Emerging, Reemerging, and Forgotten Brain Areas of the Reward Circuit: Notes from the 2010 Motivational and Neural Networks Conference

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Abstract

On April 24–27, 2010, the Motivational Neuronal Networks meeting took place in Wrightsville Beach, North Carolina. The conference was devoted to "Emerging, re-emerging, and forgotten brain areas" of the reward circuit. A central feature of the conference was four scholarly discussions of cutting-edge topics related to the conference's theme. These discussions form the basis of the present review, which summarizes areas of consensus and controversy, and serves as a roadmap for the next several years of research.

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1 GENERAL INTRODUCTION

The fifth Motivational Neuronal Networks meeting took place on April 24–27th in Wrightsville Beach, NC. As with the four previous meetings, this event brought together scientists who study the neural circuits that govern motivated behavior, including experts in anatomy, pharmacology, neurophysiology, functional imaging, computational modeling, and animal and human behavior. The theme chosen by this year's organizers was "The Reward Circuit: Emerging, Reemerging, and Forgotten Brain Areas", with the goal of looking beyond the handful of structures that are most commonly associated with reward and motivation. Four small group workshops were held, each one dedicated to a select set of brain regions; the participants shared findings, raised critical questions and issues, and sought consensus about the current state and future directions of the field. The compiled notes from these group discussions are presented in this review.

The first workshop focused on the subthalamic nucleus and the ventral pallidum; originally considered parts of classical basal ganglia motor circuitry, new evidence from basic and clinical studies points to their roles in reward and motivation. The second workshop addressed the unique contributions of the dorsal and ventral hippocampal formation to contextual conditioning, associative learning, drug-seeking and the pathophysiology of schizophrenia. The focus of the third workshop was the lateral habenula and the rostromedial tegmental nucleus, two structures that may powerfully influence the firing of dopamine neurons. Finally, the fourth workshop was dedicated to the extended amygdala, particularly the bed nucleus of the stria terminalis and its interactions with the lateral hypothalamus. In addition to the group discussions the conference included poster presentations, and plenary lectures by two distinguished guests: Gary Aston-Jones presented recent findings from his group on the role of orexin neurons in drug and natural reward seeking, and Martine Cador presented a historical review of the anatomy and chemoarchitecture of the reward system, given in memory of a major contributor to the field, the late Ann E. Kelley, Ph.D., a colleague and friend of many in attendance.

2 THE SUBTHALAMIC NUCLEUS AND VENTRAL PALLIDUM

2.1 The Subthalamic Nucleus

2.1.1—The subthalamic nucleus (STN) is physically and functionally situated at the interface between the basal ganglia and the limbic system and is reciprocally and topographically connected to both sets of structures [1–3]. Although this nucleus has received less scholarly attention than its neighbors, its function has recently become the subject of great interest. In particular, clinical scientists have become interested in its contributions to the control of motivated behavior and clinical pathologies such as Parkinson's disease (PD) and obsessive compulsive disorder (OCD).

Although it is clear that the STN is heavily recruited in motivated behaviors, its specific role is unknown. STN neurons are reward-sensitive [4, 5], and manipulations of STN activity affect both drug- and natural reward-seeking [6–8]. Reward magnitude modulates neuronal firing in STN, and many STN neurons fire selectively for trials involving only one of multiple rewards present in a given task [9]. High frequency stimulation of the STN (comparable to clinical deep brain stimulation, (DBS) [10, 11]) decreases conditioned place

preference (CPP) for cocaine and willingness to work for cocaine in a progressive ratio task, while at the same time increasing the willingness to work for food [6]. The latter may be clinically important because patients receiving DBS therapy often experience weight gain [12].

Several pieces of evidence also link STN with self-control, a decision process with clear implications for addiction [13]. Lesions of the STN result in impairment on three measures of impulsivity: 5-choice serial reaction time tasks, stop signal, and timed reactions [14, 15]. STN lesions also increase compulsive lever-pressing [16], as does functional disconnection of the mPFC-to-STN "hyperdirect" pathway [17]. However, STN lesions also appear to increase willingness to wait for a reward in a delay discounting task [18]. This seemingly paradoxical finding suggests that these measures of impulsivity are served by distinct neuronal mechanisms.

2.1.2 Functional and neuroanatomical subdivisions of the STN—Evidence suggests that the STN consists of two subdivisions: a lateral subdivision (lSTN) associated with the motor circuits of the basal ganglia and a medial subdivision (mSTN) associated with the limbic system and reward seeking; the primate STN may also have an associative segment located between the medial and lateral divisions [19, 20]. These anatomical differences may underlie the functional differences seen in pre-clinical studies and in the effects of deep brain stimulation (DBS) therapy in humans being treated for psychiatric disorders.

