HHS Public Access

Author manuscript

Mov Disord. Author manuscript; available in PMC 2022 March 22.

Published in final edited form as:

Mov Disord. 2021 March ; 36(3): 535–546. doi:10.1002/mds.28532.

Make a Left Turn: Cortico-Striatal Circuitry Mediating the Attentional Control of Complex Movements

Martin Sarter, PhD[*], **Cassandra Avila, MS**, **Aaron Kucinski, PhD**, **Eryn Donovan, MS**

Department of Psychology & Neuroscience Program, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Background: In movement disorders such as Parkinson's disease (PD), cholinergic signaling is disrupted by the loss of basal forebrain cholinergic neurons, as well as aberrant activity in striatal cholinergic interneurons (ChIs). Several lines of evidence suggest that gait imbalance, a key disabling symptom of PD, may be driven by alterations in high-level frontal cortical and cortico-striatal processing more typically associated with cognitive dysfunction.

Methods: Here we describe the corticostriatal circuitry that mediates the cognitive–motor interactions underlying such complex movement control. The ability to navigate dynamic, obstacle-rich environments requires the continuous integration of information about the environment with movement selection and sequencing. The cortical-attentional processing of extero- and interoceptive cues requires modulation by cholinergic activity to guide striatal movement control. Cue-derived information is "transferred" to striatal circuitry primarily via fronto-striatal glutamatergic projections.

Result: Evidence from parkinsonian fallers and from a rodent model reproducing the dual cholinergic–dopaminergic losses observed in these patients supports the main hypotheses derived from this neuronal circuitry-guided conceptualization of parkinsonian falls. Furthermore, in the striatum, ChIs constitute a particularly critical node for the integration of cortical with midbrain dopaminergic afferents and thus for cues to control movements.

Conclusion: Procholinergic treatments that enhance or rescue cortical and striatal mechanisms may improve complex movement control in parkinsonian fallers and perhaps also in older persons suffering from gait disorders and a propensity for falls.

Keywords

cortex; striatum; acetylcholine; dopamine; attention; gait; balance; falls; Parkinson's disease

[*]**Correspondence to:** Dr. Martin Sarter, Department of Psychology , University of Michigan, 530 Church Street, 4030 East Hall, Ann Arbor, MI 48109, USA. msarter@umich.edu.

Author Roles

M.S., C.A., A.K., and E.D. made substantial contribution to the conception of this article, and they participated in drafting and revising this article. All coauthors approved the submitted version of this article, and they agree to be accountable for all aspects of the work.

Relevant conflicts of interest/financial disclosures: The authors declare no competing financial interest. For the past 12 months, and with the exception of research funding from the National Institutes of Health, none of the authors received any funding from any institution, interests, grants, employment, affiliations, patents, inventions, honoraria, consultancies, royalties, stock options/ownership, or expert testimony.

Attentional Control of Movements

As a healthy person, you rarely think much about your everyday movements. Getting up, going up or down the stairs, and biking or walking to work, all these actions feel automatic and habitual, and they typically do not disrupt your ongoing mental activity. Occasionally, however, a stepping or balancing error, perhaps while traversing a dynamic surface or stepping onto a stable surface that was expected to have dynamic properties (eg, onto a broken escalator), disrupts the regular rhythm of movement and evokes an attentional shift toward initiating corrective action. Such an attentional shift is an effect as well as a causal agent.[1] The attentional shift is triggered by a mismatch between preprogrammed movement sequences and performed actions. As a causal agent, such a shift facilitates the evaluation of extero- and proprioceptive stimuli to identify the mismatch between planned movements and behavior. To ensure corrective action, this shift in attention prioritizes the modification of motor programs over other cognitive or behavioral activity.[2-6]

In subjects with diminished capacities for such attentional shifts, as in older persons or patients with Parkinson's disease (PD), movement errors are less likely to trigger an effective analysis of mismatches between exteroceptive cues (eg, stair height and tread dimensions), programmed movements (eg, lower-limb cyclic pattern[7]), and interoceptive cues, indicating, for example, reduced gait rhythmicity and poor trunk orientation.[8] As a result, movement errors can rapidly accumulate, thereby increasing the risk of a fall.[9-19]

This review will evaluate the evidence supporting an essential neuronal circuit for complex movement control (see footnote[1]) and discuss how age- and disease-related dysfunction and degeneration of multiple nodes within this circuit lead to gait dysfunction, imbalance, and falls. This circuit (shown in Fig. 1) consists mainly of the cortical cholinergic processing of movement-related cues, the transfer of the results of such processing to the striatum, and, in the striatum, the integration of cortico-striatal glutamatergic with midbrain-dopaminergic signaling, primarily by striatal cholinergic interneurons (ChIs). It needs to be noted that in PD patients who, in addition to the disease-defining symptoms, exhibit gait dysfunction and a propensity for falls, not all falls result from a breakdown of cognitive–motor interactions. Some falls, particularly in patients with relatively severe, advanced disease, may primarily reflect major motor or biomechanical, including proprioceptive, deficiencies (eg, MacKinnon[20]). Falls not reflecting the disruption of cognitive–motor integration, and which cannot be mapped onto the cortico-striatal neuronal circuitry proposed to mediate such integration, are not the subject of this review. As such, this review assumes a reductionist, biopsychological account of this particular category of falls (for a clinically comprehensive description of falls and a discussion of a range of behavioral and neuronal risk factors, see, eg, Fasano et al.[12,] Paul et al.[21,] and Pelicioni et al.[22]). However, it also needs to be noted that overtly kinematic risk factors for falls, such as reduced step

[1]Complex movement control conceptualizes the collective interactions between cognitive, specifically attentional, processes and the selection and sequencing of movements. Such interactions are needed, for example, to circumvent obstacles, move over unfamiliar or unstable surfaces, or, in the rodent model, traverse rotating straight and zigzag rods or make cued turns. In these cases, the regular frequency-based patterning of limb movements that define gait is challenged and often disrupted, involving changes in the direction of travel, the rapid development of torque and postural muscle activity to correct for imbalance, imperfect limb placements, or stepping errors. Complex movements involve shifting the attentional spotlight toward the processing of errors in gait and posture and the orchestration of corrective action.

lengths before turning, freezing of gate (FOG), and alterations in trunk control,[23-27] can reflect the breakdown of cognitive–motor interactions,[28,29] as opposed to solely reflecting motor or biomechanical impairments. Although the proposed circuitry model (Fig. 1) maps the relative contributions of attentional and motor variables to gait dysfunction and a heightened propensity for falls onto separate nodes of this circuitry, such a segregation of attentional versus motor function likely is primarily of heuristic significance (see, eg, Mendoza and Merchant[30]). This view is underlined by contemporary theories about striatal dopamine (DA) function that have increasingly employed cognitive concepts to explain the dopaminergic contributions to motor control (later).

