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Translating striatal activity from brain slice to whole animal neurophysiology: A guide for neuroscience research integrating diverse levels of analysis

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Abstract

An important goal of this review is highlighting research in neuroscience as examples of multilevel functional and anatomical analyses addressing basic science issues and applying results to the understanding of diverse disorders. The research of Dr. Michael Levine, a leader in neuroscience, exemplifies this approach by uncovering fundamental properties of basal ganglia function and translating these findings to clinical applications. The review focuses on neurophysiological research connecting results from *in vitro* and *in vivo* recording. A second goal is to utilize these research connections to produce novel, accurate descriptions for corticostriatal processing involved in varied, complex functions. Medium spiny neurons in striatum act as integrators combining input with baseline activity creating motivational ‘events’. Basic research on corticostriatal synapses is described and links developed to issues with clinical relevance such as inhibitory gating, self-injurious behavior and relative reward valuation. Work is highlighted on dopamine-glutamate interactions. Individual medium spiny neurons express both D₁ and D₂ receptors and encode information in a bivalent manner depending upon the mix of receptors involved. Current work on neurophysiology of reward processing has taken advantage of these basic approaches at the cellular and molecular level. Future directions in studying physiology of reward processing and action sequencing could profit by incorporating the divergent ways dopamine modulates incoming neurochemical signals. Primary investigators leading research teams should mirror Mike Levine’s efforts in ‘climbing the mountain’ of scientific inquiry by performing analyses at different levels of inquiry, integrating the findings and building comprehensive answers to problems unsolvable without this bold approach.

Keywords

Basal ganglia; Dopamine; Inhibitory gating; Motivation; Reward; Self-injurious behavior

My initial work on basal ganglia (BG) function and physiology included examining animal models of BG pathology leading to hyperkinetic movement (Cromwell and Berridge, 1993; 1997). Our work showed that choreiform-like symptoms following striatal lesions were

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expressed dependent upon sensory input and even more interesting, the hedonic or aversive quality of the sensory input (Berridge and Cromwell, 1990; Cromwell and Berridge, 1994). This early work on functional heterogeneity of striatopallidal subregions (Cromwell and Berridge, 1996) ignited an interest in me to study basic basal ganglia physiology, and at the time, there was only one research team with the type of experience and focus on this topic that met my keen interests in basal ganglia function, Mike Levine's research group at the Mental Retardation Research Center (MRRC) at the University of California at Los Angeles (UCLA). Research completed between the early 1970s through the early 1990s with pioneers such as Nathaniel Buchwald and Chester Hull significantly raised the threshold for quality work on BG physiology and function (Buchwald et al., 1979; Levine et al., 1996). The joint work over several decades captured developmental aspects, basic pharmacology and detailed physiological aspects of striatal function (see related articles in this volume) continuing to the present day. Joining this group and working in the laboratory supervised by Mike, I came to understand and appreciate basal ganglia neurocircuitry at a reduced, detailed level, and we completed projects that set the foundation for current studies on the role of BG neurochemistry and physiology in neurological diseases (Gardoni and Bellone, 2015).

The goals of this review include providing an overview of pioneering work on BG neurophysiology that set the stage for contemporary studies and highlighting several examples of research projects that established links cross a broad scale, from basic neurophysiology to clinical approaches. Mike Levine has been involved in many of these type of projects, and this review focuses on a few examples with an emphasis on the studies which focused on corticostriatal synaptic interactions, and how this synapse can be significantly modified by incoming dopamine. Another goal is to bring the research forward to contemporary work using *in vivo* electrophysiology in awake, behaving animals (Webber et al., 2016; Cromwell et al., 2018). There is value in linking the diverse levels of analysis on BG function between reduced cellular analysis to a more holistic behavioral level, and several research teams have made these types of leaps productively (Buzsáki and Tingley, 2018; Hikosaka et al., 2018; Calabresi et al., 2016). Our recent research focus has been on relative reward valuation (Binkley et al., 2014; Ricker et al., 2016; Ricker et al., 2017) and incorporating basic information on dopamine modulation of incoming neural signals could provide the information base necessary for rapid plasticity that leads to changes in motivation sensitive to shifts in reward value from trial to trial (Webber et al., 2015).

Basal Ganglia System: Function and Dysfunction

The BG system includes the subcortical structures of the striatum, globus pallidus and the substantia nigra. Other structures intimately connected with the BG system include the subthalamic nucleus, amygdala and the pedunculopontine nucleus (Nowacki et al., 2018; Pelloux et al., 2014; Kelley, Domesick & Nauta, 1982; Lee, Rinne, & Marsden, 2000). Each of these brain regions has well demarcated subregions and each subregion has a set of distinct connections that make it unique from adjacent subregions. The striatum is comprised of three well-recognized major subregions: the caudate nucleus, the putamen, and the ventral striatum or nucleus accumbens. The pallidal region has medial (i.e., internal segment), lateral (i.e., external segment) and ventral subregions; and the substantia nigra contains two main subregions: the pars compacta and the pars reticulata. This set of BG structures

comprises the largest subcortical system in the brain, and its complex connectivity and internal structure have made it extremely difficult to address questions about its functional nature. It is clear that the system participates in numerous non-motor functions that include motivational and emotional processing that involves integrating internal and external information (Schneider & Lidsky, 1981; Berridge & Cromwell, 1990; Salamone et al., 2016; Ferrazzoli et al., 2018).

