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NEUROGENETICS OF MOTIVATION FOR PHYSICAL ACTIVITY

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Introduction

Movement is energetically costly, yet many animals travel vast distances as part of their normal life history. From a Darwinian evolutionary perspective, this would be unexpected unless it provided some fitness advantage for survival or reproductive success. Movement is often necessary to find food, shelter, or mates. Therefore, it is generally assumed that gene frequencies have been shaped by natural selection to support varying levels of physical activity depending on the local ecological conditions. At least two components are necessary for an individual to perform a voluntary behavior of any kind: they must be physically capable of performing the behavior and they must be motivated to do it. Both processes involve biological traits that are moldable by evolution and which, in part, shape genetic variation in physical activity levels. Physical constraints such as aerobic capacity (the maximal amount of oxygen an organism can consume during maximal physical exertion), muscle mass or composition, bone symmetry, and many others limit the ability of animals to move quickly or travel long distances (30). Hence, if ecological conditions demand that the animal displays challenging physical acts at the limit of their physical capability to survive and reproduce, then that will lead to the evolution of increased capacity for these exercise physiological features, to the extent that they are heritable.

While physical capability sets the upper limit for what an animal can possibly accomplish, animals typically choose not to perform at their limit. A substantial portion of variation in physical activity levels is expected to arise from differences in motivation for physical exertion (79). The exercise physiological features that animals are genetically endowed with (including the full extent of phenotypic plasticity) are usually far in excess of what the animal requires on a daily basis or even within a lifetime. Consider sedentary humans compared to marathon runners: the big difference is motivation not muscles (or capability). While it is certainly true that individuals are constrained by the exercise physiological capacities they are endowed with, and there are real biological differences between good and average marathon runners, the point is that most people possess the physical capability of training their bodies to accomplish a marathon, but they choose not to. On an evolutionary time scale, the principle that motivation contributes to behavioral variation applies equally well. Consider the long-standing idea that behavior evolves first, before specialized morphological and physiological adaptations arise (7, 43). There are many interesting examples of this phenomenon in currently living species such as marine

iguanas in the Galapagos which basically are the same as mainland iguanas except for their behavior of swimming in the ocean (20). They have no special scales, webbed feet, or fins which other marine reptiles possess for swimming, because they haven't existed on earth long enough in the marine environment for these morphological features to evolve. However, one organ that probably has evolved slightly already is the iguana's brain that leads them to want to enter the marine environment and swim to obtain their food. This supports the "behavior evolves first" idea that the evolution of motivational systems in the brain precedes morphological adaptations in the periphery.

The "behavior evolves first" idea is also supported by direct experimental evidence. Over the last 25 years, Theodore Garland's group has conducted a replicated artificial selection experiment for increased voluntary wheel running in house mice (88, 94). If you look at the timeline of the discoveries, overall results suggest that the big changes initially were in neurological traits related to motivation (77–80), and then later changes in exercise physiological traits such as muscle phenotypes (41), aerobic capacity (76), and bone symmetry (31) became more evident. The interpretation is that in initial generations, variation in running was mostly attributed to differences in motivation to run, i.e., the reason why one mouse ran 5 km per day and another 1 km per day was not because of any differences in physical capability between the mice but rather because of differences in their intrinsic motivation for running. Several generations of selection increased motivation to a local maximum during which time variation in exercise physiological features became more and more significant contributors to the individual variation. As a result, changes in exercise physiological traits became more apparent in later generations. Taken together, these data strongly support the notion that motivation for physical activity can evolve, and is an important component of individual and species-level differences in activity levels. These data further imply that if the goal is to find genetic factors involved in the evolution of physical activity levels, then understanding how genes influence motivation to engage in the behavior is of paramount importance.