Attending to Movement-Related Cues: Cortical Cholinergic Signaling

The organization and diverse behavioral functions of the basal forebrain, cholinergic projection system to the cortex, have been extensively reviewed in recent years.[31-34] Therefore, the review of this component of the neuronal circuit mediating complex movement control is limited to a brief discussion of key findings relevant for the present neurobehavioral model of complex movement control (Fig. 1).

The Detection of Cues Requires Cholinergic Signaling in Cortex

"Detection" concerns a psychological process that elevates the processing of a signal or cue so that this cue evokes a response in accordance with a previously established stimulus–response rule.[35] While any salient cue may trigger an orienting response, only selected cues will be processed to the degree that they evoke or influence behavior. For example, while standing at the luggage carousel scanning bags, a red bag in a sea of black bags may elicit an orientation response but, unless this is your bag, it will not evoke approach behavior. You may miss your bag despite scanning over it because, for example, a distraction (a sniffer dog at your feet) or a weak representation of your (new) bag in memory interfered with the detection process.

In rodents performing cue detection tasks, cues that will evoke a behavior trained to report the presence of a cue evoke a fast, transient cholinergic signal in the prelimbic cortex (termed a "cholinergic transient"; see Fig. 2B and associated legend for methods used to measure cholinergic transients).[36,39] As illustrated in Figure 1, cue-evoked glutamatergic activity from thalamic afferents is necessary for evoking cholinergic transients, and complex bidirectional cholinergic–glutamatergic interactions appear to promote cholinergic transient generation in cortex.[41-45] However, the cortical circuitry and the synaptic mechanisms responsible for cues failing to generate, or suppressing, cholinergic transients, and thus yielding misses, have yet to be explained (but see "Cholinergic top-down control").

Consistent with the demonstration that cholinergic transients are evoked by detected cues, the removal of cholinergic inputs to the cortex,[46-48] or optogenetic suppression of cholinergic transients,[40] reduces detection rates. Moreover, optogenetic generation of transients enhances detection rates (Fig. 2). Perhaps an even more significant demonstration of the behavioral significance of cortical cholinergic transients is based on the effects of optogenetically generated transients in non-cued trials where such transients normally are not observed. Even if restricted to the prefrontal cortex, such cholinergic transients evoked

a high rate of false alarms.[40] In other words, in the absence of a cue, artificially generated transients are sufficient to force a false reporting of a cue.

Cholinergic transients appear to have the capacity to exert complex behavioral responses in part by generating oscillations in the gamma range and orchestrating theta-gamma cross-frequency coupling.[49] Such coordinated synchrony across multiple frequency bands suggests that cholinergic transients can organize the cooperation of multiple populations of neurons, synchronize cue-bound action, and broadcast this cooperation across cortical and subcortical regions to generate a complex, cueoriented behavior. Stimulation of M1 muscarinic acetylcholine receptors (mAChRs) is essential for such effects of ACh. These receptors are expressed by cortical interneurons[50] and cortical output neurons[51] (see green dots in Fig. 1). Consistent with the view that M1 stimulation is necessary for the generation of high-frequency oscillations and cross-frequency coupling, and thus for cues to control behavior,[34,49,52-54] the administration of an M1 positive allosteric modulator (PAM) partly rescued the detection rates of rats with partial removal of cholinergic inputs to the cortex[55] and, in a rodent model of parkinsonian falls (see later), reduced the rates of falls.[56]

Cholinergic Top-Down Control

Earlier we discussed evidence indicating a necessary role of cholinergic signaling for the detection of cues. However, studies in humans and rodents have also pointed to cholinergic influences over attentional performance across multiple trials, lasting several minutes. Collectively, these studies indicate that higher levels of cholinergic activity mediate superior top-down or goal-directed attention.[57-62] For example, persons expressing a subcapacity variant of the neuronal choline transporter (CHT), or patients with (partial) degeneration of the forebrain cholinergic system, are more distractible when performing sustained attention tasks (SATs) than wild-type humans.[63-66] Rats performing a SAT respond to a distractor challenge by further increasing cholinergic activity, and higher levels of cholinergic activity —over blocks of trials—are correlated with greater distractor resistance.[67,68]

The timescale of such supra-trial-based cholinergic control of attention may suggest the presence of a relatively slow mode of cholinergic signaling when compared with fast cholinergic transients described earlier. However, cholinergic transients produce relatively lasting postsynaptic neurophysiological effects, mentioned earlier, and such modulation of intrinsic and efferent cortical networks can serve to maintain the rules of stimulus–response mappings relevant to the current context and goal (“task sets”) over longer periods.[54] Thus, the postsynaptic effects of cholinergic transients may sufficiently explain the cholinergic mediation of attentional control.[33] As we will see next, given the complementary roles of cortical cholinergic activity in maintaining high levels of attentional control and high cue detection rates, the impact of losses of ACh for gait control, postural stability, and fall rates can be conceptualized.