The general idea of functional heterogeneity was not the original concept linked to the BG system as frameworks were adopted from neurology and movement sciences that focused on explanations for functional deficits in patients with localized damage to the system. From this historical viewpoint, it was emphasized that the system had a uniform motor function, mainly involved in movement generation, initiation or in postural control (Wilson, 1914; Carpenter, 1966; Martin, 1977). Wilson (1914, p. 478) stressed this point in writing, “When we remember the histological simplicity and comparative structural homogeneity of the corpus striatum, in contrast with the greater dimensions, much more intricate cytoarchitectural complexity, and far wider connexions of the rolandic motor cortex, the idea of attributing all of the disturbances to striatal disease and of crowding corresponding centers into that ganglion becomes nothing short of ludicrous.”

Modern neuroscience has been increasingly adding diverse functional centers into the BG system, making the system comprised of many, possibly separable subfunctions. The initial impetus for the attribution of functional heterogeneity came from the realization that the anatomy of these structures was not so simply homogeneous (Tepper et al, 2018; Haber, 2016; Berridge, 2019; Mensah, 1977; Kemp & Powell, 1970). Traditional tract-tracing methods (Nauta & Gygax, 1954, Heimer & Wilson, 1975) and histochemical identification (Falck, Hillarp, Theme & Torp, 1962; Lindvall & Bjorklund, 1978) revealed that the BG system contains diverse inputs and outputs from all regions of cortex and subcortical areas, and neurochemical patterns distributed in a topographic fashion.

Current models for BG function highlight parallel circuits each with a specified functional capacity (Kim and Hikosaka, 2015). In addition, current ways of thinking often incorporate the idea that within each circuit there are two main paths, one direct and one indirect that have been proposed to operate in qualitatively distinct ways (MacPherson et al., 2014; Hikosaka et al., 2018). Moreover, the individual paths have unique properties that include the neurochemical phenotype and the receptor subtypes that localize onto the specific neurons that receive and integrate incoming information. These characteristics have remained core aspects guiding research on BG functional neuroanatomy for decades (Albin et al., 1989; Alexander et al., 1990). A part of the legacy of work by Levine and colleagues was uncovering ways that the traditional models were not completely accurate, and that functional neuroanatomy of BG contains interactions not matching the guidelines of the traditional neuroanatomical arrangement (Cepeda et al., 1993; Levine et al., 1996).

Cortical modulation of striatal activity

One critical feature of the BG network is the size and scope of the cortical input (Webster, 1965; Kemp & Powell, 1971; Haber, 2016). The cortical to striatal projection is massive

with an estimation of some 380,000 cortical axons innervating the volume of a dendritic tree of a single neuron located within the striatum (Kincaid, Zheng & Wilson, 1998). This immense projection is coupled by a great diversity of incoming projections. At a systems level, neuroanatomists have found corticostriatal connections emanating from every cortical region, including the more ancient allocortex characterized with only 3 layers (McGeorge & Faull, 1989).

A topographic map of the projections arising from cytoarchitectonically distinct areas of cortex has been uncovered using anatomical tracing (Selemon & Goldman-Rakic, 1985) as well as physiological mapping (Brown, 1992; Brown, Hand & Divac 1996; Brown, Smith & Goldbloom, 1998). Brown and colleagues (1992; 1996; 1998) used somatosensory stimulation of the forelimbs, hindlimbs and trunk to demonstrate that a map existed for these body parts in the lateral striatum. Similar to the overlying sensory and motor cortex, the body map has the facial body parts of mouth and snout in the more ventral areas and the forelimbs and hindlimbs are represented in the more dorsal areas. Carelli and West (1991) also found similar topographical inverse mapping for both motor and sensory information using *in vivo* neurophysiology of single neuron activity. A body homunculus representation has also been found in the cat (Malach & Graybiel, 1986) and both human and nonhuman primates (Gerardin, Lehericy, Pochon, du Montchel, Mangin, Poupon, Agid, Biban & Marsault, 2003; Alexander & DeLong, 1985). Selemon and Goldman-Rakic (1985) elegantly showed that the configuration of the cortical topography from association areas in the frontal, temporal and parietal lobe could be described as a longitudinal arrangement with a series of interdigitating strips running along the anterior-posterior extent of the caudate, putamen and ventral striatum. Finally, recent mapping using functional magnetic imaging in humans has supported this earlier work by showing that connected regions during resting state depend upon functional links between cortex and striatal subareas (Jaspers et al., 2017; Jung et al., 2014; Choi et al., 2012). At the cellular level, evidence supports a massive heterogeneity of synaptic input from cortex to individual medium spiny neurons (MSNs) in striatum (Zheng and Wilson, 2002) and a driving force from the complex combination of inputs from diverse regions of cortex (Wilson, 2009). The impact of synaptic inputs onto striatal cells is dependent upon baseline activity and the complement of ion channels and intrinsic signaling processes of individual MSNs (Wilson, 2017). The present review mainly focuses on the MSNs that have projections to pallidal and nigral regions but it is certainly the case that all the synaptic plasticity and local circuitry is heavily dependent upon local, intrinsic interneurons that also receive an dense input from cortex and thalamus (Assous and Tepper, 2019).

