

Corticostriatal Plasticity and Behavioral Flexibility in Compulsivity: Convergent Influence of Physical Activity and Serotonergic Signaling

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ABSTRACT

Background: Compulsivity can be viewed physiologically as a failure to appropriately regulate, interrupt, or update actions once they become maladaptive. Contemporary models of obsessive-compulsive disorder increasingly emphasize dysfunction within cortico-striato-thalamo-cortical networks together with altered interactions among serotonin, dopamine, glutamate, and plasticity-related signaling systems. This perspective helps explain why selective serotonin reuptake inhibitors may require prolonged treatment before substantial clinical benefit emerges: increased extracellular serotonin occurs rapidly, whereas modification of network organization and behavioral control develops over a longer timescale. Physical exercise represents a complementary physiological stimulus capable of changing monoamine turnover, neurotrophic signaling, cerebral metabolism, stress regulation, synaptic efficacy, and cognitive flexibility. Rather than treating pharmacological and behavioral interventions as unrelated, a systems-physiology framework suggests that both may converge on the capacity of prefrontal-striatal circuits to remodel in response to new environmental demands. This review examines corticostriatal control of repetitive behavior, the distinction between goal-directed and habitual actions, serotonergic regulation of circuit plasticity, exercise-induced neural adaptations, and the strengths and limitations of rodent models used to study compulsive-like behavior. Particular attention is given to BDNF–TrkB signaling as one potential mediator of experience-dependent network remodeling without assuming that a single neurotrophin pathway explains the heterogeneous biology of compulsivity. Current evidence supports a model in which therapeutic improvement reflects restoration of behavioral flexibility through coordinated neurochemical and synaptic adaptation. Future experiments combining circuit-relevant behavioral assays with regional molecular profiling may clarify how physiological activity and serotonergic modulation interact to influence persistent repetitive behavior.

Keywords: corticostriatal circuitry, serotonin, exercise, behavioral flexibility.

1. Introduction

Obsessive-compulsive disorder is a heterogeneous neuropsychiatric condition in which intrusive cognition and repetitive actions become persistent despite recognition that they are excessive or counterproductive. The disorder cannot be adequately explained by a single neurotransmitter abnormality. Neuroimaging, lesion, pharmacological, genetic, and preclinical evidence instead implicate interacting abnormalities across orbitofrontal, anterior cingulate, medial prefrontal, striatal, thalamic, limbic, and increasingly extra-cortico-striatal networks. This broader view places impaired adaptive control, rather than repetitive movement alone, at the center of compulsive physiology. [1]

A major conceptual development has been the recognition that repetitive behavior may result from altered competition between goal-directed and habitual control. Goal-directed behavior depends on knowledge of the relationship between an action and its expected outcome, whereas habits become relatively insensitive to changes in outcome value after repeated reinforcement. Habit formation is physiologically normal and essential for efficient behavior; pathological compulsivity emerges when automatic response patterns persist despite punishment, changing goals, or lack of benefit. [2]

This framework has direct relevance to treatment. Selective serotonin reuptake inhibitors are clinically effective for many patients with OCD, but improvement develops slowly and frequently requires higher doses or longer treatment durations than those used for major depression. The delay implies that serotonin-transporter inhibition alone is insufficient to explain therapeutic effects. Adaptive receptor changes, transcription, synaptic remodeling, and network-level plasticity are likely required before repetitive behavior becomes more responsive to top-down control. [3]

Physical exercise is another intervention capable of gradually modifying brain physiology. Exercise alters cerebral blood flow, autonomic regulation, hypothalamic-pituitary-adrenal function, mitochondrial metabolism, monoamine turnover, neurotrophic signaling, inflammatory tone, and synaptic plasticity. Although clinical evidence supporting exercise specifically for OCD remains preliminary, these widespread adaptations make exercise scientifically valuable for investigating mechanisms that regulate behavioral flexibility. [4]