Anatomical differences between the medial and lateral STN are substantial. For example, the medial tip of the STN has reciprocal projections with the primate limbic pallidum (ventral pallidum (VP) in rodents), whereas the lSTN preferentially interacts with the external pallidal segment (globus pallidus in rodents) and entopeduncular nucleus [2, 21–23]. In primates (but not rodents), the dendritic field of an individual STN neuron occupies only a small portion of the nucleus, which may help compartmentalize the topographic inputs and outputs [24, 25]. Despite these anatomical distinctions, clear evidence for functional differences between these two subregions has been more elusive. In one nonhuman primate study, Mitchell and colleagues [26] reported an increase in metabolic activity in the dorsolateral STN during experimentally induced chorea, while the ventromedial tip was relatively unaffected. And in rodents, injections of NMDA or the GABA receptor antagonist, bicuculline, into the VP results in Fos activation only in the mSTN [27]. However there is also evidence that functional differentiation of medial and lateral STN might be limited: in nonhuman primates, electrical stimulation of the medial tip of the STN induces both motor and reward-related activity [28] and no differences in reward-related firing have been observed between the medial and lateral STN in rodents [9].

While findings from animal models may be ambiguous, clinical evidence from individuals receiving therapeutic STN DBS supports a medial/lateral distinction, as more medial stimulation evokes strong emotions with little effect on motor behavior [11]. In addition, DBS of the ventromedial STN also relieves the symptoms of OCD [29]. Although compelling, these results must be interpreted with caution. Due to the architecture of the STN and surrounding tissue, it is probable that electrical current spreads away from the body of the STN and directly activates distant neurons, terminals of afferent inputs, or nearby traversing axons [30–32]. Thus, the effects of DBS in the STN could be mediated in whole or in part by effects that occur outside of the STN itself.

Clearly, further research using a wider spectrum of the methodologies available to behavioral, anatomical, molecular and physiological neuroscience is needed to delineate the particular role of the medial and lateral STN. Evaluations across species will be particularly

important as in vivo studies of STN subdivisions in rodents are technically difficult because of the small size, location and orientation of the STN.

2.2 The ventral pallidum

The VP is involved several different reward modalities, including drug-seeking, natural rewards, and intracranial self-stimulation [33–35]. Pharmacological disruption of the VP interferes with morphine-induced CPP [36], and with the formation and reinstatement of cocaine CPP [37, 38]. After lesions of the VP, previously palatable foods become aversive [39], and VP inactivation reduces self-stimulation of the medial forebrain bundle [40]. This functional evidence is corroborated by in vivo electrophysiological recordings: VP neurons respond to sucrose delivery and to sucrose-predictive cues [41], and show phasic firing rate changes related to cocaine-seeking lever presses [42]. Finally, a pair of recent studies in nonhuman primates has suggested that the VP may contribute to reward prediction error signaling via its input to the LHb [35, 43]. Although these findings link VP to processing information about rewards, they leave its precise role unclear.

The VP receives strong inputs from both the nucleus accumbens core (NAcc) and the STN [44, 45] and it has been hypothesized that the VP integrates these inputs to generate modality-independent responses. Indeed, there is evidence that single VP neurons encode many different stimuli and events in behavioral tasks [46, 47] – in contrast to the more selective responses found in striatum and NAcc [48, 49]. However, the organization of even these two prominent VP inputs is poorly understood. The NAcc neurons projecting to the VP are GABAergic and also contain opioids and other peptides [50, 51]. In contrast, STN projections to the VP are largely glutamatergic [52]. Physiological and pharmacological evidence suggests that NAcc inputs converge with and modulate other inputs to the VP. For example, exogenous application of opioid agonists modulate cortical- and amygdala-driven excitation in VP neurons [51], whereas inactivation of the NAcc can potentiate responses to cocaine administration [53]. However, the anatomical substrate for these effects is not known.

If the NAcc and STN inputs show a high degree of convergence on VP neurons, it would suggest that VP neurons integrate these sources of information and that single neurons may indeed be capable of encoding multi-modal rewards and cues. In contrast, if the NAcc and STN inputs do not converge in the VP, it would suggest that the VP contains multiple parallel channels that mediate distinct functions. Thus, the function of the VP may rely critically on the organization of its NAcc and STN afferents.