The purpose of this chapter is to provide an updated review on what is known about genetic variation underlying motivation for physical activity levels across individuals and species. The material is relevant in the broad sense, for understanding how behavior evolves, but also important in the narrower sense for human health. Arguably the single most important factor that has contributed to the decline of health in Western society is our increasingly sedentary lifestyle, which contributes to metabolic syndrome (28), obesity (65), diabetes (42), heart disease (67), stroke (55), and cancer (63). Not only is physical activity crucial for maintaining physical health, but evidence accumulated over the past 30 years has established that there are profound benefits of exercise on mental health as well (21, 39). Exercise is a useful strategy for coping with stress (37), treating depression (89), preventing relapse in drugs abuse (11), and delaying cognitive aging (16). Randomized human clinical trials have established that walking quickly for 40 minutes a day, three times a week for 6 months results in changes in brain functional and anatomical measures which support the pro-cognitive outcomes (24). An enormous literature in rodent models has established profound effects of exercise on brain anatomy, chemistry, and physiology providing mechanistic support for pro-cognitive outcomes (as reviewed in 18, 19, 97). One of the highlights of this literature is the landmark discovery that several weeks of voluntary wheel running increases the formation of entire new neurons in the dentate gyrus, a region of the brain crucial for learning and memory (96). Taken together, what this means for medicine is that we already know how to prevent the bulk of our health problems in a pretty broad sweeping way, and we usually have the physical capability to do it, yet we generally lack the motivation. Therefore, understanding genetic pathways which increase motivation for physical activity could have broad implications for preventative medicine.

The natural reward circuit as a molding block for evolution of behavior

The natural reward circuit is defined as a collection of interconnected brain regions involved in the perception of pleasure. In the 1950s, Olds and Milner conducted experiments with rats placed in operant boxes in which a lever could be pressed by the rat on a voluntary basis that would deliver mild electric shocks to various parts of the brain through differential placement of the electrode (69). They discovered that the rats would learn to self-administer shocks when the electrode was placed in numerous places throughout the brain. However, when they placed the electrode in certain regions, results were particularly striking. If the electrode was placed anywhere along the medial forebrain bundle, the axonal projections from the ventral tegmental area to the nucleus accumbens, or passing through the lateral hypothalamus, the rats would display an extraordinary motivation for the shock to the point of pressing so often as to forgo eating, drinking, and sleeping (Figure 8.1) (69). It is interesting to note from the original work that rats self-administered shocks to many different regions throughout the brain, suggesting the existence of an extended reward circuit that includes most of the brain (64, 100). This is consistent with the idea that a lot of real estate in the brain is involved in the perception of reward, and that a fundamental function of the brain, the organ which shapes behavior, is reward processing, in a manner that informs decision-making.

If one extends the idea of the stimulating electrode to extrinsic stimuli which are naturally capable of electrically activating the same circuit (albeit at a physiological level, and much less intensely than the electrode), then one way to coerce animals to behave a certain way is to make the behavior result in the electrical activation of the reward circuit and thereby perception of reward. In other words, if genes regulated the development of neural circuits in the brain in such a way that high levels of physical activity were perceived as rewarding because they activated the reward circuit and served as a positive reinforcer, then individuals would choose to display heightened activity. Therefore, the next logical question to ask is how physical activity stimulates
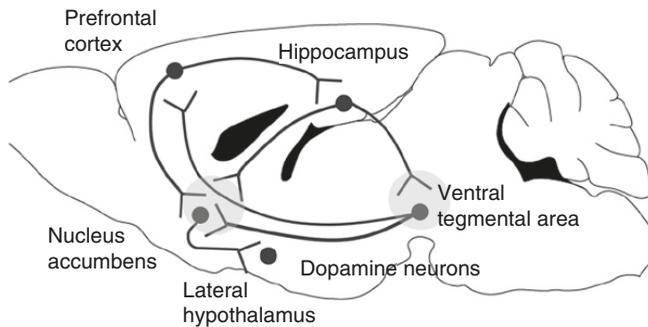

Figure 8.1 The natural reward circuit. A simplified illustration of interactions between the hippocampus and the natural reward circuit in the rodent brain. Forceful movement activates the hippocampus in proportion to the intensity or effort. The ventral midbrain and the nucleus accumbens, core nodes of the natural reward circuit, receive input from the hippocampus (32, 51). The highlighted areas indicate places where the neurophysiology may differ between individuals highly motivated for activity as compared to those less motivated. If the hippocampal input results in stronger activation of the ascending limb of the reward circuit through dopamine innervation of the nucleus accumbens, and prefrontal cortex, and subsequent activation of the lateral hypothalamus, physical activity would be reinforced. The precise cellular and molecular signatures and underlying sequence variants responsible for motivating physical activity as distinguished from other natural or artificial rewards (such as drugs of abuse) are not known and are currently actively being investigated.