The aim of this review is to examine how physical activity and serotonergic signaling may converge on cortico-striatal plasticity and adaptive action control. The central research gap is that most preclinical studies investigate serotonin, exercise, or compulsive behavior separately, while relatively few integrate circuit-relevant behavioral endpoints with molecular measures of plasticity. A systems approach could identify mechanisms through which distinct interventions influence the same functional property: the capacity to disengage from maladaptive repetitive behavior. [5]

2. Cortico-striatal Organization of Compulsive Behavior

The traditional neurocircuit model of OCD emphasizes parallel cortico-striato-thalamo-cortical loops. Cortical information reaches the striatum, is processed through direct and indirect basal ganglia pathways, and returns through thalamic relays to frontal cortical territories. Although simplified versions portray the direct pathway as behavior-promoting and the indirect pathway as behavior-suppressing, modern physiology demonstrates extensive pathway interactions, collateral connectivity, neuromodulation, and region-specific functions. Compulsivity is therefore better conceptualized as altered network balance than as simple overactivity of one anatomical route. [6]

Within these networks, orbitofrontal cortex contributes to valuation, prediction of outcomes, and updating behavior when contingencies change. The anterior cingulate participates in performance monitoring, conflict,

and error processing, whereas medial prefrontal regions contribute to action selection and inhibitory regulation. Striatal territories integrate these cortical signals with dopaminergic information concerning salience, reinforcement, and action history. Dysfunction at any of these levels can increase persistence of previously reinforced behavioral sequences. [2]

Recent evidence also argues against limiting OCD exclusively to the classical CSTC loop. Amygdala, hippocampus, cerebellum, hypothalamus, insula, and broader frontoparietal networks may contribute to threat evaluation, contextual memory, emotional salience, interoception, and cognitive control. Such distributed involvement helps explain clinical heterogeneity and suggests that treatment-related plasticity may need to occur across multiple interacting networks rather than within a single anatomical circuit. [7]

3. Serotonin as a Modulator of Network Plasticity

The clinical efficacy of serotonin reuptake inhibition historically led to the serotonin hypothesis of OCD, but pharmacological response does not establish that the disorder originates from a primary serotonin deficiency. Serotonin instead acts as a broad neuromodulator influencing cortical excitability, striatal output, anxiety processing, learning, punishment sensitivity, impulsivity, and interactions with dopamine and glutamate. Multiple serotonin receptor subtypes exert different and sometimes opposing effects, making the physiological consequence of increased extracellular serotonin dependent on receptor distribution and treatment duration. [8]

Early preclinical work demonstrated that fluvoxamine and other serotonin reuptake inhibitors suppress marble-burying behavior in rodents under conditions that may avoid marked locomotor impairment. These findings contributed to the predictive use of marble burying for screening compounds with potential anti-compulsive activity. However, serotonergic sensitivity of a behavioral assay does not prove that the behavior itself is homologous to human obsession or compulsion. It does, nevertheless, demonstrate that repetitive rodent behavior can be modulated by serotonergic mechanisms. [9]

Chronic fluoxetine also modifies signaling pathways associated with longer-term neural adaptation. In rodent studies, repeated treatment has increased BDNF expression in selected prefrontal and mesolimbic regions, while other studies demonstrate changes in TrkB signaling, dendritic architecture, spine density, and cellular plasticity. Such adaptations provide a physiological explanation for why sustained treatment may progressively alter network function even though serotonin transporter occupancy occurs rapidly. [10]

Particularly important is evidence that fluoxetine-related plasticity cannot be reduced entirely to serotonin transporter blockade. Experiments using serotonin-transporter-deficient systems have identified persistent effects of fluoxetine on BDNF/TrkB-associated signaling, while direct interaction of antidepressants with TrkB has been proposed as an additional mechanism facilitating neurotrophin responsiveness. These findings support a model in which serotonin initiates only part of a broader cascade leading to circuit remodeling. [11]

4. Exercise as a Systems-Level Neural Stimulus

Exercise changes the brain through multiple convergent mechanisms. Increased motor and sensory activity raises neuronal metabolic demand, promotes vascular adaptation, influences lactate signaling, stimulates peripheral endocrine and myokine responses, modifies autonomic balance, and activates neurotrophic pathways. These responses are distributed across hippocampal, cortical, striatal, hypothalamic, cerebellar, and brainstem systems. The resulting physiological state is therefore capable of influencing both cognitive and

emotional control networks relevant to repetitive behavior. [12]