A long-term research goal of the basal ganglia physiology group that included Mike, Nat Buchwald, Chester Hull and many other prominent neuroscientists at the Mental Retardation Research Center at UCLA was to determine how the corticostriatal connection developed and what the basic physiological properties of the connection were (Buchwald et al., 1967; Buchwald et al., 1969; Hull et al. 1970). The input from cortex to striatum utilizes glutamate and acts on numerous receptors located on the most prevalent striatal cell-type, the medium-sized spiny projection neuron (McGeer, McGeer, Scherer, & Singh, 1977). These glutamate receptors are varied and include N-methyl-d- aspartate (NMDA) and non-NMDA subtypes (Cepeda, Walsh, Buchwald, & Levine 1991a; Cepeda, Peacock, Levine, & Buchwald,

1991b). Having such a large excitatory input arriving to the BG makes the system susceptible to excitotoxic damage caused by dysregulation of glutamate receptor function at the level of the striatum. BG pathology is consistently linked to a large set of developmental and neurodegenerative disorders thought to be partially caused by developmental or chronic excitotoxic reactions in the brain. Glutamate receptors appear early in the development of the brain with populations of striatal neurons expressing different types of glutamate receptors within the second week of life in the rat (Nansen et al., 2000). These glutamate receptors are functional early in the developing rat and cat (Colwell, Cepeda, Crawford, & Levine, 1998; Cepeda, Walsh, Buchwald, & Levine, 1991). Interestingly, compared to glutamate responses in the adult animal, the developing animal has enhanced evoked potentials following local stimulation (Siviy, Buchwald, & Levine, 1991). Thus, overstimulation of the glutamate receptors can produce excitotoxic damage including cell loss and altered connectivity (Brunsen, Khanna, Cromwell, & Cohen 2001). This early development of the massive corticostriatal glutamate input as well as the enhanced responsivity to glutamate during development could leave the striatum as well as other BG structures particularly vulnerable to damage early in life. Several studies have found a high susceptibility of BG structures to hypoxia and ischemia, complications that may be seen during birth and that have been thought to be related to the etiology of some developmental disabilities (Pastuszko et al., 1993; Mallard, Waldvogel, Williams, Faull, & Gluckman 1995; Toft, 1999). Neurotoxicity associated with hyperbilirubinemia, another cause of developmental disability, also appears to be mediated by glutamatergic mechanisms (McDonald, Shapiro, Silverstein, & Johnson, 1998; Grosjean, Kozziel, Vert, & Daval, 2000). Similar neurotoxic mechanisms have been postulated to play a role in the progressive cell death seen in neurodegenerative BG disorders such as Huntington's and Parkinson's disease (Lancelot & Beal, 1998).

Effects of cortical damage on striatal activity

Exploring how the cortical input compared to and interacted with other inputs has been a key focal point of previous research and this included an in depth examination of thalamic inputs onto different classes of striatal cells (Lidsky et al., 1976; Cherubini et al., 1979). Damage to specific regions of neocortex, thalamus or midbrain has been clearly shown to alter local evoked potentials or behavioral responses and neuron numbers in striatum (Schonfeld et al., 2017; Marklund, 2016; Loopuijt et al., 1997; Scatton et al., 1982). This previous work had significant implications for understanding the pathology of several neural disorders including epilepsy, stroke, traumatic brain injury and diverse neurodegenerative diseases. For the earliest work, *in vivo* neurophysiology was a standard procedure and findings supported a clear corticostriatal force that mediated medium spiny cell activity, regulating firing rate and burst activity (Buchwald et al., 1973). A combination excitatory postsynaptic potential (EPSP)-inhibitory postsynaptic potential (IPSP) sequence was the most frequent response found with a shorter duration excitation (5–50 msec) and longer lasting inhibition (200–300 msec). The most frequent site of stimulation was precruciate cortex and subregions of the thalamus (e.g., centromedian and parafascicularis nuclei) with direct axonal connections to neurons in the caudate nucleus (Figure 1). These early studies suggested a rapid 'pure' synaptic driven excitation followed by an inhibitory period possibly

caused by activation of inhibitory interneurons surrounding the neuron being recorded. These potent intrastriatal connections have been supported by more recent work (Tepper et al., 2004). Removing cortical input was predicted to lead to an inhibitory profile with reduced or absent evoked depolarizing postsynaptic potentials (DPSPs) and lower levels of spontaneous activity. Instead, early studies found a mix of excitatory and inhibitory influences. For example, alterations included slower spontaneous activity yet increasing action potential frequency (Levine et al., 1982). Partner papers examined interesting sensorimotor consequences of these ablations, leading to the early ideas that corticostriatal connections were crucial for complex sensorimotor integration (Levine et al., 1978). In primate models, precentral cortical lesions led to an increase in baseline activity but a decrease in the number and frequency of bursts (Aldridge et al., 1990; Aldridge and Gilman, 1991). Several studies have supported the idea that altering corticostriatal connection reduces variability in striatal neuronal activity (Aldridge et al., 1990; R dulescu et al., 2017). The predicted straightforward reduction in activity was not the primary outcome in several studies and this led to the formulation of the ideas that these striatal cells could actually be ‘released’ in some forms after neocortical damage and possibly ‘driven’ by other afferents besides the massive cortical input. Several candidates for post-cortical lesion plasticity have been proposed. Early work by Buchwald and colleagues supported a strong role for thalamic afferents arising to the striatum (Buchwald et al., 1973; Cherubini et al., 1979). Recent work has focused on this thalamostriatal pathway as another modulator of distinct cell types within the striatum. For example, subregions such as the parafascicular and medial part of the posterior nuclei have been proposed to play distinct roles in mediating behavioral habit formation by regulating or ‘gating’ sensory information flow in dorsolateral striatum (Alloway et al. 2017).