the natural reward circuit, and what the difference is between the reward circuit of an animal that is unmotivated for physical activity versus an animal that is highly motivated for physical activity and which seeks out physical activity despite its high energetic costs and generation of fatigue. Here we come to a point where it starts getting complicated, because the old view that it will be one molecule or even a few has proven false (23). The reality is more likely a story about billions of neurons interacting with each other and with glial cells, with complex chemical signaling pathways involving hundreds if not thousands of molecules. These signaling pathways transmit information from one cell to the next, but there are numerous receptors and neurochemicals implicated at any one synapse. Realistically, it is a combination of multiple mixes that influence reward processing and that distinguish physical activity reward from other natural rewards or drugs of abuse.

Beyond dopamine

Dopamine has historically been considered the substrate for reward, and there is abundant evidence in the literature supporting this idea (91, 103). For example, dopamine levels increase in extracellular spaces in the nucleus accumbens in response to inherently rewarding stimuli such as sweet flavor (61), orgasms (72), and drugs of abuse (102). Moreover, the dopamine release depends critically on the perceived rewarding value of the stimuli which can change depending on the circumstances. In one study, rats were fed either a diet deficient or replete with salt, and then administered a saline solution directly into the mouth and extracellular dopamine in the nucleus accumbens was measured using carbon fiber voltammetry methods. This showed that the saline solution elicited a dopamine response only when the rats were deprived of salt, not when the diet contained sufficient salt. Moreover, the dopamine response was severely reduced in the salt-deprived rats if the salt taste receptors were pharmacologically blocked (17). In addition, the same group in a different study found clear evidence, as others have, that a bitter solution that elicits an aversive taste reaction reduces dopamine release (62). Taken together these data suggest that dopamine release in response to a stimulus is context dependent and matches the perceived rewarding value of the stimulus, rather than a direct response to the perception of the stimulus itself. Furthermore, these data constitute strong recent evidence in support of the dopamine reward hypothesis, demonstrating that stimuli that are perceived as rewarding increase dopamine in the nucleus accumbens (103).

On the other hand, serious questions have been raised about the validity of the hypothesis that dopamine is a substrate for reward as opposed to a more general role for dopamine as a salience detector, or in learning (5, 87). First, dopamine-deficient mice appear to find sweet flavor rewarding, and display the normal preference for sweet solutions, suggesting dopamine is not necessary for reward (14). More recent studies have established that dopamine-deficient mice can also perceive opioid reward (40). Second, stress and pain have also been found to increase dopamine in the nucleus accumbens, suggesting dopamine release is not specific to reward (1, 48, 85). In light of the conflicting evidence, it has been suggested that dopamine is released into the nucleus accumbens in response to an emotionally important event but does not distinguish between aversive and rewarding qualities, at least at this level of biological organization (nucleus accumbens dopamine as a whole) (85, 87). The large literature suggesting a role for dopamine in regulating neuronal plasticity, and especially reinforcement learning, supports this idea (4, 73, 86, 90, 101).

In light of the fact that physical activity involves rewarding and aversive emotional reactions, and that dopamine also functions in voluntary control of movement through the nigrostriatal pathway (35, 58), it is not surprising that the dopamine signaling pathway has been implicated in