Exercise also modifies serotonergic physiology. Classic rodent work demonstrated region-specific changes in serotonin synthesis and turnover after acute and chronic exercise, with chronic training producing adaptations extending beyond brainstem serotonin nuclei to cortical regions. More recent work has reinforced the existence of reciprocal relationships between BDNF and serotonin systems, whereby exercise can alter BDNF, serotonin, serotonin transporter expression, and receptor-related signaling. [13]

Neurotrophic signaling is one of the most consistently investigated molecular mediators of exercise-induced plasticity. Exercise can increase BDNF expression and activate TrkB, CREB, PI3K/Akt, and related pathways involved in synaptic stabilization and cellular survival. Importantly, effects differ according to intensity and duration, and recent systematic evidence continues to show substantial heterogeneity in BDNF responses across exercise protocols. This variability argues against using "exercise" as if it represented a standardized pharmacological dose. [14]

The physiological distinction between voluntary and forced exercise is especially important in rodents. Wheel running typically allows self-selected intensity and may have rewarding properties, whereas forced treadmill or swimming protocols can introduce handling, aversive motivation, fatigue, and stress. Because glucocorticoids themselves influence prefrontal function, serotonin, BDNF, and repetitive behavior, poorly controlled exercise stress can obscure the pathway under investigation. [15]

5. Behavioral Flexibility as a Translational Endpoint

If compulsivity is fundamentally related to inappropriate persistence of behavior, then behavioral flexibility provides a more informative translational endpoint than repetition alone. Reversal-learning tasks assess the ability to change a previously rewarded response after contingencies are reversed. Set-shifting paradigms examine the capacity to redirect attention or change response rules. Outcome-devaluation procedures distinguish goal-directed from habitual control. These assays allow interventions to be evaluated according to whether they restore adaptive regulation rather than simply suppress motor output. [2]

Excessive checking provides another dimension of compulsivity. Quinpirole-sensitized rats repeatedly return to specific locations or objects with an organized, ritualized structure resembling excessive checking. The behavior develops progressively after repeated D2/D3 receptor stimulation, implicating dopaminergic sensitization and corticostriatal adaptation. Because checking can be interrupted and subsequently re-emerge, the model also captures persistence without implying complete motor stereotypy. [16]

The observing-response task provides a more cognitive approach by distinguishing information-seeking checks from excessive checks without programmed consequences. Recent studies suggest that dysfunctional checking can be associated with cue-driven behavioral styles and may persist after degradation of the relationship between checking and its informative outcome. Such paradigms help separate adaptive uncertainty reduction from pathological behavioral repetition. [17]

Marble burying remains useful as a rapid screen but requires more cautious interpretation. Burying can reflect species-typical digging, neophobia, defensive behavior, exploration, or repetitive responding. Therefore, an intervention that reduces marble burying should be interpreted together with locomotor activity and preferably at least one additional assay of flexibility or checking. A multi-domain behavioral battery provides stronger evidence than reliance on a single repetitive behavior. [18]

6. BDNF–TrkB Signaling as a Bridge Between Interventions and Circuits

BDNF is well positioned to translate both physical activity and pharmacological neuromodulation into

structural change. TrkB signaling regulates dendritic growth, synaptic receptor trafficking, local protein synthesis, long-term potentiation, and transcriptional programs through MAPK, PI3K/Akt, and PLC- γ pathways. These mechanisms are relevant to prefrontal-striatal circuits because modifying the strength of competing synaptic inputs is required for behavioral updating and extinction of maladaptive response patterns. [19]

Exercise can enhance BDNF-related signaling in prefrontal cortex as well as hippocampus. Experimental work has shown that acute exercise can restore or increase TrkB and CREB phosphorylation in prefrontal tissue under metabolically compromised conditions. Such findings emphasize that exercise-induced plasticity is not restricted to memory-related hippocampal circuits and may influence cortical areas directly involved in executive control. [20]