Cholinergic Control of Movement Cues

Just as cues in attentional tasks require cholinergic signaling to be detected, exteroceptive and proprioceptive cues are hypothesized to require cortical cholinergic processing to guide complex movements and trigger corrections. As relatively high cholinergic signaling

levels mediate relatively better attentional control, including higher cue detection rates over extended periods of time, disruption of cholinergic signaling would be predicted to deprive the orchestration of complex movements from attentional supervision and effective error detection. For example, parkinsonian fallers, who exhibit cholinergic losses and attentional control deficits,[66,69-71] differ from non-fallers by exhibiting impairments in cued-turning behavior.[11,72-74] While walking, cued turning requires the detection of exteroceptive cues, including the cue that commands the turn and spatial cues (where is the wall, the corner, what is the nature of the surface, are there potential obstacles, etc.). Moreover, turning involves the disruption of regularly patterned, automatic movement and the execution of complex shifts in gait, posture, and balance.[75] Attention to such proprioceptive information fosters the detection of deviations in gait, posture, and balance and thus is necessary for triggering corrective action. In the presence of cholinergic-attentional deficits, failures to detect such cues contribute to turning errors, and a failure to execute corrective actions increases the risk for falls (see also Schulz et al.,[76] Weaver et al., [77] and Amboni et al.[78]).

Despite the finding that, in parkinsonian fallers, cholinergic-attentional losses, but not striatal DA losses, are associated with higher fall rates,[70] the impact of the former necessarily results from interactions with the disease-defining DA losses. Even in older persons not suffering from PD but exhibiting gait abnormalities and an enhanced risk of falls,[79] the age-related decline in cholinergic function and associated limitations of attentional capacities[17-19,80,81] likely interacts with age-related losses of basal ganglia DA[82] to yield impairments in gait and balance. Consistent with this view, rats with combined (or dual) cortical cholinergic and dorsomedial striatal DA losses (“DL rats”), modeling the combined cholinergic–dopaminergic degeneration observed in parkinsonian fallers, exhibit heightened fall rates while traversing dynamic surfaces and fail to execute cued turns. In contrast, rats with only cholinergic losses[48,83,84] or only dorsomedial striatal DA losses do not produce elevated fall rates.[85] However, falls associated with more complete striatal DA loss are associated with major sensory-motor impairments and freezing behavior, reflecting the falls in severe, advanced PD.[86] Such falls belong to a category separate from our focus on the impact of disruption of the cognitive–motor interface.

In DL rats, the analyses of the relationships between cholinergic and dopaminergic losses and their fall rates indicated a correlation between fall rates and DA but not cholinergic losses.[48] This finding suggested that cortical cholinergic loss unmasks the impact of striatal DA losses: larger striatal DA losses yield greater behavioral impairments once the attentional (compensatory) supervision of the impaired striatum is no longer available (the impact of striatal loss will be discussed further later). Consider an example to illustrate this interpretation: approaching the end of a moving walkway you would normally plan your steps for transitioning and attend to the execution of these steps by adjusting posture and balance. A stepping mistake, or a balancing error following a stepping mistake, will be effectively corrected. In parkinsonian fallers, such planning of movements is considered to be drastically slower and less effective, because of striatal DA loss,[87-90] and therefore requires substantially greater attentional monitoring, including the detection of multiple movement errors and the initiation of corrections of movement, posture, and balance. In interactions with cholinergic-attentional limitations, such supporting and compensatory attentional control is deficient, revealing gait disorders and a high risk for falls.

Evidence from studies in PD patients is consistent with this conceptualization. During walking and obstacle negotiation, PD patients exhibit greater activation than healthy older adults in right frontal regions considered to be part of the visuospatial attention network. However, frontal activation was insufficient to fully compensate for the impaired gait control in PD patients.[91,92] Assuming that a portion of the right frontal activation reflects cholinergic signaling,[64] these findings support the interpretation of the cortico-striatal interactions derived from the aforementioned rodent model. In particular, frontal attention systems are recruited to supervise complex movement control but, in the vulnerable subjects, the efficacy of such compensatory recruitment remains limited, revealing the impact of (striatal) impairments in gait and balance control.

Directly comparable evidence from parkinsonian fallers appears unavailable, perhaps due in part to the challenges in recruiting such patients to imaging studies, but would be expected to indicate attenuated (cholinergic) activation of such regions and thus the loss of attentional control over striatal functions.[93-96] In PD patients with a history of freezing of gait, which is a major risk factor for falls and potentially a behavioral expression of disrupted cortico-striatal control,[29,97] attenuated functional connectivity within the right-hemispheric attention network may in part reflect the loss of cortical cholinergic mediation of attentional control.[98]

Cortico-Striatal Transfer of Movement Cues

Following the cholinergically mediated detection of movement-related cues in the cortex, this information is transferred to the striatum to guide the selection and sequencing of movement and movement corrections and to maintain postural stability and balance (Fig. 1). Glutamatergic projections from frontal regions to the dorsomedial striatum[99,100] are a major constituent of the fronto-striatal cognitive loop.[101] In addition, cortico-thalamic-striatal circuitry forms a parallel network via which the frontal cortex exerts top-down control over striatal functions, with both direct cortico-striatal and thalamo-striatal projections seemingly “importing” overlapping information[102,103] and equally influencing striatal ChIs.[104,105] ChIs will be discussed later as essential attentional–motor integrators.[106,107]

There is substantial evidence indicating the role of cortico-striatal information transfer for, in broad terms, adapting to changing action outcomes or switching between behavioral alternatives.[93,108-112] However, exactly what aspects of movement-related cues are imported into striatal circuitry awaits to be addressed by, for example, recording glutamate signaling[113] in rats performing complex movements and committing errors, such as while traversing complex beams or executing cued turns.[48,114-116] Understanding the glutamatergic coding of movement cues would then also allow to directly assess the impact of cortical cholinergic denervation on the cortico-striatal transfer of cues. The finding that enhanced cortico-striatal connectivity in PD patients is associated with increased severity of FOG[29] may reflect the impact of cortical cholinergic losses on cortico-striatal transfer of movement cues.