As the NAcc-VP and STN-VP pathways use GABA and glutamate, respectively, they may have distinct – and possibly opposed – functions. As a part of the indirect basal ganglia pathway, the NAcc-VP input may be important for the initiation of goal-directed behaviors. It may also be critical for learning new associations and actions, given the strong influence of the ventral subiculum on both the output neurons and interneurons of the NAcc [54, 55]. In contrast, the input from the STN may act as a "brake," opposing previously learned actions in order to facilitate reversal learning or response inhibition. Thus, future investigations of the VP and its inputs will benefit by contrasting the effects of novel learning with the effects of reversal learning and extinction.

Given the essential role of dopamine in movement and motivated behaviors, it is possible that many of the functions of VP and STN in reward-seeking behavior are mediated via their actions on the dopamine system. There are two distinct, parallel pathways by which the STN and VP influence DA neuronal firing. First, the VP sends a direct inhibitory projection to the ventral tegmental area (VTA) and the STN sends direct excitatory projections to the substantia nigra pars compacta (SNc). Second, both the STN and the VP project indirectly to

dopamine neurons via brainstem cholinergic nuclei. Through these parallel pathways, the VP can influence both the number of active dopamine neurons as well as their tendency for burst firing in the VTA [56]. Adding to the complexity of these interactions is the direct innervation of the STN, VP, and many of their afferent regions by DA [57–59]. Though DA innervation of STN and VP is moderate, local application of DA can modulate the firing of both VP [60] and STN neurons [61]; in the latter case, DA modulates burst firing, a function thought to be particularly important in the pathology of Parkinson's disease [62]. Thus, the VP and STN can directly influence the firing of dopamine neurons but are themselves subject to the modulatory influence of DA.

3 THE SUBICULUM AND RELATED HIPPOCAMPAL AREAS

3.1 The subiculum

The subiculum is a transitional cortical area that lies adjacent to the CA1 subfield of the hippocampus, and along with the entorhinal cortex and hippocampus, is considered to be an integral part of the hippocampal formation. It has been traditionally viewed as an output structure for the hippocampal formation, as its major efferents include numerous cortical and subcortical regions (described below), and its major inputs arise from the CA1 and entorhinal areas [63]. Although the hippocampal formation is typically associated with episodic memory and spatial navigation, the subiculum appears to play a role in stress, contextual conditioning, and drug abuse. Moreover the different subregions of the hippocampal formation appear to have different outputs and different roles: the dorsal hippocampus projects to the NAcc and is implicated in context-based conditioning and reinstatement of drug seeking [64] whereas the ventral subiculum projects to NAcc shell (and other extended amygdala structures) and has a role in stress, and the pathophysiology of schizophrenia [65, 66].

Importantly, the role of the subiculum in reward appears to derive from its interconnections with reward-related structures [67] rather than intrinsic encoding of reward. Neither dorsal nor ventral hippocampal neurons appear to encode value or reward [68, 69], but there is evidence for some post-reward related firing [70]. Neural activity in the subiculum often follows hippocampal CA1 firing with strict temporal correlation but can also persist after CA1 neurons become quiescent. These data suggest that that the subiculum acts as memory buffer for both transfer and retrieval of memory-related information [71], consistent with the idea that the subiculum may act both as an input and output nucleus of the hippocampal formation [72].

3.2 Different roles for dorsal and ventral hippocampus—The dorsal subiculum (DSub) is the major output structure for surrounding dorsal hippocampal (DH) areas, connecting the hippocampus to many structures in the cortical reward system (Fig 1a) [73]. DSub in turn receives input from DH CA1, which itself receives input from the entorhinal cortex and lateral septum (LS) (Fig 1b). DSub outputs include the NAcc core, which then projects to the lateral VP and the medial SN (Fig 1b). These outputs allow the DSub to impact and modulate behavioral responses to rewards.

DH plays a key role in contextual memory processes, including occasion setting [74]. This function of the DH is known to extend to drugs of abuse because DH is involved in ethanol- and cocaine-seeking induced by contextual stimuli. The firing properties of DH neurons are well-suited to providing this detailed contextual information because DH neurons demonstrate finely tuned place sensitive firing and process spatial contexts with very high resolution [75, 76]. Unlike the fine spatial tuning of DH neurons, ventral hippocampal (VH) neurons have broad spatial tuning [77, 78] and are sensitive to head direction [79, 80]. Unlike hippocampal CA1 neurons, subiculum neurons do not "re-map" their place fields as

a result of changes in the spatial context in which an animal is placed [77]. This suggests that the place-sensitive firing in the dorsal and ventral hippocampus serve two functionally distinct roles in guiding behaviors [81].