Interrelated with the ideas of post-cortical lesion plasticity was the notion that intrinsic circuits within the striatum played a key role in modulating local DPSPs. It is clear that acetylcholine (ACh) receptor agonists can modulate glutamate responses in the striatum (Sabatino et al., 1999). Using iontophoretic application of carbachol, a cholinergic agonist, significantly increased NMDA-mediated responses in medium spiny cells *in vitro*. The potency and valence of this ACh mediated impact on MSN has been highly debated, possibly subsets of cholinergic neurons have potent effects depending upon the combination transmitter co-release (Trudeau and Mestikawy, 2018). The impact of neocortical ablations on locally evoked synaptic potentials of MSNs has been explored in detail (Cromwell and Levine, 1996). Surprisingly, there was no significant difference between DPSP amplitude or duration between controls and slices from neocortical lesion group. A significant difference was found when the responses were examined in Mg^{2+} -free solution as the control DPSP was enhanced while the MSN from the cortical ablation group was not significantly changed. 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), a non-NMDA receptor antagonist blocked the DPSP in controls but was ineffective in the decorticate experimental group tissue. The compound effective in reducing the DPSP in experimental group was hexamethonium, a nicotinic receptor antagonist and the effect was selective for the experimental group compared to controls (Figure 2). These findings led to the hypothesis that local cholinergic neurons could be substituting for extrinsic glutamate following cortical ablations (Cromwell and Levine, 1996). Current work has explored similar ideas and the

local plasticity of MSN firing has been found to be much greater than previously thought in the brain slice preparation from typical tissue as well as after alteration in brain connectivity or physiology (Giordano et al., 2018). Furthermore, recent work has pinpointed significant contributions of acetylcholine interneurons influencing thalamostriatal activity and found applications to better understand the neuropathology of Parkinson's disease (Li and Daur, 2019; Tanimura et al., 2019). Behavioral work on the decorticate rat pointed to substantial changes following the damage (Villablanca et al., 1976; Whishaw et al., 1981) but also suggested that subcortical areas could compensate for complex behaviors involved in social interactions (Whishaw et al., 1985; Pellis et al., 1992). Different classes of MSNs uniquely depend upon cortical versus thalamic afferents with a subset receiving converging input as predicted by the earlier neurophysiological studies. Newer anatomical methods are able to tease apart these phenotypes based on connectivity in more precise detail (Huerta-Ocampo et al., 2014).

Facilitation and inhibition in striatum: Paired pulses to sensory gating

A primary research question involves understanding how patterns of inputs alter neural activity and more interestingly, how inputs arriving from diverse brain regions interact as combinations of synaptic input. Some of the earliest, most elegant work on the question came from the laboratory at UCLA by using temporally and spatially integrated input to striatum from cortex, thalamus and substantia nigra (Hull et al., 1973). Cortical evoked EPSPs in caudate were enhanced with coincident thalamic or nigral stimulation while a cortical evoked IPSP could reduce EPSPs evoked from other regions. An often used test for externally guided presynaptic excitation and convergence of inputs is rapid paired-pulse (PP) facilitation (Bueno-Junior and Leite, 2018; Blomeley et al., 2015; Akopian and Walsh, 2007). The mechanism occurs due to accumulation of Ca^{++} ion in the presynaptic neuron leading to greater release of neurotransmitter on subsequent stimulation (Robles Gómez et al., 2018; Akopian and Walsh, 2002). The time intervals for this effect are rapid with main effects occurring using 10 ms intervals between pulses. This example of short-term plasticity most likely occurs pervasively and continuously and plays a major role in information processing of inputs as a form of temporal summation (Anwar (Nadim) et al., 2017). The paired facilitation effect has been thoroughly studied using the *in vitro* slice technique with well controlled stimulation parameters (Pofantis et al., 2015; Akopian et al., 2000). How would decortication impact this synaptic plasticity? Not surprisingly, paired-pulse facilitation was significantly diminished (Cromwell et al., 1995). Lesions including primary motor and sensory cortices as well as supplementary motor area led to a significant reduction in PP facilitation using 10 ms interpulse intervals and even led to a subset of cells (4/18) expressing PP depression, something unobserved in the control MSN population at this time interval (Figure 3). Surprisingly, dopamine-depleting lesions did not have the same effect. Animals with 6-OHDA mediated dopamine depletion displayed normal PP facilitation. Animals with thalamic lesions also displayed normal PP facilitation pinpointing the cortical inputs massively arising to the MSN as the key synaptic input for this rapid temporal summation effect on DPSPs. Using longer intervals completely different effects can be obtained. Several groups have expanded work on LTP and LTD finding these effects of plasticity in striatal circuits and expressed by single striatal neurons (Calabresi et al.,

2016). The work has moved to examining effects of external paired sensory stimulation on striatal and cortical responses. This related field examines the short-term plasticity of sensation-induced inhibitory gating (IG).