Serotonergic pharmacotherapy converges on some of the same pathways. Repeated fluoxetine has been associated with increases in BDNF/TrkB expression and persistent structural remodeling within medial prefrontal cortex. A reasonable systems hypothesis is therefore that physical activity and serotonergic therapy can each increase the responsiveness of neural networks to experience, allowing corrective learning to become more effective. This concept resembles the idea that pharmacological treatment may open a state of heightened plasticity rather than directly encode a specific adaptive behavioral pattern. [10]

This interpretation also explains why environmental context matters. Plasticity itself is not inherently beneficial: increased capacity for synaptic modification could reinforce either adaptive or maladaptive experiences depending on the behavioral environment. In clinical OCD, exposure and response prevention supplies structured corrective learning. In animal studies, the nature of environmental enrichment, exercise access, testing conditions, and training contingencies may similarly determine the direction in which enhanced plasticity is expressed. [11]

7. Potential Interaction Between Exercise and Serotonergic Treatment

Rodent studies outside the OCD field provide proof of principle that physical activity and antidepressant treatments can interact at the molecular level. Combined exercise and antidepressant exposure has produced additive or accelerated increases in specific BDNF transcripts in hippocampal regions compared with either intervention alone. Such findings do not prove an equivalent interaction in compulsivity, but they establish a biological basis for testing combined interventions rather than assuming independent mechanisms. [21]

Combination effects may arise because the interventions act at different points within a shared plasticity cascade. Exercise can increase neuronal activity, metabolic signaling, neurotrophin transcription, serotonin turnover, and synaptic demand, whereas serotonergic drugs can alter neuromodulatory tone, receptor signaling, and TrkB responsiveness. Their combined effect might therefore increase the probability that activity-dependent synapses undergo lasting remodeling. Conversely, if both interventions saturate the same downstream mechanism, the combination could show no advantage over either alone. [21]

A factorial experimental design is particularly well suited to distinguish these alternatives. Four groups—control, physical activity alone, serotonergic treatment alone, and combined treatment—allow estimation of main effects and statistical interaction. Including a compulsive-like disease model in parallel with healthy controls further distinguishes normalization of pathology from nonspecific enhancement of plasticity. The molecular endpoints should ideally be obtained from prefrontal cortex and striatum rather than relying solely on hippocampus. [22]

8. Importance of Regional Neurochemistry

Different components of the corticostriatal network may respond differently to the same treatment. Chronic

fluoxetine has been reported to upregulate BDNF expression in prefrontal and mesocorticolimbic regions while producing less consistent changes in dorsal striatum. Similarly, exercise-induced neurotrophic responses can vary between cortex, hippocampus, and striatum. Whole-brain analysis could therefore conceal physiologically meaningful redistribution of signaling. [23]

The striatum deserves special consideration because serotonin, dopamine, and glutamate converge on medium spiny neurons responsible for action selection. Dopamine D1- and D2-family receptor signaling modulates direct and indirect pathway activity, while corticostriatal glutamate drives action-related synaptic transmission. Serotonergic terminals can influence both systems through receptor-subtype-specific mechanisms. Plasticity-related proteins should thus be interpreted in the context of local neurotransmitter interactions rather than independently. [6]

The medial and orbitofrontal prefrontal cortices represent complementary targets. These regions participate in outcome evaluation, extinction, rule updating, and inhibitory control. If an intervention reduces compulsive-like behavior while enhancing plasticity-related signaling specifically in prefrontal regions, this pattern would support improved top-down regulation. If changes occur primarily in striatum, altered action-selection or habit circuitry may be more likely. Regionally resolved data therefore strengthen mechanistic inference. [7]

9. Model Validity and Experimental Interpretation

Animal models should be selected according to the component of compulsivity being studied. Quinpirole sensitization is useful for repetitive checking and dopaminergic-circuit interactions; signal attenuation models persistent responding following degradation of feedback; marble burying provides high-throughput pharmacological screening; deer mice display spontaneous stereotypy and related naturalistic phenotypes; and operant checking paradigms provide stronger access to cognitive mechanisms. No single model is superior for every research question. [24]