VH and ventral subiculum (VSub) neurons have ideal circuit connections for a role in stress, reward, and fear (Figure 1c). The VSub has substantial outputs to the LS, amygdala nuclei, and bed nucleus of the stria terminalis (BNST), all of which can influence the hypothalamic-pituitary axis by sending projections to the paraventricular nucleus of the hypothalamus [82]. The VSub receives inputs from the ventral tegmental area and basolateral amygdala and sends efferents to the prelimbic and infralimbic medial prefrontal regions and to NAcc shell [83–87], both of which also receive amygdala and VTA inputs.

Consistent with these diverse anatomical connections, the VH has been implicated in a host of reward-related functions. VH lesions and inactivation decrease cue- drug- and contextual-induced reinstatement of cocaine-seeking [88–91], effects likely mediated by VH outputs to the medial prefrontal cortex or ventral striatum [92–94]. Additional studies have shown that stimulation of the VSub increases locomotor activity and dopamine release in the NAcc, prefrontal cortex and VTA [93, 94]. Via a multi-synaptic circuit through the NAcc and VP, the VSub also regulates the number of tonically active dopamine neurons in the VTA [95, 96]. Disruption of this pathway in particular may be relevant to the pathophysiology of schizophrenia (Figure 2, [92]), as hallucinations and paranoia have been attributed to elevated levels of tonic dopamine. In addition, high frequency stimulation of the subiculum increases dopamine levels in the NAcc, though this may be mediated by local activation of dopamine terminals [97]. Finally, dopamine afferents to the vSub are important in instrumental learning and motivation [83]. In short, the neural circuitry of the VH is distinct from the DH and has ideal neural connections for a role in stress, affect, and reward.

3.3 Summary—The DSub and VSub have distinct contributions to motivated behavior, arising from their distinct firing properties and anatomical connections. The DH encodes specific spatial and episodic information that may then facilitate conditioning based on fine spatial discrimination or specific configurations of discrete cues. The VH, with less-specific spatial encoding and outputs to the extended amygdala and (indirectly) to dopamine neurons, may modulate arousal or mood according to memories of context. In other words, the DH answers the question, "Where am I?", whereas the VH addresses, "Should I care?" (Figure 1). To reconcile these accounts of hippocampal formation function with the more well-known function of the hippocampus in episodic memory, it was suggested during our discussions that the hippocampal formation may be particularly tuned for encoding memories of rewarding events. Specifically, it has been hypothesized that rewarding events may increase dopamine release within the hippocampus, which may promote late phase LTP and embed experiences into long term memory [98].

4 THE LATERAL HABENULA AND MESOPONTINE ROSTROMEDIAL TEGMENTAL NUCLEUS

4.1 The lateral habenula

The lateral habenula (LHb) is a bilateral telencephalic nucleus located dorsal to thalamus, adjacent to the third ventricle. Its primary inputs are from the VP and internal segment of the globus pallidus [99, 100], as well as from the lateral hypothalamus and preoptic hypothalamic areas [101]. The outputs of the LHb are to mesencephalic structures, including the VTA and SNc, median and dorsal raphe nuclei, and the laterodorsal and pedunculopontine tegmental nuclei [102–104]. The majority of LHb neurons, including those that project to the ventral midbrain, are glutamatergic [105, 106]. Thus, the LHb links

the hypothalamus and striatopallidal output nuclei with the dopamine, serotonin, and acetylcholine neurotransmitter systems – critical systems implicated in arousal, voluntary movement, attention, learning, mood, and drug abuse.

Recent findings suggest that the LHb is a unique contributor to reward prediction signals generated by dopamine neurons. In electrophysiological recordings, presumed dopamine neurons initially exhibit increased firing rates in response to primary rewards, but shift their firing rate increases to occur at the earliest cue that predicts reward as the predictor-reward association is learned [107, 108]. If the reward is omitted following the presentation of a predictor, presumed dopamine neurons decrease firing, signaling a reward prediction error [107]. In contrast, LHb neurons phasically increase firing following reward omission and inhibit firing in response to reward-predicting cues [109]. Given that LHb stimulation decreases presumed dopamine neuron firing, Matsumoto and Hikosaka [109] proposed the LHb as the source of negative reward prediction error signals to the dopaminergic midbrain.

