

Finding motivation at Seabrook Island: the ventral striatum, learning and plasticity

The first biennial meeting* of a new society, the Motivational Neuronal Network, was held in the idyllic surroundings of the secluded and peaceful Seabrook Island, SC, USA. The purpose of the conference was to address theoretical and experimental issues relating to the structure and function of the ventral striatum and connected structures such as the prefrontal cortex and pallidum. The format was exciting and somewhat experimental: focus groups had posted questions and issues on the internet several months in advance. Issues from these message boards were addressed over the weekend by five workshops, within which scientists held round-table discussions on topics including gene regulation, physiology, neuroanatomy, behavior and psychopathology.

The format worked well and there was a positive atmosphere about the discussion generated at this meeting. Participants of the workshop system welcomed the alternative, as opposed to meetings where one has become accustomed to rushing from one poster or lecture to the next. The relatively small number of participants was consistent with the primary objective of the meeting: to promote detailed discussions among contemporaries. These discussions were less confrontational and more constructive than the discourse typically experienced following lectures at large meetings. Further, this workshop structure provided a forum for experts of distinct fields such as learning, anatomy and molecular biology to discuss and clarify specific points of agreement and disagreement. These between-field discussions also enabled a flow of novel ideas not commonly considered within the individual fields.

With the excitement engendered by this new initiative, we look forward to the next meeting of the Motivational Neuronal Network in 2002. Some of the discussions engendered within each workshop are described here.

Involvement of the ventral striatum in learning

The ventral striatum, and in particular the nucleus accumbens, has been implicated in motivation for several decades. However, its precise involvement in learning, performance, or response-selection is

imprecisely known. Converging evidence from molecular biological and electrophysiological investigations demonstrate activity-dependent plasticity within the ventral striatum and also profound effects of drugs of abuse on signal transduction mechanisms, transcription factors and gene expression, within the nucleus accumbens. Further, both LTD and LTP have been demonstrated in the ventral striatum. Discussion focused on issues related to the involvement of the ventral striatum in learning, such as whether the ventral striatum actually mediates associative processes underlying goal-directed behavior, or rather integrates associative information from various input structures and acts more specifically on the response-selection process. For example, recent behavioral research has demonstrated the involvement of the nucleus accumbens in instrumental learning, in response-choice and effort, and in the influence of Pavlovian cues on complex behavior.

An important issue raised within the discussion was to consider the neuroanatomical context within which a structure operates to understand its involvement in particular neural and behavioral processes. Further issues seen as critical to our understanding of ventral striatal function were: the ways in which it would be possible to dissociate learning from response processes, the nature in which the accumbens actually handles information, the functional differences between the core and shell subregions of the nucleus accumbens and the different results that alternative techniques produce (e.g. dialysis versus electrophysiology and permanent lesions versus transient inactivation techniques). During the workshop it became clear that the nucleus accumbens is involved in both appetitively and aversively motivated behavior, although such an involvement might not necessarily be symmetrical. Further, the core subregion of the nucleus accumbens appears to underlie learning- or conditioning-dependent behavior, whereas the shell subregion might provide an unconditioned or primary motivational influence on behavior. Finally, choosing or switching between competing behaviors is an important role of striatal function. In the dorsal striatum this might apply to motor activity as a whole, whereas in the ventral striatum it applies to motivationally significant behavior.

Dopamine-glutamate interactions in the ventral striatum

The ventral striatum is innervated by converging afferents originating in the prefrontal cortex, basolateral amygdala, hippocampal formation and various thalamic nuclei. These pathways are all thought to be glutamatergic and provide the excitatory drive necessary to trigger firing activity in ventral striatal neurons. In addition, the ventral tegmental area supplies a dense dopaminergic input that has been implicated in drug addiction and other neuropsychiatric disorders. Research is directed towards interactions between glutamate and dopamine as well as the plasticity of both transmitter systems.

Although dopamine attenuates glutamatergic inputs to the ventral striatum, it is not thought to shutdown all such inputs indiscriminately. Instead it has been suggested that it might regulate which input gains access to the ventral striatum in favor of others. For example, dopamine might play a role in 'gating' of hippocampal versus amygdaloid inputs as they enter the striatum and activate different ensembles of neurons. In addition, by modulating protein kinase A-mediated signal transduction, dopamine can affect the biochemical machinery of ventral striatal cells without direct physiological manifestations. Conversely, there is also evidence that glutamate can modulate dopamine-mediated transmission. For instance, metabotropic glutamate receptors mediate an inhibition of dopamine release. Thus, current evidence suggests that negative reciprocal interactions between glutamatergic and dopaminergic afferents exist. Because of the multi-faceted-action spectrum of dopamine, further research is required to determine how its actions at the cellular level affect cortico-striatal network activity during ongoing behavior.

There is a growing interest in the involvement of dopaminergic and glutamatergic input in long-term plasticity, either in the context of learning or in maladaptive processes such as drug addiction. Although both LTP and LTD can be induced in cortico-ventral striatal pathways, LTP induction at least, has been shown to depend on NMDA-receptors. Although pioneering studies suggest a role of ventral striatal NMDA-receptors in instrumental conditioning, further behavioral research is needed to determine the precise components of behavior that involve these receptors and the causal role of LTP in this type

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of learning. *In vivo* electrophysiological evidence in the ventral tegmentum suggests that, during conditioning, plasticity in the circuitry afferent to dopamine neurons might mediate a temporal shift in their firing activity. This shift occurs when, during conditioning, the impending reward becomes more predictable and hypothesizes that dopamine neurons might code an error in the prediction of reward. The important implications of this hypothesis remain to be tested.