In clinical neurophysiology a paired pulse or two-tone paradigm has been used to test inhibitory function in clinical disorders such as schizophrenia, post-traumatic stress disorder, obsessive compulsive disorder (OCD) and addiction (Adler et al., 1982; Adler et al., 2001; Boutros et al., 2004; Olincey et al., 2000; Neylan et al., 1999; Jessen et al., 2001; Stojanov et al., 2003; Rossi et al., 2005). It was found that patients with these disorders have defective inhibition of the neural response that follows an identical initial or “conditioned” response. This defect in inhibiting the second or “test” response has been thought to reflect a breakdown in rapid sensory processing and has been shown to be related to the symptoms of schizophrenia such as working memory deficits and negative symptomology (Cullum et al., 1993; Louchart de la Chapelle et al., 2005). IG has been examined using chronic microwire implants located directly in specific brain structures or even simultaneously in multiple brain regions. Long-term simultaneous single unit and local field potential (LFP) recording has allowed us to examine the stability of gating over several days and across different motivational states. We have recorded these signals from the amygdala, striatum, medial prefrontal cortex (mPFC) (Cromwell et al., 2007; Mears et al., 2006) and midbrain dopamine cell region (Anstrom et al., 2008). Medial prefrontal cortex had the highest proportion of single units displaying the gating of activity using a 500 ms interstimulus interval. Regions of basal ganglia were more variable with midbrain putative dopamine cells not expressing the inhibitory phenomenon and striatal units being mixed with a subset ‘gating’ while others showed identical responses even after 100s of trials (see Figure 4). The majority of research on this inhibitory mechanism emphasizes sensation as the key influence and inhibitory trigger (Moxon et al., 2001). Our previous work decoded other factors including emotional and motivational influences that modulated the inhibitory process (Cromwell et al., 2009). An acute stressor of saline injection led to an increase in the amplitude of the existing neural responses to tones (Cromwell et al., 2005; Cromwell et al., 2007). IG was actually strengthened meaning that the increase in the amplitude was primarily during the initial tone response and less during the subsequent ‘test’ tone presentation. Other motivational state manipulation such as hunger led to a weakening of IG found in single unit records but an enhancement of gating from LFPs (Cromwell et al., 2007). This is another example of how intrinsic processes can alter the degree of inhibitory control. Finally, in the basal ganglia region of the striatum, movement led to enhanced gating in the local single units suggesting that during exploration animals are better at discriminating repetitious information leading to better accuracy for novel stimuli. Initial work using *in vitro* slice methods and voltage clamp analysis of DPSPs during paired pulses contributed to the later development of experiments predicting inhibition and relying on incoming afferents to striatal intrinsic circuitry (Assous and Tepper, 2019) to produce effective modulation especially feedforward inhibition of neural responses. The nicotinic receptor plays a key role in this inhibitory mechanism. Nicotine administration improves gating by single units in amygdala in freely moving rats (Cromwell et al., 2005). Nicotine restores SG that has been impaired by previous amphetamine administration and this improvement is blocked by central delivery of d-tubocurarine (Cromwell and Woodward,

2007; Stevens et al., 1995). It is interesting that cholinergic mechanisms within striatal networks play key roles in mediating synaptic activity at the cellular level and action potential firing rate dependent upon local inputs. The insights from the *in vitro* neurophysiological analysis of cortical damage and the influence on paired pulse facilitation led to the insights that aided the development of work on *in vivo* inhibitory gating (Cromwell et al., 2009; Cromwell and Atchley, 2014). The work at different levels of analysis informed each other in unique ways setting up a new way to view BG function as unique from other structures and highly interdependent upon afferents including the neocortex in regulating rapid plasticity reflected by short-term changes in regulation of synaptic strength and action potential firing rate.

Translating among levels of inquiry: Dopamine-glutamate interactions and self-injury

In collaboration with Dr. Bryan King, a pediatric psychiatrist, multi-level research focused on the brain basis of self-injurious behavior (SIB; Cromwell and King, 2004). Previous work showed that SIB or stereotyped movements could involve striatopallidal processing. Lesions of the striatopallidal complex in the rat led to alterations in action sequences involved in general locomotion (Sanberg, Pisa, & Fibiger, 1979) forepaw use (Pisa, 1988; Whishaw, Funk, Hawryluk, & Karbasheski, 1986), taste reactions (Cromwell & Berridge, 1994) and grooming (Cromwell & Berridge, 1996). Hyperactivity occurs following lesions to the pallidal regions with a concomitant decrease in other specific actions such as scratching, sniffing, rearing and grooming (Norton, 1976; Cromwell and Berridge, 1997). SIB can be highly debilitating and lead to self-harm involving biting behavior directed at the fingers and limbs (King et al., 2014). The extreme form is observed in children with severe mental retardation and treatments were very ineffective leading to restraint being used as the main route to stop the self-injury. A series of studies was completed using the pemoline-induced model of self-injury and moved from brain slice to whole animal pharmacology, finally translating to clinical trials using new compounds to target the debilitating behavioral impairment. Beginning with recording from neurons in brain slices obtained from animals while emitting pemoline-induced self-injury, we targeted alterations in corticostriatal circuitry (Cromwell et al., 1997). Recording from brain slices taken from rats who had emitted SIB provided us the groundwork to target dopamine-glutamate interactions involved in this behavior. We found neurons from rats that received the vehicle or that had received pemoline but had not engaged in self-injury, dopamine (DA, 20 microM) application produced a significant decrease in the size of the cortically evoked neostriatal DPSP. The opposite effect was obtained from neurons from rats which had received pemoline and had engaged in self-injury. These responses were actually enhanced by dopamine. There is a shift in the way dopamine modulates the glutamate signal coming to the MSN in striatum and the balance is shifted to over-excitation and possible excitotoxicity in different brain regions (King et al., 1998). Pre-treatment of animals with a glutamate receptor antagonist, MK-801 reduced or prevented self-biting seen after pemoline injection (King et al., 1993). Similar findings have been noted when examining self-biting in the 6-OHDA model (Criswell, Johnson, Mueller, & Breese, 1993). The enhancement seen in the brain slice *in vitro* recording could be blocked by pretreatment with the competitive N-methyl-D-aspartate