genetics of increased physical activity in several model systems now (10, 27, 53, 60, 79, 81, 83, 84, 99). However, the simple hypothesis that the difference would be in the amount of dopamine released or in the number of receptors has turned out to be false. For example, in the replicated selective breeding experiment for increased voluntary wheel running referenced previously, we discovered that the high-runner mice responded completely differently to drugs which block the dopamine reuptake transporter protein (77, 78). Similarly in a selective breeding experiment for increased and decreased voluntary wheel running in rats, the lines responded differently to a dopamine reuptake transporter blocker (10). The main cellular mechanism of action attributed to the psychoactive effects of the drugs which were used, cocaine, methylphenidate (Ritalin), and GBR 12909, was thought to be through increased dopamine in extracellular spaces. These drugs decreased wheel running in high-runner mice in a dose-dependent fashion whereas they had no effect or the opposite effect, and increased wheel running, in control mice (77, 78). The results demonstrated that some feature of the dopamine system had been altered by selection, but follow-up experiments found no differences in dopamine levels, or dopamine turnover in the nucleus accumbens (unpublished observations). Dopamine levels appear to have decreased in the dorsal raphe, the region of the brain containing the greatest density of serotonin neuron cell bodies, and DOPAC, which is a metabolite of dopamine, appears to have been reduced in the substantia nigra (98). Further, genes for two dopamine receptors displayed 20% increased expression in the hippocampus of the high-runner mice (9), but dopamine has diverse roles in different brain regions and the direct implications of these results for reward processing remain unclear. Additional experiments found no differences in dopamine receptors, or transporters in the nucleus accumbens or frontal cortical brain regions (unpublished data) using radiolabeled ligand binding assays established by Aaron Janowsky (45, 46). As described and characterized so well by the Nobel Prize laureate, Paul Greengard, dopamine receptors are only at the tip of an iceberg in terms of activing an entire intracellular signaling cascade involving many enzymes, interacting proteins, and molecular complexes (33). Any one of these could be altered at the genetic level to cause a change in the dopamine signal in response to a stimulus such as physical activity. Furthermore, dopamine neurons interact with neurons of many other types, so changes in other neurotransmitter systems could influence dopamine function through these interactions. Other neurotransmitter systems implicated in reward processing and motivation for physical activity include serotonin (38, 88, 98), glutamate (34, 92), gamma aminobutyric acid (GABA) (54), opioids (8, 71), and cannabinoids (22, 49, 50, 59, 74, 75, 93, 95). Each of these systems comes with their own degree of complexity in terms of signaling molecules downstream of receptors. Some of these receptors can be on presynaptic terminals and postsynaptic terminals to elicit a diverse array of effects on the reward circuit. Taken together, this paints a complex picture, and one that is only meaningful if considered at a systems level. The dopamine signaling system is clearly involved in the motivation for physical activity, but the specific molecular underpinnings are only beginning to become realized, and the answer is not one or two molecules, but the way in which systems-level gene expression is coordinated through development of a nervous system and alterations in chromatin structure in a cell type-specific manner (88).

Specificity of reward circuitry for promoting physical activity remains elusive

Unfortunately, determining the reward circuitry that promotes physical activity is an area in its infancy with little progress. Our understanding of how circuits in the brain are involved in motivation for specific behaviors is still remarkably rudimentary. Only a few reports illustrate

specificity in the neural physiology underlying the perception of different types of rewards. Regina Carelli has done work showing that specific neurons in the nucleus accumbens are activated in response to sugar but are not activated in response to cocaine reward (13, 15). Other studies, attempting to find differential patterns of brain activation associated with expecting a food reward versus cocaine, have been only moderately successful in finding differential patterns of brain activation (106), and even then it is difficult to know whether these differences can be attributed to the magnitude of the perceived reward rather than the reward type. Even finding differential patterns of brain activation in response to aversive stimuli versus a reward is difficult as the majority of the brain activation response appears to reflect relative emotional potency rather than valence (47). In other words, when a subject is presented with a stimulus that is either very rewarding or very aversive, many of the same brain regions become activated. One possible explanation is that the majority of the brain response is a reflection of attention or arousal to the stimulus or learning about the stimulus so it can be approached or avoided in the future, and the learning, attention, and arousal are consistent between the two valences.