Attentional–Motor Integration in the Striatum: ChIs as Essential Integrators

Cortical and thalamic glutamatergic projections converge onto ChIs (see Fig. 1).[106,107,117] ChI-derived cholinergic signaling in turn modulates the activity of these glutamatergic inputs and enforces inhibitory control on striatal output neurons.[118] This anatomical organization has been interpreted as reflecting the capability of ChIs to select among cortico-striatal inputs for influencing movement shifts and triggering movement corrections.[119] Moreover, the interactions between ChIs, cortico-, thalamo-, and nigro-striatal afferents appear to be reciprocal (Fig. 1),[120-124] further supporting the view that ChIs serve as an essential striatal integrator that orchestrates complex movements and error-triggered corrections.[125-128]

A recent series of experiments were designed to test the general hypothesis that ChIs are essential attentional–motor integrators.[116] In addition to the beam-traversal task previously used to demonstrate a heightened propensity for falls in rats modeling the combined cortical cholinergic and striatal DA losses of parkinsonian fallers (DL rats), these studies assessed the ability to execute cued turns and cued stops in rats walking a treadmill that paused and reversed direction following turn cues and stopped and resumed in the same direction following a stop cue. The development of this task was inspired by the finding that parkinsonian fallers exhibit (cued) turning deficits relative to non-fallers.[72,73] The turning rates of DL rats were robustly reduced, signifying impairments in the capacity to detect movement cues or utilize such cues to initiate shifts from forward walking to turning. In DL rats, the extent and location of striatal DA depletion, but not the degree of cortical cholinergic deafferentation, were correlated with impaired turning performance, mirroring previous observations about the relationships between deafferentation patterns and performance.[48] This finding again supports the view that the loss of cortical cholinergic inputs unmasks the impact of striatal DA losses. These results extend the usefulness of DL rats as a model of the disrupted attentional–motor interface of parkinsonian fallers.

The essential role of ChIs for these behaviors was demonstrated by transfecting ChIs in the dorsomedial striatum of otherwise-intact rats with an inhibitory designer receptor exclusively activated by designer drug (DREADD). Activation of this DREADD fully reproduced the cued turn deficits and partially replicated the high fall rates of DL rats (Fig. 3). These findings suggest that on inhibition of these neurons, cue-guided modification of behavior was disrupted,[129] consistent with the hypothesis that ChIs integrate cortico-striatal input with striatal functioning.

In addition, ChIs in DL rats were transfected with an excitatory DREADD. Chemogenetic stimulation of ChIs in DL rats reduced fall rates and restored cued-turning performance. Importantly, the stimulation of ChIs was relatively more effective in rats with viral transfection spaces situated lateral to the DA depletion areas in the dorsomedial striatum, suggesting that the benefits of ChI stimulation required the interplay with DA afferents and therefore also with glutamatergic afferents from cortex and thalamus. Consistent with such bidirectional interactions between ChIs and striatal afferent systems, ChI inhibition per se was previously demonstrated to impair the selection of cortico-striatal input for further processing[130,131] and to suppress the regulation of striatal DA.[122,132] Furthermore, striatal DA denervation causes diminished ChI function.[133] Thus, ChI inhibition disrupts the

reciprocal interactions between ChIs, cortico- and thalamo-striatal, and nigrostriatal activity. These considerations also begin to illustrate how ChI inhibition can reproduce, at least in part, the effects of dual cholinergic–dopaminergic losses on complex movement control.

The results from experiments on the effects of chemogenetic stimulation of ChIs in DL rats further support the view that ChIs integrate cortico-striatal with nigro-striatal activity. In these rats, stimulation of ChIs in intact striatal tissue rescued performance more robustly than in cases where transfected ChIs were partly situated within DA-depleted areas. This finding is expected given that ChI stimulation also activates DA signaling.[122,123,132] Furthermore, ChIs are characterized by relatively large dendritic and axonal spaces[134] and broad responsiveness to sensory cues.[135] Therefore, the specific region in which the stimulation of striatal ChIs produces beneficial performance effects may be less crucial than preservation of their connectivity, particularly with midbrain DA neurons.

These experiments[116] did not address the important question of how chemogenetic inhibition or stimulation of ChIs modifies their neurophysiological characteristics during complex movements. ChIs typically exhibit autonomous, tonic firing patterns interspersed with pauses.[128,135-137] After striatal DA loss, ChI firing rates are reduced, and the firing and pausing patterns become uncorrelated.[133] Chemogenetic inhibition may similarly have suppressed these patterns of ChI activity (see also Zucca et al.[118]). The performance effects of stimulation of ChIs are more difficult to map onto ChI firing patterns. In vitro, chemogenetic stimulation increases in ChI firing rates and reduces pausing.[125,138] The function of pauses currently does not seem to be sufficiently understood to explain how the absence of pauses could benefit the integrational function of ChIs and rescue the behavior of DL rats (see also Kharkwal et al.[139]).

Our focus on the role of ChIs in integrating cortico-striatal with nigro-striatal input does not account for the role of noncholinergic populations of striatal interneurons,[117,140-142] or additional complexities within circuitry linking cortico-striatal with nigro-striatal input to multiple types of striatal output neurons.[130,143,144] Furthermore, the precise impact of DA losses on complex movement control remains undefined. Contemporary theories of striatal DA function have focused on movement-energizing effects of DA, suggesting that slowed and disorganized movement selection reflects an amotivational motor state, including a loss of attention to movement cues.[90,145-147] Although such a view of striatal DA function amplifies the dependency of a DA-depleted striatum on cortico-striatal transfer of information about movement cues, and thus is consistent with the “unmasking” effects of cortical cholinergic deafferentation discussed earlier, the precise impact of DA losses on striatal information processing remains unclear. Clarification of this issue may require monitoring of striatal circuitry in rodents performing complex movement in the presence and absence of striatal DA innervation.

Status of ChIs in Parkinsonian Fallers

ChIs have been conceptualized as a major integrator of cortico-striatal information about movement cues with the movement-energizing function of nigro-striatal, dopaminergic activity. The integrational capacity of ChIs is considered compromised as a result of striatal DA and cortical-cholinergic losses that characterize parkinsonian fallers (references

provided earlier). However, ChI function may independently decline in parkinsonian fallers as well. Using a positron emission tomography ligand ([^{18}F]FEOBV) to visualize the vesicular acetylcholine transporter, lower striatal FEOBV binding was observed in parkinsonian fallers exhibiting freezing of gait when compared with fallers not exhibiting freezing of gait.[148] Loss of striatal FEOBV binding was also observed in healthy, aged controls.[80] Loss of FEOBV binding may indicate a loss of cholinergic neurons[149-151] or reflect compensatory effects in neurons with elevated firing rates,[152] which, in the striatum, have been considered to result from DA loss.[153] Regardless of these interpretational complexities, the evidence indicates robust alterations in ChIs in PD patients with gait dysfunction and heightened fall risk. Thus, the disruption of the integrational capacity of ChIs in parkinsonian fallers may be not only secondary to a functional loss of cortico-striatal input and degeneration of nigral afferents but also a decline in their own integrity. Among the numerous nodes constituting the larger circuit mediating complex movement control (Fig. 1), such a direct and indirect disruption of ChI function, therefore, may represent a key neuronal mechanism responsible for gait disorder and falls. The finding that, in otherwise-intact rats, ChI inhibition alone causes falls and complex movement deficits[116] is consistent with this conclusion.