While these results suggest a role for LHb in aversive conditioning and negative affect, under some circumstances, the LHb supports positive reinforcement. Rats will engage in intracranial self-stimulation of the LHb [110], and LHb lesions attenuate the efficacy of self-stimulation of lateral hypothalamus, VTA, and other sites [111]. Furthermore, in a particularly compelling case study, a patient suffering from drug-resistant depression was successfully treated via high-frequency DBS of the LHb [112]. Stimulation decreased depression symptoms (assessed by the Hamilton Rating Scale for Depression), but only after 12 weeks of continuous treatment. Interestingly, during an occasion when the stimulator battery failed, the patient's symptoms returned. The symptoms subsided after a new battery was installed, again after a delay of several weeks. LHb DBS may act via a stimulation-induced inactivation of the LHb (as appears to be the case for DBS of the STN [113] and consequent alteration of the VTA and mesocorticolimbic pathways. However, stimulation-induced depression is thought to occur only with high stimulation frequencies (100Hz or greater, [113]), and so this mechanism is unlikely to be the basis for low-frequency LHb self-stimulation in rodents. Thus, the LHb may have a yet-undefined role in positive reinforcement, as well as in negative reward prediction error.

To explain the suppression of VTA neuronal firing by LHb activation, it was originally hypothesized that LHb neurons project directly to VTA and SNc neurons. However, the projection from the LHb to the VTA is relatively sparse [114], primarily glutamatergic, and forms synapses equally onto GABAergic and dopaminergic neurons of the VTA [106]. Therefore, it is unclear how activation of the LHb can inhibit VTA neuronal firing. One possibility, discussed below, is that the LHb may inhibit VTA neurons via an intermediary structure, e.g., the mesopontine rostromedial tegmental nucleus (RMTg).

Additional anatomical projections of the LHb may also mediate negative reward signals. The LHb provides excitatory input to the dorsal raphe [115], a brain region that has long been implicated in signaling aversive events. Further, the dorsal raphe projects directly to the VTA and this may provide inhibitory input that contributes to negative reward signals. However, it is not known whether the dorsal raphe encodes reward-omissions or if activation of the dorsal raphe-to-VTA projection can inhibit VTA dopamine neurons.

4.2 The mesopontine rostromedial tegmental nucleus (RMTg)

The RMTg is a midbrain structure that lies adjacent to the interpeduncular nucleus and expands upward behind the retrorubal area into the paramedian region, to further ascend toward the most medial aspect of the pedunculopontine tegmental nucleus [104]. Although it is located caudal to the VTA and has been referred to as the "tail" of the VTA (tVTA) [116], the RMTg is a reticular structure. Its neurons are not distinguishable from those of the

surrounding tissue and its boundaries can only be identified by immunohistochemical localization of markers like the mu-opioid receptor, somatostatin, or Fos (when evoked by external stimuli or pharmacological challenge, see below [104, 117]).

RMTg afferents arrive from a vast array of cortical and subcortical sources, including prelimbic cortex, cingulate cortex, NAcc, VP, ventral BNST, periaqueductal gray, lateral hypothalamus and preoptic areas, and habenula [104]. RMTg projects most densely to the VTA and SNc but also to dorsal raphe nucleus, pedunculopontine tegmental nucleus, lateral dorsal tegmental nucleus, locus coeruleus, and reticular formation [104, 118]. RMTg projections to VTA form symmetrical GABAergic synapses onto dopaminergic neurons. In this way, the connections of the RMTg are similar to those of the LHb, receiving descending inputs from many structures including the hypothalamus and ventral striatal-pallidal system, and subsequently providing descending projections to critical components of the ascending arousal system. However, unlike the LHb, the RMTg appears to use GABA as its primary neurotransmitter.

Several studies link the RMTg to aversion and negative affect. For example, Jhou and colleagues [118] showed that Fos protein was highly expressed in RMTg neurons in rats following foot shock, or following cues that had been previously associated with foot shock. In the same study, lesions of the RMTg disrupted freezing in response to cued foot shock or predatory odor and increased the proportion of time spent in open arms of an elevated plus maze. However, the same lesions increased defensive treading, suggesting that the RMTg primarily governs passive behaviors such as freezing and avoidance rather than active behaviors such as escape or defensive treading [118]. In RMTg neurons that project to the VTA, Fos immunoreactivity increases after administration of psychostimulants [117, 119], but not morphine [120]; this elevated Fos expression may be related to stress or arousal, rather than the positive hedonic properties of psychostimulants.