While some relevant regions and molecules have been identified for many different types of rewards, the question of specificity remains a major issue. When specificity is explicitly evaluated, often it is not found (29, 47, 68, 106). Therefore, how the different regions and molecules that have been identified mix differently to create different versions of motivation, particularly when it is directed at one or another reward such as a drug or exercise, the understanding becomes increasingly cloudy. The regions including the limbic system (amygdala, hippocampus, frontal cortex), natural reward circuit (ventral tegmental area to nucleus accumbens), and hypothalamus are activated for all sorts of natural and artificial rewards as well as for aversive stimuli such as in response to pain and stress. This variety of activation triggers suggest that in order to find specificity one will have to look at a more detailed aspect of the physiology, such as examining specific neurons and their firing rates similar to the work by Carelli mentioned briefly above. It appears that no one has tried to determine whether neurons can be found that are selectively sensitive to physical activity reward over other rewards. This area of investigation, finding the specificity of motivation for different types of natural rewards, will be important before we can really understand the motivation for physical activity at a neurobiological level.

An important clue about how the reward circuit may be modified to specifically promote one behavior over another comes not from studies exploring motivation for physical activity but rather from studies exploring motivation for pair-bonding behavior in voles. The leading hypothesis is that the evolution of monogamy in voles involves genetic changes in the pro-motor regions of genes which affect the way oxytocin and arginine vasopressin receptors are distributed and expressed on different nodes of the reward circuit (105). So, the idea is that the reward circuit itself remains unchanged (e.g., in terms of dopamine, opioids, cannabinoids, medial forebrain bundle, etc.). However, whenever two voles come into contact with each other, the peptides oxytocin in females and arginine vasopressin in males are released. The receptors for these two peptides in the brain are situated in such a way that they cause a differential level of electrical activation of the reward circuit and perception of reward. For example, monogamous female Prairie voles have more oxytocin receptors in the nucleus accumbens than polygynous female Montane voles (44, 82, 105). In males, the arginine vasopressin V1a receptor is concentrated in regions of the reward circuit in Prairie voles as compared to Montane voles (57, 104, 105). Moreover, individual differences in affiliative behavior in Prairie voles are associated with differential expression of the peptide receptors in the nodes of the natural reward circuit in expected ways based on their behavior (3, 36). Incredibly, the genetic regulatory mechanism

for this differential spatial distribution and expression of the V1a receptors has been fairly well worked out in the voles, and appears to involve tandem repeated DNA sequences in the pro-motor region (57). Although the tandem repeat sequences cannot underlie variation in mon-ogamy/polygyny in *Microtus* voles more generally because many polygynous voles also have the repeated sequences (26), strong, direct molecular evidence supports the hypothesis that at least the Prairie vole variant of the promotor and resulting change in neuroanatomical distri-bution and expression of arginine vasopressin V1a receptors facilitates pair bonding. Both mice and meadow voles, which are polygynous species, can be coerced into displaying affiliative behavior if the appropriate neurons are engineered to express the Prairie vole variant of the V1a receptor (57, 104). Moreover, recent evidence demonstrates that this differential distribu-tion of receptors may increase the synchronicity of electrical activation between two key nodes of the reward circuit, the nucleus accumbens and prefrontal cortex, when the voles come in contact with each other (2). The degree of future affiliative behavior is greatly predicted by a measure of coherence between the electrical rhythms in each reward region during initial con-tact. Taken together, the vole work suggests that the evolution of a voluntary behavior results from changes in the way signaling systems involved in the behavior interact with the different nodes of the reward circuit. More specifically, the circuit appears to have to function in such a way that it facilitates coherence between different regions of the reward circuit at the time when the animals are performing the behavior. To the best of our knowledge, no study has explored coherence in electrical activation of the different nodes of the reward circuit during high levels of physical activity. It is possible that the evolution of increased motivation for physical activity required a change in the physiology of the circuit in such a way that coherence occurs between prefrontal cortex and nucleus accumbens during exhaustive physical exercise.

Physical activity activates the hippocampus, but the functional significance remains a mystery

Although no study has examined coherence between nodes of the reward circuit during phys-ical activity as was performed in the vole affiliative study, several studies have examined neuronal activation of different regions of the brain during physical activity. As it turns out, the region most activated from voluntary wheel-running behavior and forced treadmill running is the hippocampus (80). This is somewhat unexpected because the hippocampus is more known for its role in learning and memory than movement. However, a large literature has established that the hippocampal formation is instantaneously engaged at the onset and duration of strenuous physical movements, displaying a rhythmic synchronous activity of large numbers of neurons, which is proportional to the speed (or force) of the movement and persists for as long as phys-ical activity persists (6, 12, 56).