The binding problem and motivation

Binding, a term derived from research into visual perception, refers to the association of information for perceptual unity. This workshop considered whether a similar process underlies the unification of motivational information; motivational state is temporally consistent and guides ongoing goal-directed behavior. The theoretical discussion of motivational binding was highly speculative because there is little direct evidence for the nature of this process.

Nevertheless, the workshop addressed how the brain might carry out such a process and whether the ventral striatum would be involved. A crucial question relates to what sort of information needs to be bound for motivational unity. The suggestion that cortico-ventral striatal circuitry contributes to this process is consistent with anatomical and behavioral data. For example, there is a large visceral and somatic representation within the prefrontal cortex and both medial and orbital prefrontal cortices appear to be critical for the process by which motivational information guides behavior, which might occur through interaction with the striatum. Information from different modalities must be integrated, though the level of information processing which this corresponds to is unknown. Information from separate modalities may be funneled through cortico-striatal circuitry, which would ultimately enable a final common pathway of bound perceptual and motivational information. For example, species-specific behaviors appear to involve similar neural systems including the ventral pallidum.

Ultimately, experiments need to be devised to explore the existence and nature of motivational binding. For example, the demonstration of motivation-related 'illusory conjunctions' would be an intriguing foundation.

Defining the extended amygdala

The idea of the 'extended amygdala' was debated from an anatomical perspective. In part, the definition of the extended amygdala depends on the meaning of 'amygdala'. Older descriptions of the amygdala as a unitary structure have been challenged for

some time by the recognition that related, yet distinct, nuclear groups make up this brain region. The central amygdaloid nucleus is unique because its lateral aspects are composed of medium spiny neurons, and thus are considered 'striatal-like'. In the concept of the extended amygdala, the entire central nucleus forms a continuum through the basal forebrain to the bed nucleus of the stria terminalis.

Active debate centered on whether the extended amygdala should be considered as an anatomic and functional 'macrostructure', or whether it would be better to consider this forebrain continuum as 'extended striatum'. Histochemical and cytoarchitectural data have been used to distinguish the striato-pallidal system from the extended amygdala, but are only a first step in determining the functional boundaries of these two systems. Indeed, transitional regions exist between the two systems. It was agreed that more work is required to determine the anatomic pathways associated with specific parts of the extended amygdala, and the extent to which it is or is not 'striatal-like'.

One major concept raised was that although many basal forebrain structures receive similar inputs, their outputs are fundamentally different. Striatal structures participate in cortico-striato-pallido-thalamic loops. On this basis, the shell of the nucleus accumbens is considered striatal, and not part of the extended amygdala. By contrast, a distinguishing feature of the central extended amygdala, including the central nucleus and bed nucleus of the stria terminalis, is a projection to the caudal brainstem. However, parts of the extended amygdala such as the lateral-most portions of the central amygdaloid nucleus might not strictly follow this efferent pattern. Delineating the efferents of specific central nucleus subdivisions and their 'extended' components in the forebrain should help elucidate separate anatomic and functional systems. The point was raised that recent behavioral and physiologic studies show that discrete portions of the extended amygdala are likely to be associated with specific functions.

Drug-associated learning and plasticity

The question of whether changes involved in addiction are representative of learning and plasticity is related to tenets of 'incentive motivational' theories of addiction. Specifically, it is proposed that compulsive and uncontrollable drug seeking, the primary symptoms of addiction, are attributable, at least in part, to acute drug actions or to drug-induced plasticity in brain regions involved in natural learning. Drug effects on learning pathways are hypothesized to generate 'exaggerated'

incentive learning and a hyper-responsiveness to conditioned drug-associated stimuli. Consistent with the learning theory, the neural circuitry that contributes to drug-taking behavior overlaps with the circuitry that is important to certain types of natural learning. In particular, the nucleus accumbens and its dopaminergic, limbic (e.g. amygdala) and cortical afferents contribute to behavior acquired as a consequence of either natural or drug reinforcement.

By contrast, functional and physiological dissociations appear to exist between the contributions that the shared circuitry makes to behavior controlled by drug and natural reinforcers. For example, ventral striatal neurons are necessary for the maintenance of drug-reinforced instrumental behavior but not for behavior maintained by natural reinforcers. Moreover, although elevations in dopamine are associated with both types of reinforcers, the increases vary in magnitude, regional distribution and relation to phasic firing of dopamine neurons. Workshop participants reported that behaviors associated with natural reinforcers include reinforcer- and species-specific behaviors that are regulated by reinforcer-specific negative feedback (i.e. satiety) mechanisms; the same is not true for drugs. In addition, addictive drugs have varied and non-specific pharmacological effects that are unrelated to neural events associated with natural reinforcers.

The discussion emphasized that differences between the effects of drugs and natural reinforcers on the brain might hold important keys to the etiology of addiction. As was the case in other workshops, it was agreed that successful discussion and investigation of ventral striatal function hinges on rigorous and uniform definitions of behavioral terminology. Although drug-dependent plasticity within the nucleus accumbens was not considered in detail, participants noted that there is evidence of drug-induced sensitization to certain effects of addictive drugs. Whether this sensitization contributes to addiction remains to be determined. How neural plasticity might engender the selective increase in drug-seeking behaviors characteristic of addiction is also an open and largely unexplored question.

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