. A., Morrison, S. E., and Salzman, C. D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature* 439, 865–870. doi: 10.1038/nature04490

Phelps, E. A., and LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* 48, 175–187. doi: 10.1016/j.neuron.2005.09.025

Reynolds, S. M., and Berridge, K. C. (2002). Positive and negative motivation in nucleus accumbens shell: bivalent rostrocaudal gradients for GABA-elicited eating, taste “liking”/“disliking” reactions, place preference/avoidance, and fear. *J. Neurosci.* 22, 7308–7320.

Richard, J. M., and Berridge, K. C. (2011). Metabotropic glutamate receptor blockade in nucleus accumbens shell shifts affective valence towards fear and disgust. *Eur. J. Neurosci.* 33, 736–747. doi: 10.1111/j.1460-9586.2010.07553.x

Roberts, E., and Frankel, S. (1950). γ-Aminobutyric acid in brain: its formation from glutamic acid. *J. Biol. Chem.* 187, 55–63.

Root, D. H., Mejias-Aponte, C. A., Zhang, S., Wang, H. L., Hoffman, A. F., Lupica, C. R., et al. (2014). Single rodent mesolimbic axons release glutamate and GABA. *Nat. Neurosci.* 17, 1543–1551. doi: 10.1038/nn.3823

Root, D. H., Mejias-Aponte, C. A., Zhang, S., Wang, H. L., Hoffman, A. F., Lupica, C. R., Morales, M.

Sangha, S., Chadick, J. Z., and Janak, P. H. (2013). Safety encoding in the basol amygdala. *J. Neurosci.* 33, 3774–3751. doi: 10.1523/JNEUROSCI.3302-12.2013

Saunders, A., Oldenburg, I. A., Berezovskii, V. K., Johnson, C. A., Kingery, N. D., et al. (2015). A direct GABAergic output from the basal ganglia to the frontal cortex. *Nature* doi: 10.1038/nature14179. [Epub ahead of print].

Shabel, S. J., and Janak, P. H. (2009). Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. *Proc. Natl. Acad. Sci. U.S.A.* 106, 15031–15036. doi: 10.1073/pnas.0905580106

Shabel, S. J., Proulx, C. D., Trias, A., Murphy, R. T., and Malinow, R. (2012). Input to the lateral habenula from the basal ganglia is excitatory, aversive, and suppressed by serotonin. *Neuron* 74, 475–481. doi: 10.1016/j.neuron.2012.02.037

Sharrott, A., Moll, C. K. E., Engler, G., Denker, M., Grün, S., and Engel, A. K. (2009). Different subtypes of striatal neurons are selectively modulated by cortical oscillations. *J. Neurosci.* 29, 4571–4585. doi: 10.1523/JNEUROSCI.5097-08.2009

Sohal, V. S. (2012). Insights into cortical oscillations arising from optogenetic studies. *Biol. Psychiatry* 71, 1039–1045. doi: 10.1016/j.biopsych.2012.01.024

Squire, L., Berg D., Bloom, F., du Lac, S., Ghosh, A., and Spitzer, N. (eds.). (2012). *Fundamental Neuroscience, 4th Edn*. USA: Academic Press.

Stan, A. D., Schirda, C. V., Bertocci, M. A., Bebko, G. M., Kronhaus, D. M., Aslam, H. A., et al. (2014). Glutamate and GABA contributions to medial prefrontal cortical activity to emotion: implications for mood disorders. *Psychiatry Res.* 223, 253–260. doi: 10.1016/j.psychres.2014.05.016

Steffen, S. C., Lee, R. S., Stobbs, S. H., and Henrikson, S. J. (2001). Responses of ventral tegmental area GABA neurons to brain stimulation reward. *Brain Res.* 906, 190–197. doi: 10.1016/S0006-8993(01)02581-1

Stratford, T. R., and Kelley, A. E. (1997). GABA in the nucleus accumbens shell participates in the central regulation of feeding behavior. *J. Neurosci.* 17, 4434–4440.

Swanson, L. W. (1982). The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. *Brain Res. Bull.* 9, 321–353. doi: 10.1016/0361-9230(82)90145-9

Tachibana, Y., and Okhida, H. (2013). The primate ventral pallidum encodes expected reward value and regulates motor action. *Neuron* 62, 985–994. doi: 10.1016/j.neuron.2012.09.030

Tindell, A. J., Berridge, K. C., and Aldridge, J. W. (2004). Ventral pallidal representation of pavlovian cues and reward: population and rate codes. *J. Neurosci.* 24, 1058–1069. doi: 10.1523/JNEUROSCI.1437-03.2004

Tritsch, N. X., Ding, J. B., and Sabatini, B. L. (2012). Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. *Nature* 490, 262–266. doi: 10.1038/nature11646

Vickery, T. J., Chun, M. M., and Lee, D. (2011). Ubiquity and specificity of reinforcement signals throughout the human brain. *Neuron* 72, 166–177. doi: 10.1016/j.neuron.2011.08.011

Wang, L., Shen, M., Yu, Y., Tao, Y., Zheng, P., Wang, F., et al. (2014). Optogenetic activation of GABAergic neurons in the nucleus accumbens decreases the activity of the ventral pallidum and the expression of cocaine-context-associated memory. *Int. J. Neuropsychopharmacol.* 17, 753–763. doi: 10.1017/S1461145713001570

Wiecking, C., Duncan, N. W., Qin, P., Hayes, D. J., Lyttelton, O., Gravel, P., et al. (2014a). External awareness and GABA-A multimodal imaging study combining fMRI and [(18) F]fluromazenil-PET. *Hum. Brain Mapp.* 35, 173–184. doi: 10.1002/hbm.22166

Wiecking, C., Duncan, N. W., Tiret, B., Hayes, D. J., Marjaška, M., Doyon, J., et al. (2014b). GABA in the insula - a predictor of the neural response to interoceptive awareness. *Neuroimage* 86, 10–18. doi: 10.1016/j.neuroimage.2013.04.042

Wilson, T. D., Reinhard, D. A., Westgate, E. C., Gilbert, D. T., Ellebeck, N., Hahn, C., et al. (2014). Just think: the challenges of the disengaged mind. *Science* 345, 75–77. doi: 10.1126/science.1250830

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