Several lines of evidence suggest that the RMTg may play an intermediary role in a circuit mediating aversion. First, the RMTg receives a massive projection from the LHb. Similar to the LHb, a subpopulation of RMTg neurons exhibits increased firing rate following reward omission or cues that predict the absence of reward [118]. In experiments that measured firing in the LHb, RMTg and VTA, reward omission increased firing in the LHb and the RMTg and suppressed firing in the VTA (T.C. Jhou, personal communication). Based on these anatomical and physiological findings, it was proposed that activation of GABAergic RMTg neurons by glutamatergic LHb neurons results in inhibition of VTA dopaminergic neurons. However, this model cannot account for the finding that (when compared across several studies) the onset latency of RMTg neurons to a conditioned stimulus appears to be approximately 20 ms faster than the onset latency in LHb neurons [T.C. Jhou, personal communication, 118, 121] Thus, while the anatomical evidence suggests that the RMTg is an interlocutor between LHb and the VTA, physiological evidence suggests a more complex role for the RMTg.

4.3 Different roles for LHb and RMTg?

Aversive events can include both punishment (the arrival of an unpleasant stimulus) and disappointment (the omission of reward). While both can induce negative affect, they are different phenomena and could be represented by separate brain circuits or by distinct nodes of a network that also include common points of signal integration. In the latter case, the RMTg may be able to integrate signals involved in both punishment and disappointment, as it receives input from the extended amygdala and periaqueductal grey, structures involved in processing aversive stimuli [116], as well as the LHb, which responds to reward omissions [122]. If this model is correct, then the circuits that couple the LHb and amygdala/periaqueductal grey to dopamine neurons, though they respond to different classes of

negative stimuli, would both use the RMTg as a common node. Otherwise, the RMTg may be selectively involved in encoding a specific subclass of negative events.

Another possibility proposed is that the RMTg may selectively regulate the motor component of responses to disappointment, punishment or both. According to this hypothesis, the strong inhibitory projection from the RMTg to the VTA and SNc acts as a "brake" or no-go signal for motor actions. Acting in parallel, the weak excitatory input from the LHb to the VTA/SNc provides input that encodes the positive or negative valence or external events. Supporting such a distinction between motivational and motor aspects of RMTg function is the observation that RMTg lesions selectively affect passive—but not active—defense behaviors [118].

4.4 Dopamine release and aversive events

As reviewed above, there is ample evidence that the RMTg may suppress firing in dopamine neurons in response to aversive events. However, primary or conditioned aversive stimuli can increase extrasynaptic (or tonic) dopamine release in terminal regions such as NAcc and prefrontal cortex, as measured by microdialysis [123, 124]. This apparent contradiction may be explained by the differential effects of tonic and phasic dopamine neuron firing on dopamine release. Changes in dopamine release measured with microdialysis appear to be driven primarily by increases in the number of tonically active dopamine neurons, and by local activation of dopamine terminals by excitatory inputs within terminal regions [56, 96, 125, 126]. In contrast, phasic burst firing of dopamine neurons (traditionally linked to reward-related stimuli) does not appear to make a substantial contribution to tonic dopamine levels [56]. Thus, tonic and phasic transmission may be two distinct and quasi-independent signals through which the dopamine system processes rewarding or aversive events. Whereas rewarding stimuli may enhance both tonic and phasic dopamine activity, aversive stimuli may preferentially suppress phasic dopamine activity via activation of the RMTg, while concurrently increasing extrasynaptic dopamine efflux through other mechanisms.

5 THE EXTENDED AMYGDALA, THE BED NUCLEUS OF THE STRIA TERMINALIS, AND THE HYPOTHALAMUS

The extended amygdala has been defined as a continuum of inter-related basal forebrain structures that includes the central amygdaloid nucleus (CEA), the sublenticular extended amygdala nuclei, the bed nucleus of the stria terminalis (BNST), and the shell of the NAcc [127–129]. These nuclei share much in common and are involved in many motivated behaviors including reward-based operant conditioning and stress- or cue-induced reinstatement of drug seeking in animals [130–134].

Among the extended amygdala structures, the BNST appears to be particularly important in motivated behaviors, including those driven by pharmacological agents [135–137]. The BNST has been characterized as a cluster of approximately 12 interconnected nuclei [127, 138, 139]. Whether BNST nuclei should be referred to a single unitary structure is a matter of debate. However, each of the neuronal clusters currently considered as BNST subnuclei are highly interconnected and have similar neuronal electrophysiological signatures, suggesting it may be appropriate to consider the BNST as a unit [140–147]. These BNST nuclei are intricately interconnected with major components of the brain reward circuitry such as the VTA, the ventral striatum, and the hypothalamus [c.f. 144 and others from these authors].