Conclusions

Attentional impairments in PD patients have long been documented and have more recently been attributed to cholinergic deficiencies in telencephalic regions and associated with complex movement control deficits.[17,18,96,154,155] This review identifies the key nodes of the cortico-striatal circuitry integrating the cognitive–motor functions, which are at the core of complex movement control (Fig. 1). The available evidence in support of this circuit also suggests potential treatments aimed at reducing fall rates in PD patients and perhaps also in the non-parkinsonian elderly. Given the limitations of acetylcholinesterase inhibitors to improve or rescue transient cholinergic signaling,[156] such signaling may be more effectively enhanced or restored by modulating postsynaptic, specifically M1-mediated, mechanisms. As mentioned, we found that an M1 PAM improved the attentional performance of rats with partial losses of the cortical cholinergic input system.[55] More recently, we also observed that such a treatment benefits the complex movement control of DL rats (see earlier for a description of these rats as a model of the dual cortical cholinergic–striatal dopaminergic losses that characterize PD fallers). The M1 PAM was particularly effective in testing conditions that interfered with the execution of relatively rhythmic, stable walking patterns and thus required nearly continuous reprogramming of gait and balance.[56] Such testing conditions may model real-life situations, such as encountering unexpected obstacles or an unstable surface, which provoke gait and balancing errors and falls and thus which require the continuous monitoring of dynamic environmental and proprioceptive cues. However, such monitoring is deprioritized over walking even in healthy people[2,6] and thus is likely to be drastically impaired in patients with gait disorders and a history of falls, as well as with cholinergic-attentional losses. Therefore, it will be important that the clinical efficacy of such a potential therapeutic treatment be assessed using behaviors that tax the capacity for cognitive–motor interactions. Other treatments may be designed to enhance the functions of the striatal nodes of the cognitive–motor interface,[83,84] particularly ChI function, although

the latter target involves neurophysiological complexities that require careful evaluation to avoid worsening of the primary motor symptoms of PD.[120]

Acknowledgments:

This research was supported by PHS grant P50NS091856 (Morris K. Udall Center of Excellence for Parkinson's Disease Research, University of Michigan, Ann Arbor, MI).

References

1. Krauzlis RJ, Bollimunta A, Arcizet F, Wang L. Attention as an effect not a cause. Trends Cogn Sci 2014;18(9):457–464. [PubMed: 24953964]
2. Mersmann F, Bohm S, Bierbaum S, Dietrich R, Arampatzis A. Young and old adults prioritize dynamic stability control following gait perturbations when performing a concurrent cognitive task. Gait Posture 2013;37(3):373–377. [PubMed: 23122597]
3. Yogev-Seligmann G, Hausdorff JM, Giladi N. Do we always prioritize balance when walking? Towards an integrated model of task prioritization. Mov Disord 2012;27(6):765–770. [PubMed: 22419512]
4. Doumas M, Smolders C, Krampe RT. Task prioritization in aging: effects of sensory information on concurrent posture and memory performance. Exp Brain Res 2008;187(2):275–281. [PubMed: 18273609]
5. Brown LA, Sleik RJ, Polych MA, Gage WH. Is the prioritization of postural control altered in conditions of postural threat in younger and older adults? J Gerontol A Biol Sci Med Sci 2002;57(12):M785–M792. [PubMed: 12456737]
6. Ladouce S, Donaldson DI, Dudchenko PA, Ietswaart M. Mobile EEG identifies the re-allocation of attention during real-world activity. Sci Rep 2019;9(1):15851. [PubMed: 31676780]
7. Livingston LA, Stevenson JM, Olney SJ. Stairclimbing kinematics on stairs of differing dimensions. Arch Phys Med Rehabil 1991;72(6):398–402. [PubMed: 2059107]
8. Conway ZJ, Blackmore T, Silburn PA, Cole MH. Dynamic balance control during stair negotiation for older adults and people with Parkinson disease. Hum Mov Sci 2018;59:30–36. [PubMed: 29602049]
9. Lord S, Rochester L, Hetherington V, Allcock LM, Burn D. Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's disease. Gait & Posture 2010;31(2):169–174. [PubMed: 19896382]
10. Allcock LM, Rowan EN, Steen IN, Wesnes K, Kenny RA, Burn DJ. Impaired attention predicts falling in Parkinson's disease. Parkinsonism Relat Disord 2009;15(2):110–115. [PubMed: 18487069]
11. Stuart S, Galna B, Delicato LS, Lord S, Rochester L. Direct and indirect effects of attention and visual function on gait impairment in Parkinson's disease: influence of task and turning. Eur J Neurosci 2017;46(1):1703–1716. [PubMed: 28444834]
12. Fasano A, Canning CG, Hausdorff JM, Lord S, Rochester L. Falls in Parkinson's disease: a complex and evolving picture. Mov Disord 2017;32(11):1524–1536. [PubMed: 29067726]
13. Naismith SL, Shine JM, Lewis SJG. The specific contributions of set-shifting to freezing of gait in Parkinson's disease. Mov Disord 2010;25(8):1000–1004. [PubMed: 20198644]
14. O'Halloran AM, Penard N, Galli A, Fan CW, Robertson IH, Kenny RA. Falls and falls efficacy: the role of sustained attention in older adults. BMC Geriatr 2011;11(85):85. [PubMed: 22182487]
15. Persad CC, Jones JL, Ashton-Miller JA, Alexander NB, Giordani B. Executive function and gait in older adults with cognitive impairment. J Gerontol A Biol Sci Med Sci 2008;63(12):1350–1355. [PubMed: 19126848]
16. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. Gait Posture 2002;16(1):1–14. [PubMed: 12127181]
17. Shumway-Cook A, Woollacott M. Attentional demands and postural control: the effect of sensory context. J Gerontol A Biol Sci Med Sci 2000;55(1):M10–M16. [PubMed: 10719767]