receptor antagonist, 2-amino-5-phosphonopentanoic acid. We knew from previous work that pemoline-induced SIB was related to a long-lasting dopamine release. Work in whole animal had found that pemoline injection led to ipsilateral rotation after unilateral 6-OHDA lesions (Cromwell et al., 1996). It seemed that the bolus injection of pemoline diffused slowly over time and led to long-term enhanced dopamine release. From the work using the brain slice method, we moved to examine the impact of cortical lesions on the SIB. We observed that bilateral frontal cortical lesions both decreased self-biting latency and increased the incidence of pemoline-induced self-biting behavior, leading to a much greater level of SIB (Figure 5; Cromwell et al., 1999). These findings are similar to other data demonstrating cortical lesions enhance amphetamine-induced behavior (Iversen, 1971; Braun et al., 1993), and are of particular interest given that individuals with cortical pathology (such as in severe and profound mental retardation) are more likely to exhibit self-injurious behavior (King, 1993). Discussing these findings, it was noted that small cortical ablations not decortications were used. In these cases, the cortical damage can lead to compensatory changes both locally and globally. One finding of interest was that glutamate receptors were found to be upregulated in striatum following cortical ablations (Wullner et al., 1994). Additionally, pemoline administration has been found to alter dopamine receptor subtypes specifically decreasing D₂ receptors within striatal subregions (McColl and Rice, 1962). These findings support the idea that cortical glutamatergic influences are critical in the mediation of self-injurious behavior and the massive corticostriatal projection could be one of the pathways involved in this influence.

This particular set of research studies is a fine example of dissecting a problem and utilizing different approaches to answer key questions. The team initially examined how striatal activity using *in vitro* approaches was altered during the expression of the SIB. Combining this with detailed behavioral analysis and an exploration on the impact of altering neural circuit processing in the whole animal. Additionally, neurochemical profiles were developed to match the behavioral expression of SIB and the culmination of this work led to clinical trials based upon the set of findings (King et al., 2000; Schroeder et al., 2001). For example, lamotrigine was used effectively to reduce SIB in children (Davanzo and King, 1996) and this approach would not have been used had it not been for this basic research. Currently similar approaches are being explored and the general model the involves glutamate excitotoxicity is a large part of the neural model for pathological changes in neurodegenerative diseases (Raymond et al., 2011; Abdijadid et al., 2015 and related articles in this volume).

Dopamine-glutamate interactions: Possible influences on relative reward valuation

One of the most influential basic research findings from the laboratory focused on uncovering the complex relationship between dopamine and glutamate receptors and working out the details for how dopamine modulated responses evoked by excitatory amino acids (e.g., initial work in human neocortex; Cepeda et al., 1992). A highly influential paper using microphoretic application of dopamine compounds found that the direction of dopamine's (DA) ability to modulate neostriatal neuronal responses depended upon the

subtype of receptor activated. DA potentiates responses mediated by activation of N-methyl-D-aspartate (NMDA) receptors, but attenuates responses mediated by activation of non-NMDA receptors in neostriatum (Cepeda et al. 1993). The next step was to examine whether this differential modulation also applies to components of synaptic responses evoked by electrical stimulation of neostriatal afferents and mediated by activation of specific subtypes of EAA receptors (Levine et al., 1996). The work used brain slices and found that responses mediated by NMDA receptors were potentiated by DA while those mediated by non-NMDA receptors were attenuated. The specific subtype of EAA receptor activated was crucial to the direction of effect. The group extended the study to examine specific dopamine receptors. The increase of NMDA receptor-mediated responses was obtained by application of SKF 38393, a D₁ receptor agonist. It was one of the initial observations of this dramatic D₁ receptor mediated effect. Conversely, D₂ agonist (quinpirole) consistently attenuated responses mediated by activation of non-NMDA receptors. These initial findings could explain quite a lot in terms of the variable effects of dopamine on glutamate responses and could aid in understanding dopamine subtype specific effects in other brain regions. Early work suggested that the similar effects were not obtained in other brain regions (Huang and Kandel, 1995; Law-Tho et al., 1994). Recent studies have found that other brain regions do express a synergy between dopamine and glutamate receptor and greater details have uncovered the molecular foundation for these interactions (Tomasetti et al., 2017; Sarantis et al., 2009). There are both similarities and differences obtained for dopamine-glutamate interaction making neostriatal modulation distinctive and an influence from the internal, local neural connectivity in each brain region important (Sesack et al., 2003). The next step was to examine the effects in D_{1A} receptor mutant mice (Levine et al., 1996). This study was one of the earliest projects examining brain slice electrophysiology of these mutants. Results were clear, in that D₁ receptor agonists did not enhance NMDA-mediated responses in striatal cells. Surprisingly, the attenuation of responses were also impacted, suggesting that the decrease in non-NMDA receptor response required both D₁ and D₂ effects. The basic work provided a foundation to expand and explore how other combinations and receptor subtypes influenced one another (Bonaventura et al., 2017). In addition the work has influenced behavioral studies of BG function. An early study examined action sequencing in the D_{1A} mutant mice finding an impairment in grooming chain sequential structure (Cromwell et al., 1998). This grooming syntax was shown to depend on integrity of the dorsolateral striatum (Cromwell and Berridge, 1996) and rely on D₁ receptor activation in control animals (Berridge and Aldridge, 2000). Currently, there are multiple research teams exploring how dopamine-glutamate interactions embedded in the striatal pathways are involved in reward processing and addiction (Fouyssac and Belin, 2019; Roberts-Wolfe et al., 2018; Nimitvilai et al., 2014).