The nuclei of the BNST have clear lateral/medial and ventral/dorsal gradients based on their function and anatomical connectivity. Lateral BNST nuclei preferentially connect with the lateral hypothalamus and lateral regions of the CEA, and medial BNST nuclei connect with

medial CEA and medial hypothalamus [127, 128]. While the medial and lateral BNST networks are thought to influence endocrine function and motivated behaviors, respectively, anatomically specific lesions or pharmacological interventions will be required to clarify this issue.

There are also clear neurochemical distinctions between the ventral and dorsal BNST. Dopamine-containing terminals are restricted to BNST regions dorsal to the anterior commissure, whereas noradrenaline-containing terminals are preferentially, although not exclusively, located in the ventral BNST [148–151]. As with the medial and lateral parts of the BNST, these anatomical distinctions may correspond to different functions: pharmacological manipulations of the dorsal BNST interfere with appetitive-motivated behaviors such as drug self-administration whereas noradrenergic antagonists in the ventral BNST reduces withdrawal-induced place aversion [135–137, 152].

The BNST contributes to coding the appetitive outcome of a given situation, responding to stimuli associated with both positive and negative affect. However, there is a relatively clear distinction between the types of stimuli that activate the BNST and those that activate other regions of the extended amygdala such as the CEA. Whereas the CEA is critical for discrete cue-induced conditioning, the BNST seems to play a special role in contextual conditioning [153–156]. As such, the BNST is thought to contribute to a general `awareness' loosely linked to a particular context, rather than the prediction of specific outcomes by discrete cues [157]. Consistent with this idea, the BNST, but not the CEA, receives a strong input from the VSub, which plays a key role in contextual conditioning [158, 159] (see Section 3).

One key feature of the BNST and other extended amygdala structures are their bidirectional anatomical connections with hypothalamic nuclei. Indeed, the extended amygdala is the main input to hypothalamic nuclei and, in return, several hypothalamic nuclei project back to regions of the extended amygdala [127, 128, 141–146]. The extended amygdala seems to act as an important relay and integration center between cortical regions and hypothalamic nuclei [160, 161]. For example, the BNST projection to the paraventricular nucleus may be a pathway that allows contextual information (from the ventral subiculum) to influence motivated behavior. Of particular relevance to motivated behaviors is the relationship between the lateral hypothalamus and the lateral extended amygdala. Both the ventral BNST and the NAcc shell send projections to the lateral hypothalamus, which contains orexinergic neurons recently identified as important for drug-seeking behaviors [162]. The lateral hypothalamus in turn projects back to the ventral BNST, though the functional significance of this reciprocal projection is not known (but see [163]).

6 CONCLUSION

More than just recognizing understudied brain regions, the purpose of this meeting was to expand what we think of as the "reward circuit". Indeed, the importance of reward in all aspects of our decisions –what food to eat, what job to take – belies the notion that reward processing is only a small part of our brain. The many, diverse brain structures discussed above are at the center of a current blizzard of studies, comprising work in anatomy, behavioral pharmacology, in vivo and in vitro electrophysiology, neuroimaging, and theoretical modeling. From these studies is emerging a new understanding of the essential players in motivation and reward.

One consistent point that became apparent from our discussions was that brain regions cannot be simply labeled as either contributing, or not contributing, to motivated behavior; rather, it's necessary to consider the specific circumstances under which the region is being engaged. For example, while the large inhibitory input from the RMTg to the VTA is clearly

of functional significance, this pathway may only drive passive defensive responses such as freezing or avoidance (See Section 4 and Jhou et al 2009a). Thus, a major thread in our discussions was whether these regions were tied to specific classes of behaviors or specific kinds of reward. A second major thread was that the anatomy of these forgotten regions – afferent and efferent connections, cytoarchitecture, local neurotransmitters and peptides – can provide important clues to their function, and can shape our hypotheses and interpretations. However, when crucial anatomical details are lacking, it is that much more difficult to understand their function. In the case of the medial STN (Section 2), its direct excitatory projection to the VP may powerfully influence cortical-striatal-pallidal transmission; but without knowing how the inputs from the STN are arranged relative to other major VP afferents, the functions of this pathway can only be guessed. In this way, our discussions showed that to expand the reward circuit, two questions must be answered: Under what specific circumstances are these brain regions required for reward and motivation? And how does their anatomy make this possible?