18. Brown LA, Shumway-Cook A, Woollacott MH. Attentional demands and postural recovery: the effects of aging. J Gerontol A Biol Sci Med Sci 1999;54(4):M165–M171. [PubMed: 10219006]
19. Shumway-Cook A, Woollacott M, Kerns KA, Baldwin M. The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. J Gerontol A Biol Sci Med Sci 1997;52(4):M232–M240. [PubMed: 9224435]
20. MacKinnon CD. Sensorimotor anatomy of gait, balance, and falls. Handb Clin Neurol 2018;159:3–26. [PubMed: 30482322]
21. Paul SS, Sherrington C, Canning CG, Fung VS, Close JC, Lord SR. The relative contribution of physical and cognitive fall risk factors in people with Parkinson's disease: a large prospective cohort study. Neurorehabil Neural Repair 2014;28(3):282–290. [PubMed: 24243915]
22. Pelicioni PHS, Menant JC, Latt MD, Lord SR. Falls in Parkinson's disease subtypes: risk factors, locations and circumstances. Int J Environ Res Public Health 2019;16(12):2216. 10.3390/ijerph16122216.
23. Virmani T, Pillai L, Glover A, et al. Impaired step-length setting prior to turning in Parkinson's disease patients with freezing of gait. Mov Disord 2018;33(11):1823–1825. [PubMed: 30306629]
24. Cole MH, Silburn PA, Wood JM, Worringham CJ, Kerr GK. Falls in Parkinson's disease: kinematic evidence for impaired head and trunk control. Mov Disord 2010;25(14):2369–2378. [PubMed: 20737542]
25. Galna B, Murphy AT, Morris ME. Obstacle crossing in Parkinson's disease: Mediolateral sway of the centre of mass during level-ground walking and obstacle crossing. Gait Posture 2013;38(4):790–794. [PubMed: 23647655]
26. Cowie D, Limousin P, Peters A, Hariz M, Day BL. Doorway-provoked freezing of gait in Parkinson's disease. Mov Disord 2012;27(4):492–499. [PubMed: 21997389]
27. Cole MH, Silburn PA, Wood JM, Kerr GK. Falls in Parkinson's disease: evidence for altered stepping strategies on compliant surfaces. Parkinsonism Relat Disord 2011;17(8):610–616. [PubMed: 21676644]
28. FGDM C, Stella F, de Andrade LP, et al. Gait and risk of falls associated with frontal cognitive functions at different stages of Alzheimer's disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2012;19(5):644–656. [PubMed: 22360785]
29. Ehgoetz Martens KA, Hall JM, Georgiades MJ, et al. The functional network signature of heterogeneity in freezing of gait. Brain 2018;141(4):1145–1160. [PubMed: 29444207]
30. Mendoza G, Merchant H. Motor system evolution and the emergence of high cognitive functions. Prog Neurobiol 2014;122:73–93. [PubMed: 25224031]
31. Picciotto Marina R, Higley Michael J, Mineur Yann S. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron 2012;76(1):116–129. [PubMed: 23040810]
32. Ballinger EC, Ananth M, Talmage DA, Role LW. Basal forebrain cholinergic circuits and signaling in cognition and cognitive decline. Neuron 2016;91(6):1199–1218. [PubMed: 27657448]
33. Sarter M, Lustig C. Forebrain cholinergic signaling: wired and phasic, not tonic, and causing behavior. J Neurosci 2020;40(4):712–719. [PubMed: 31969489]
34. Sarter M, Lustig C, Berry AS, Gritton HJ, Howe WM, Parikh V. What do phasic cholinergic signals do? Neurobiol Learn Mem 2016;130:135–141. [PubMed: 26911787]
35. Posner MI, Snyder CR, Davidson BJ. Attention and the detection of signals. J Exp Psychol 1980;109(2):160–174. [PubMed: 7381367]
36. Parikh V, Kozak R, Martinez V, Sarter M. Prefrontal acetylcholine release controls cue detection on multiple timescales. Neuron 2007;56(1):141–154. [PubMed: 17920021]
37. Parikh V, Pomerleau F, Huettl P, Gerhardt GA, Sarter M, Bruno JP. Rapid assessment of in vivo cholinergic transmission by amperometric detection of changes in extracellular choline levels. Eur J Neurosci 2004;20(6):1545–1554. [PubMed: 15355321]
38. Giuliano C, Parikh V, Ward JR, Chiamulera C, Sarter M. Increases in cholinergic neurotransmission measured by using choline-sensitive microelectrodes: enhanced detection by hydrolysis of acetylcholine on recording sites? Neurochem Int 2008;52(7):1343–1350. [PubMed: 18346819]