Altering basal ganglia function using the lesion approach was one of the first methods to uncover the complex sensorimotor-motivational functions of the basal ganglia (Levine et al., 1971; Levine and Schwartzbaum, 1973; Cromwell and Berridge, 1993). Using *in vivo* electrophysiology in awake behaving animals, striatal neurons have been shown to encode differences in reward type (quality of reward) or reward amount (quantity of reward; Hassani et al., 2001; Cromwell and Schultz, 2003). This work and related findings did not extend beyond examining the static nature of these reward processing units. It was somewhat

unexpected when the reward activations were found to change within a session due to the different available outcomes the animal was experiencing in a single session period. This 'relative reward effect' found in activity of MSNs in primate striatum was well described using an array of fluid or food outcomes (Cromwell et al., 2005). In the striatum, we have argued that the relative effect can be dependent upon preference so that an activation for a mildly preferred outcome can increase if this outcome becomes paired with a less preferred outcome; however, we also found activity dependencies that were independent of preference in the striatum and could reflect the sensory qualities or basic parameters (amount) of the outcomes (Cromwell et al., 2005). Our most recent work has parametrically analyzed reward comparisons using a standard test of reward relativity: incentive contrast (see Figure 6). Incentive contrast is a paradigm that allows for reward comparisons to be examined from a reference point or 'absolute' value. When reward value downshifts, negative contrast occurs while value upshift leads to positive contrast, each state relative to a reference or baseline level of motivation (Crespi, 1942; Webber et al., 2015). We found a rapid process of reward revaluation in striatum that does support shifts in valuation similar to an 'instant transformation' of outcome value from highly aversive to appetitive (Figure 6; Webber et al., 2016). This updating can occur parametrically within both positive and negative valences and can scale to previously learned values as a reference with current experience. These dynamic striatal activations could combine with stable representations. 'Stable' activity would be linked to events and outcomes and not significantly change within the timescale under study. These two different types of representations could produce accurate value updating and acutely, they would be used to compute an immediate value temporarily stored.

Several research groups are linking components of reward processing or bivalent reward vs. punishment outcome updating to specific dopamine receptor activation (Hikosaka et al., 2018) in addition to specific pathways coursing through the corticostriatal loops (Proulx et al., 2018; Wickens, 2008). The direct pathway has been the proposed pathway involved in choosing good objects and this could intimately depend upon the simultaneous interaction between dopamine D_1 and glutamate signaling (Hikosaka et al., 2019). In contrast, the indirect pathway activation mediates the effects of negative stimuli, suppressing unwanted movements or generating avoidance reactions. These two functional pathways are intimately reliant upon D_1 (direct) and D_2 (indirect) receptor subtypes to enable opponent processing and divergent strategies (Hikada et al., 2013; Hikida et al., 2010). It seems that the circuit is broadening to include regions outside of the traditional pathways and including more diverse processing nodes (i.e., lateral habenula and olfactory tubercle) which bypass certain locations in the circuit (Proulx et al., 2018; Murata et al., 2019). The extensions of the dopamine receptor subtype differential effects support the earlier work and allow for a specific gateway for which positive and negative valence information diverges. One novel perspective would be to focus not on distinct differences in reward updating between 'good' and 'bad' (Miller et al., 2019) but to focus as the reward relativity perspective allows on shifts in reward value between an absolute state of 'good' versus a relative state of 'not as good as before' based upon outcome comparisons. This more subtle shift might depend upon more subtle processing. For example, one could propose positive contrast as a D_1 mediated NMDA effect, an 'elation' related to increased dopamine and greater binding at low affinity D_1 receptors. Negative contrast as a D_2 receptor-non-NMDA mediated effect,

may be more sensitive and have a wider range of influence. These effects would be most salient and operational on single MSNs in striatum to allow for rapid shifts in activity from one trial to another or even moments of consumption to one another. These kinds of intracellular modulations would involve a subset of MSNs, those with the capability to register diverse inputs and have the receptor complements that enable integration of incoming signals. The integrator of the MSN becomes more diverse in functionality and rapidly shifts activity depending upon the combination of incoming signals. These signals could carry information concerning different components of reward value including discrimination, preference and reward relativity. Each one can be behaviorally fractionated from the other (Ricker et al., 2016) and each subfunction must rely on rapid, effective neural activity changes driven by a flexible corticostriatal synapse. These ideas could impact the ways we think about and study the etiology of neurodegenerative disorders. Emotional and reward processing is defective in neurodegenerative diseases such as Huntington's and Parkinson's disease (Baez et al., 2018; Perry and Kramer, 2015; Enzi et al., 2012; Swainson et al., 2006) fitting into the scope of recent work by the Levine laboratory focusing on animal models of neurodegenerative disease and revealing specific breakdown in neurochemical interactions (Cepeda et al., 2014; Chen et al., 2013; Galvan et al., 2012; and see related articles in this volume). Understanding how the cellular implementation level translates to the information processing level will aid in the development for new ways to predict and treat these debilitating disorders.

Conclusions

The scope of work completed and being done by Mike Levine and his many collaborators helped shape current research perspectives and build models that were not perfect fits for traditional BG functional neuroanatomical framework. The lure of the standard views has been strong but novel perspectives have been useful in finding deficits in these views (Calabresi et al., 2014). The direct and indirect pathway is highly useful; however, it breaks down in significant ways when examining details of the circuitry (Kupchik and Kalivas, 2017). Developing ways to incorporate the variety of neuronal phenotypes into the framework will enable the models to match the high level of diversity and complexity of the basal ganglia.