The consensus, common ground, and unresolved issues from our discussions are summarized in the reviews above. If nothing else, they show that the reward system is large and multi-faceted – that it may not be a unitary system with clear borders, but rather may be interwoven throughout the structure of the brain, influencing all aspects of cognition and behavior. The borders – or lack thereof – of the reward circuit will continue to be important points of discussion at the next MNN conference scheduled for 2012, and in our continued gatherings in the future.

Acknowledgments

ABBREVIATIONS

BNST	bed nucleus of the stria terminalis
CEA	central amygdaloid nucleus
CPP	conditioned place preference
DA	dopamine
DBS	deep brain stimulation
DH	dorsal hippocampal formation
DSub	dorsal subiculum
LHb	lateral habenula
LS	lateral septum
lSTN	lateral subthalamic nucleus
mSTN	medial subthalamic nucleus
NAcc	nucleus accumbens
OCD	obsessive compulsive disorder
PD	Parkinson's Disease
RMTg	mesopontine rostromedial tegmental nucleus

SNc	substantia nigra pars compacta
STN	subthalamic nucleus
tVTA	tail of the VTA
VH	ventral hippocampal formation
VP	ventral pallidum
VSub	ventral subiculum
VTA	ventral tegmental area

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Research Highlights

The 2010 Motivational Neuronal Networks conference took place on April 24–27.

Discussions focused on understudied brain regions involved in reward and motivation.

Topics included subthalamic nucleus, subiculum, lateral habenula, and several others.

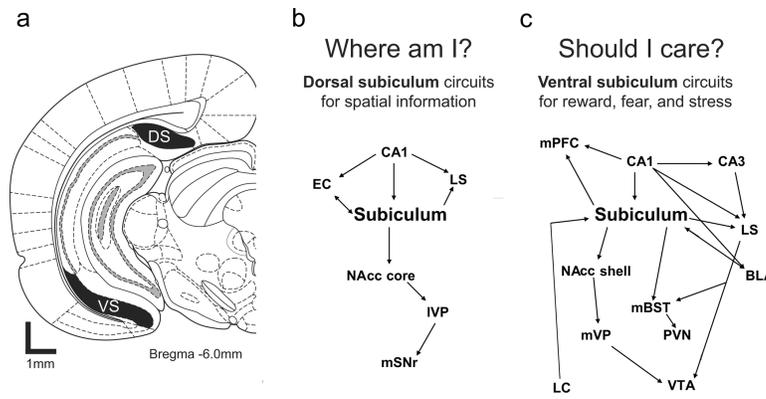These discussions are summarized in this review.

FIGURE 1.

a) Anatomical locations of the dorsal and ventral subiculum. b–c) Schematic diagram to illustrate differences in dorsal (b) and ventral hippocampal (c) connections. The dorsal subiculum (DS) helps determine spatial location, `Where am I?', whereas the ventral subiculum (VS) determines contextual relevance, `Should I care?'. Abbreviations: BLA, basolateral amygdala; EC, entorhinal cortex; LC, locus coeruleus; lVP, lateral ventral pallidum; mBST, medial bed nucleus of the stria terminalis; mPFC, medial prefrontal cortex; mSNr, medial substantia nigra pars reticulate; PVN, hypothalamic paraventricular nucleus.
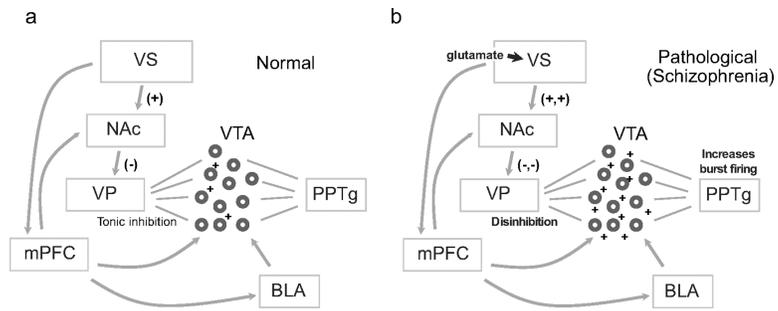
FIGURE 2.
a) Projections from the ventral subiculum (VS) to the NAcc and VP normally provide tonic inhibition of firing of ventral tegmental area dopamine neurons. b) However, when the VS is activated by glutamate injection, or is overactive as in schizophrenia, this leads to disinhibition of the VP-to-VTA pathway, allowing more VTA dopamine neurons to fire in response to pedunculopontine tegmental nucleus (PPTg) input. This ultimately increases burst firing in the VTA. This over-responsivity in VTA neurons may lend inappropriate salience to stimuli that would otherwise be irrelevant, a process that may underlie the development of psychotic delusions and ideas of reference.