Predictive validity is particularly important when studying serotonergic treatment. A model whose phenotype changes after chronic but not necessarily acute serotonin reuptake inhibition may better resemble the delayed clinical response of OCD than an assay suppressed immediately after a single dose. Conversely, acute drug sensitivity can still be valuable for pharmacological screening but should not be interpreted as evidence of chronic circuit remodeling. [24]

Motor and anxiety confounds require explicit exclusion. Exercise can change baseline locomotion, endurance, exploratory motivation, and anxiety-like behavior, while serotonergic drugs can influence arousal and motor performance. A reduction in repetitive behavior accompanied by severe hypoactivity cannot confidently be classified as improved compulsivity. Open-field locomotion, rotarod performance where appropriate, and complementary behavioral endpoints should be incorporated into experimental interpretation. [18]

10. Clinical Translation

Human studies of exercise in OCD remain small. A pilot randomized trial of aerobic exercise added to ongoing OCD treatment improved fitness and exercise behavior, but symptom outcomes did not clearly differ from the comparison intervention. Systematic reviews nevertheless identify encouraging pre-post improvements and potential benefits for anxiety and depressive symptoms. Collectively, these findings justify mechanistic investigation but not presentation of exercise as a proven primary OCD treatment. [25]

A systems-plasticity model generates a more realistic translational hypothesis: exercise may serve as an adjunct that changes the physiological conditions under which established treatments operate. Improved sleep, metabolic health, autonomic regulation, stress resilience, neurotrophin signaling, and cognitive function could increase capacity for therapeutic learning even if exercise does not independently produce a large anti-

compulsive effect. This possibility is particularly relevant to patients with residual symptoms after first-line treatment. [4]

Recent neurobiological models also emphasize that OCD extends beyond a single CSTC circuit, reinforcing the need for multidimensional outcomes. Future translational studies could combine symptom scales with cognitive flexibility, habit-learning tasks, neuroimaging, cardiorespiratory fitness, peripheral biomarkers, and treatment-response trajectories. Such integration would help determine whether physiological interventions modify a general plasticity phenotype or a disorder-specific neural mechanism. [7]

11. Future Directions

Future rodent work should prioritize chronic treatment schedules that parallel the temporal properties of human serotonergic therapy. Exercise intensity should be objectively defined, and forced exercise stress should be monitored through physiological indices when relevant. Behavioral testing should quantify both repetitive behavior and adaptive flexibility, while molecular analysis should include prefrontal and striatal tissue. These design elements would greatly improve the interpretability of intervention-induced changes. [15]

Molecular profiling should also move beyond single biomarkers. BDNF and TrkB are valuable candidates, but synaptic plasticity depends on interacting pathways involving CREB, Akt, ERK, glutamatergic receptors, inhibitory interneurons, dopamine signaling, neuroinflammation, mitochondrial function, and protein-processing systems. Multilevel analysis may reveal whether behavioral improvement reflects a coherent plasticity signature rather than an isolated change in one protein. [12]

Finally, studies of combination therapy should test mechanistic interaction rather than simply compare group means. If physical activity modifies the molecular response to serotonergic treatment and that interaction predicts improved flexibility or reduced checking, evidence for convergence would be considerably stronger. Such work could identify plasticity-related biomarkers that help explain why some individuals respond incompletely to serotonin reuptake inhibition and whether physiological interventions can enhance treatment responsiveness. [21]

12. Conclusion

Compulsive behavior is most usefully understood as a disorder of adaptive control arising from interactions among corticostriatal circuitry, neuromodulatory systems, and experience-dependent plasticity. Serotonin reuptake inhibition initiates neurochemical changes rapidly, yet meaningful behavioral adaptation likely depends on slower synaptic and network remodeling. Exercise produces a complementary pattern of physiological adaptations involving monoamines, neurotrophins, metabolism, and neuronal activity. Their potential convergence on corticostriatal plasticity provides a strong mechanistic framework for preclinical investigation while avoiding the oversimplification that either serotonin or BDNF alone explains compulsivity. Integrating molecular measurements with rigorous assays of behavioral flexibility may provide a clearer route from experimental physiology to clinically relevant mechanisms.

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