   In addition to the literature establishing activation of the hippocampus in proportion to the intensity of physical activity, the hippocampus has an extensive literature for its role in motiv-ation, and it is often included as a peripheral reward region well interconnected with the central nodes of the reward circuit such as the ventral midbrain, nucleus accumbens, and prefrontal cortex (Figure 8.1) (70). It is possible that the physical activity–related electrical activation of the hippocampus stimulates the reward circuit to a greater degree in mice that are highly motivated for physical activity, though this would require additional testing to confirm. Finding sequence variants which affect the resulting development and function of hippocampus–reward circuit interactions could be a fruitful avenue for future research on the neurogenetics of motivation for physical activity.

Genetic regulatory mechanisms for increasing motivation for physical activity

It was thought that science would eventually find genetic differences in dopamine receptors and transporters in cocaine addiction, opioid receptors for heroin addiction, GABA and glutamate for alcoholism, and cannabinoid receptors for marijuana. However, results from human genetics over the past 20 years suggest instead that the heritability of drug addiction is highly overlapping with personality traits such as novelty seeking, and usually not specific to any one type of reward (52). Furthermore, the contribution of single candidate genes such as a dopamine receptor to a complex trait accounts for only a tiny fraction of the heritability, if any at all (66). Therefore, it is exceedingly unlikely that an approach that examines single candidate genes such as dopamine receptors will make headway into understanding the genetic mechanisms which regulate motivation for physical activity, at least with any degree of specificity distinguishing it from other rewards (25).

As described previously, genetic changes that lead to the development and function of a reward circuit that reinforces physical activity is a more realistic mechanism (25, 81, 88). Systems genetic analysis of gene expression changes in the striatum (both dorsal and ventral nucleus accumbens, main dopamine innervation region) of the high-runner mice implicated a network of genes that affect chromatin and/or transcriptional states (88). Chromatin can exist in multiple functional states, either in a condensed state that prohibits gene expression or a relaxed state that facilitates gene expression. Thus, sequence variants that affect chromatin structure could explain gene expression patterns in crucial regions of the reward circuit which could affect the way the cells respond to physical activity. Specifically, for the evolution of voluntary wheel running a structural polymorphism in the SMARCA4 protein is suggested to cause differential interaction with the BAZ1A protein, altering the distribution of the H1F0 histone subunit protein and thereby creating a chromatin state conducive for increased expression of the serotonin receptor and an orphan G protein-coupled receptor. Future work is needed to rigorously test this hypothesis by assessing the chromatin state through direct measurement.

Conclusions

In conclusion, heritable variation in motivation for physical activity is hypothesized to result from differences in the way neural signals involved in regulating the intensity of the physical activity interact with the natural reward circuit. Therefore, genetics of motivation for increased physical activity likely involve genetic programs for building a nervous system in which the act of intense physical activity produces a strong reward signal that leads to reinforcement of the behavior, and subsequent drive for the activity. We propose that a crucial location for the occurrence of neurological differences is at the interface between the hippocampus and various nodes of the reward circuit (Figure 8.1, shaded regions). This is because the hippocampus becomes electrically activated like no other region in the brain in proportion to exercise intensity. If the brain were wired in such a way that physical activity–induced neuronal activation stimulated the reward circuit, that would lead to reinforcement. However, the precise molecules and developmental trajectories that result in a brain predisposed for high or low motivation for physical activity are far from known. Models such as long-term selective breeding experiments for increased voluntary wheel running in mice and rats provide promising avenues for research and discovery in this area. Finding neurogenetic pathways that increase motivation for physical activity has broad implications for evolution of behavior. It also has important applications in preventative medicine. The health benefits of exercise are profound on all dimensions. Getting

people to exercise is the hard part. Understanding the pathways which increase intrinsic drive for physical activity therefore holds the key to prolonged health and prosperity in the 21st century.

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