Current findings suggest that fixed states for neuronal phenotypes are rarer than previously thought in the brain. Short- and long-term plasticity seems more the rule than the exception. Controlling factors for the firing of action potentials include the resting state membrane potential, the neurochemical inputs and the reward value, each level of explanation useful and important. At one level *in vitro* neurophysiology provides a close-up view of the properties of synaptic strength using highly controlled procedures and other levels such as whole animal *in vivo* electrophysiology provides a broader view of cell ensembles, circuits sometimes during complex action. Different findings arise but do not necessarily conflict. Previous work found locally-evoked synaptic potentials dependent upon non-glutamate signals using *in vitro* striatal slices after cortical ablation yet the same preparation (e.g. cortical lesion) can lead to enhanced glutamate signaling as plasticity occurs at the remaining corticostriatal synapses that continue functioning following the partial cortical damage (King et al., 1998). The different levels of explanation can give different answers

focusing on similar factors coalescing together to perform similar output. To reconcile what appears to be conflicting results, one needs to appreciate the local vs. global interactions which can be dissociated precisely (i.e., *in vitro*) or included as a key variable (i.e., *in vivo* recording). The research examples described in this review all utilize multiple scales to tackle neuroscience problems. Combining work from the microscopic, mesoscopic and macroscopic levels enables vital comparisons of synaptic features, local networks and large-scale circuits. Transferring the information, checking on similarities and differences and creating predictions from one level to another allows for convergence of evidence and stronger ‘proof’ for mechanisms that can be translated from basic work to clinical applications. No one approach will answer these questions, no one method will provide the necessary results, it takes a team effort and multiple experts but it also takes an individual willing to put it all together. Mike Levine has been doing this for a long time and neuroscience has greatly benefited because of it.

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Significance

This review was written as a tribute to the research of Dr. Michael Levine who pioneered the study of basic properties of basal ganglia physiology. Goals of this review include to present an historical overview of work on basal ganglia neurophysiology that linked different levels of neurophysiological and behavioral analysis and to connect this work to current research in the field. The overall scientific approach of Dr. Levine can serve as a template for scientists to use in planning and implementing their research goals to address and solve complex problems in an effective and comprehensive manner.

Figure 1.

A caudate neuron responding to stimulation of each of three primary inputs including cortex, thalamus and midbrain in kittens of 21, 47 and 72 days of age. Note that stimulation of each input in 21- and 47-day-old kitten evoked an EPSP and/or spike. The same neuron is being recorded from during each of the stimulation tests from the different brain regions. Adapted from Morris et al., 1979.

Figure 2.

Effects of cortical ablation on neurochemical mediation of the striatal postsynaptic potential (PSP). **A.** CNQX, an antagonist of the non-NMDA receptor subtype significantly decreases the PSP in control slice but not cortical lesion. **B.** Cholinergic antagonist (hexamethonium dichloride) produced a significant decrease in the PSP of neurons ipsilateral to the cortical damage but not in control non-ablated group. Adapted from Cromwell and Levine, 2006.

Figure 3.

Effects of decortication or 6-OHDA lesion on paired-pulse facilitation. Left panel is control facilitation at 10, 20 and 50 interstimulus intervals. Dopamine depletion did not alter the facilitation at these intervals but cortical damage did significantly decrease the effect of the paired stimulation. Adapted from Cromwell et al., 2005.

Figure 4.

Examples of single unit responses that display inhibitory gating from the striatum. Each unit is displayed in a perievent time histogram. The rasters show single dots for neural impulses and each row of dots is a single trial. Below the raster is a histogram of neural impulses from all trials. The two tones are presented 500 ms apart. **A)** Striatal single units show inhibition to stimuli and during movement. This is an inhibitory response to the tones that is 'gated' or reduced in terms of inhibition to the second tone (Tone2). **B)** Excitatory response that immediately follows the tone onset. Tones were 10 ms in duration so the duration of the activation continues beyond tone presentation. The firing is very reliable to the 100% predictable tone onset (every 10 s). The excitation to second tone (Tone2) is significantly reduced. This form of gating is found in many diverse structures. Striatal units were unique in that a subset of units did not express inhibitory gating (not shown). Each response displays inhibitory gating as defined by a T/C Ratio of at least 0.75. Adapted from Cromwell et al., 2007.

Figure 5.

F. Self-biting behavior following pemoline challenge in lesioned vs. control animals. The percentage of animals in each group displaying the behavior appears at each time point. The 24-h time point is cumulative, indicating the percentage of animals in each group that displayed self-biting behavior of sufficient intensity to produce erythema at any time during the preceding 24 h. Self-biting behavior over 24 h is significantly greater in lesioned animals than in controls. Adapted from Cromwell et al., 1999.

Figure 6.

Perievent histograms and rasters showing examples of neural activity and incentive relativity. **A. Negative Contrast unit:** Nosepoke-related unit is significantly active during and several seconds following the nosepoke response. The top panel shows the responses to the medium-sized outcome (2 pellets) during the single, mixed and single sessions. Activity significantly decreases to the medium outcome during the mixed session when it alternates with the large outcome. **B. Positive Contrast unit:** Activity following the nosepoke response during the sessions with the top panel showing the response to the large outcome during the single, mixed and single sessions. Activity significantly increases to the large outcome in the mixed session when the alternate is the small outcome. Adapted from Webber et al., 2016.