39. Howe WM, Berry AS, Francois J, et al. Prefrontal cholinergic mechanisms instigating shifts from monitoring for cues to cue-guided performance: converging electrochemical and fMRI evidence from rats and humans. J Neurosci 2013;33(20):8742–8752. [PubMed: 23678117]
40. Gritton HJ, Howe WM, Mallory CS, Hetrick VL, Berke JD, Sarter M. Cortical cholinergic signaling controls the detection of cues. Proc Natl Acad Sci U S A 2016;113(8):E1089–E1097. [PubMed: 26787867]
41. Parikh V, Ji J, Decker MW, Sarter M. Prefrontal beta2 subunit-containing and alpha7 nicotinic acetylcholine receptors differentially control glutamatergic and cholinergic signaling. J Neurosci 2010;30(9):3518–3530. [PubMed: 20203212]
42. Parikh V, Man K, Decker MW, Sarter M. Glutamatergic contributions to nicotinic acetylcholine receptor agonist-evoked cholinergic transients in the prefrontal cortex. J Neurosci 2008;28(14):3769–3780. [PubMed: 18385335]
43. Lambe EK, Picciotto MR, Aghajanian GK. Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. Neuropsychopharmacology 2003;28(2):216–225. [PubMed: 12589374]
44. Runfeldt MJ, Sadovsky AJ, MacLean JN. Acetylcholine functionally reorganizes neocortical microcircuits. J Neurophysiol 2014;112(5):1205–1216. [PubMed: 24872527]
45. Wester JC, Contreras D. Differential modulation of spontaneous and evoked thalamocortical network activity by acetylcholine level in vitro. J Neurosci 2013;33(45):17951–17966. [PubMed: 24198382]
46. McGaughy J, Sarter M. Sustained attention performance in rats with intracortical infusions of 192 IgG-saporin-induced cortical cholinergic deafferentation: effects of physostigmine and FG 7142. Behav Neurosci 1998;112(6):1519–1525. [PubMed: 9926833]
47. McGaughy J, Kaiser T, Sarter M. Behavioral vigilance following infusions of 192 IgG-saporin into the basal forebrain: selectivity of the behavioral impairment and relation to cortical AChE-positive fiber density. Behav Neurosci 1996;110(2):247–265. [PubMed: 8731052]
48. Kucinski A, Paolone G, Bradshaw M, Albin R, Sarter M. Modeling fall propensity in Parkinson's disease: deficits in the attentional control of complex movements in rats with cortical-cholinergic and striatal-dopaminergic deafferentation. J Neurosci 2013;33(42):16522–16539. [PubMed: 24133257]
49. Howe WM, Gritton HJ, Lusk NA, et al. Acetylcholine release in prefrontal cortex promotes gamma oscillations and theta-gamma coupling during cue detection. J Neurosci 2017;37(12):3215–3230. [PubMed: 28213446]
50. Chen N, Sugihara H, Sur M. An acetylcholine-activated microcircuit drives temporal dynamics of cortical activity. Nat Neurosci 2015;18(6):892–902. [PubMed: 25915477]
51. Oda S, Tsuneoka Y, Yoshida S, et al. Immunolocalization of muscarinic M1 receptor in the rat medial prefrontal cortex. J Comp Neurol 2018;526(8):1329–1350. [PubMed: 29424434]
52. Dasilva M, Brandt C, Gotthardt S, Gieselmann MA, Distler C, Thiele A. Cell class-specific modulation of attentional signals by acetylcholine in macaque frontal eye field. Proc Natl Acad Sci U S A 2019;116(40):20180–20189. [PubMed: 31527242]
53. Cui ED, Strowbridge BW. Selective attenuation of Ether-a-go-go related K(+) currents by endogenous acetylcholine reduces spike-frequency adaptation and network correlation. Elife 2019;8: e44954. https://pubmed.ncbi.nlm.nih.gov/31032798/. [PubMed: 31032798]
54. Lu Y, Sarter M, Zochowski M, Booth V. Phasic cholinergic signaling promotes emergence of local gamma rhythms in excitatory-inhibitory networks. Eur J Neurosci 2020;52(6):3545–3560. [PubMed: 32293081]
55. Kucinski A, Phillips KB, Koshy Cherian A, Sarter M. Rescuing the attentional performance of rats with cholinergic losses by the M1 positive allosteric modulator TAK-071. Psychopharmacology (Berl) 2020;237:137–153. [PubMed: 31620809]
56. Kucinski A, Sarter M. Reduction of falls in a rat model of PD falls by the M1 PAM TAK-071. Psychopharmacology 2021 (under review).
57. Danielmeier C, Allen EA, Jocham G, Onur OA, Eichele T, Ullsperger M. Acetylcholine mediates behavioral and neural post-error control. Curr Biol 2015;25(11):1461–1468. [PubMed: 25959965]

58. Herrero JL, Roberts MJ, Delicato LS, Gieselmann MA, Dayan P, Thiele A. Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. Nature 2008;454(7208):1110–1114. [PubMed: 18633352]
59. Avery MC, Dutt N, Krichmar JL. Mechanisms underlying the basal forebrain enhancement of top-down and bottom-up attention. Eur J Neurosci 2014;39(5):852–865. [PubMed: 24304003]
60. Rokem A, Landau AN, Garg D, Prinzmetal W, Silver MA. Cholinergic enhancement increases the effects of voluntary attention but does not affect involuntary attention. Neuropsychopharmacology 2010;35(13):2538–2544. [PubMed: 20811340]
61. Kozak R, Bruno JP, Sarter M. Augmented prefrontal acetylcholine release during challenged attentional performance. Cereb Cortex 2006;16(1):9–17. [PubMed: 15788700]
62. Hasselmo ME, McGaughy J. High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. Prog Brain Res 2004;145:207–231. [PubMed: 14650918]
63. Sarter M, Lustig C, Blakely RD, Koshy Cherian A. Cholinergic genetics of visual attention: human and mouse choline transporter capacity variants influence distractibility. J Physiol Paris 2016;110 (1–2):10–18. [PubMed: 27404793]
64. Berry AS, Blakely RD, Sarter M, Lustig C. Cholinergic capacity mediates prefrontal engagement during challenges to attention: evidence from imaging genetics. Neuroimage 2015;108:386–395. [PubMed: 25536497]
65. Berry AS, Demeter E, Sabhapathy S, et al. Disposed to distraction: genetic variation in the cholinergic system influences distractibility but not time-on-task effects. J Cogn Neurosci 2014;26(9):1981–1991. [PubMed: 24666128]
66. Kim K, Muller M, Bohnen NI, Sarter M, Lustig C. The cortical cholinergic system contributes to the top-down control of distraction: evidence from patients with Parkinson's disease. Neuroimage 2019;190:107–117. [PubMed: 29277400]
67. St Peters M, Demeter E, Lustig C, Bruno JP, Sarter M. Enhanced control of attention by stimulating mesolimbic-corticopetal cholinergic circuitry. J Neurosci 2011;31(26):9760–9771. [PubMed: 21715641]
68. Dalley JW, McGaughy J, O'Connell MT, Cardinal RN, Levita L, Robbins TW. Distinct changes in cortical acetylcholine and noradrenaline efflux during contingent and noncontingent performance of a visual attentional task. J Neurosci 2001;21(13):4908–4914. [PubMed: 11425918]
69. Bohnen NI, Muller ML, Kotagal V, et al. Heterogeneity of cholinergic denervation in Parkinson's disease without dementia. J Cereb Blood Flow Metab 2012;32(8):1609–1617. [PubMed: 22569194]
70. Bohnen NI, Müller MLTM, Koeppe RA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. Neurology 2009;73(20):1670–1676. [PubMed: 19917989]
71. Bohnen NI, Albin RL. Cholinergic denervation occurs early in Parkinson disease. Neurology 2009;73(4):256–257. [PubMed: 19535769]
72. Cheng FY, Yang YR, Wang CJ, et al. Factors influencing turning and its relationship with falls in individuals with Parkinson's disease. PLoS One 2014;9(4):e93572. [PubMed: 24699675]
73. Stack E, Ashburn A. Dysfunctional turning in Parkinson's disease. Disabil Rehabil 2008;30(16):1222–1229. [PubMed: 18608364]
74. Boonstra TA, van der Kooij H, Munneke M, Bloem BR. Gait disorders and balance disturbances in Parkinson's disease: clinical update and pathophysiology. Curr Opin Neurol 2008;21(4):461–471. [PubMed: 18607208]
75. Oh K, Stanley CJ, Damiano DL, Kim J, Yoon J, Park HS. Biomechanical evaluation of virtual reality-based turning on a self-paced linear treadmill. Gait Posture 2018;65:157–162. [PubMed: 30510358]
76. Schulz J, Pagano G, Fernandez Bonfante JA, Wilson H, Politis M. Nucleus basalis of Meynert degeneration precedes and predicts cognitive impairment in Parkinson's disease. Brain 2018;141(5):1501–1516. [PubMed: 29701787]
77. Weaver TB, Robinovitch SN, Laing AC, Yang Y. Falls and Parkinson's disease: evidence from video recordings of actual fall events. J Am Geriatr Soc 2016;64(1):96–101. [PubMed: 26782857]

78. Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. Mov Disord 2013;28(11):1520–1533. [PubMed: 24132840]
79. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. Mov Disord 2006;21(7):950–957. [PubMed: 16541455]
80. Albin RL, Bohnen NI, Muller M, et al. Regional vesicular acetylcholine transporter distribution in human brain: a [(18) F] fluoroethoxybenzovesamicol positron emission tomography study. J Comp Neurol 2018;526:2884–2897. [PubMed: 30255936]
81. Ayers EI, Tow AC, Holtzer R, Verghese J. Walking while talking and falls in aging. Gerontology 2014;60(2):108–113. [PubMed: 24192342]
82. Cham R, Perera S, Studenski SA, Bohnen NI. Age-related striatal dopaminergic denervation and severity of a slip perturbation. J Gerontol A Biol Sci Med Sci 2011;66(9):980–985. [PubMed: 21746736]
83. Koshy Cherian A, Kucinski A, Wu R, de Jong IEM, Sarter M. Co-treatment with rivastigmine and idalopirdine reduces the propensity for falls in a rat model of falls in Parkinson's disease. Psychopharmacology (Berl) 2019;236(6):1701–1715. [PubMed: 30607479]
84. Kucinski A, de Jong IE, Sarter M. Reducing falls in Parkinson's disease: interactions between donepezil and the 5-HT6 receptor antagonist idalopirdine on falls in a rat model of impaired cognitive control of complex movements. Eur J Neurosci 2017;45(2):217–231. [PubMed: 27469080]
85. Kucinski A, Albin RL, Lustig C, Sarter M. Modeling falls in Parkinson's disease: slow gait, freezing episodes and falls in rats with extensive striatal dopamine loss. Behav Brain Res 2015;282:155–164. [PubMed: 25595423]
86. Bohnen NI, Frey KA, Studenski S, et al. Extra-nigral pathological conditions are common in Parkinson's disease with freezing of gait: an in vivo positron emission tomography study. Mov Disord 2014;29(9):1118–1124. [PubMed: 24909584]
87. Redgrave P, Rodriguez M, Smith Y, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat Rev Neurosci 2010;11(11):760–772. [PubMed: 20944662]
88. da Silva JA, Tecuapetla F, Paixao V, Costa RM. Dopamine neuron activity before action initiation gates and invigorates future movements. Nature 2018;554(7691):244–248. [PubMed: 29420469]
89. Gepshtein S, Li X, Snider J, Plank M, Lee D, Poizner H. Dopamine function and the efficiency of human movement. J Cogn Neurosci 2014;26(3):645–657. [PubMed: 24144250]
90. Mazzoni P, Hristova A, Krakauer JW. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. J Neurosci 2007;27(27):7105–7116. [PubMed: 17611263]
91. Maidan I, Rosenberg-Katz K, Jacob Y, et al. Altered brain activation in complex walking conditions in patients with Parkinson's disease. Parkinsonism Relat Disord 2016;25:91–96. [PubMed: 26861167]
92. Maidan I, Nieuwhof F, Bernad-Elazari H, et al. The Role of the frontal lobe in complex walking among patients with Parkinson's disease and healthy older adults: an fNIRS study. Neurorehabil Neural Repair 2016;30(10):963–971. [PubMed: 27221042]
93. van Schouwenburg MR, O'Shea J, Mars RB, Rushworth MF, Cools R. Controlling human striatal cognitive function via the frontal cortex. J Neurosci 2012;32(16):5631–5637. [PubMed: 22514324]
94. Cools R, Rogers R, Barker RA, Robbins TW. Top-down attentional control in Parkinson's disease: salient considerations. J Cogn Neurosci 2010;22(5):848–859. [PubMed: 19320545]
95. Strafella AP, Ko JH, Grant J, Fraraccio M, Monchi O. Corticostriatal functional interactions in Parkinson's disease:a rTMS/[11C]raclopride PET study. Eur J Neurosci 2005;22(11):2946–2952. [PubMed: 16324129]
96. Stam CJ, Visser SL, Op de Coul AA, et al. Disturbed frontal regulation of attention in Parkinson's disease. Brain 1993;116(Pt 5):1139–1158. [PubMed: 8221052]
97. Heremans E, Nieuwboer A, Vercruysse S. Freezing of gait in Parkinson's disease: where are we now? Curr Neurol Neurosci Rep 2013;13(6):350–359. [PubMed: 23625316]

98. Tessitore A, Amboni M, Esposito F, et al. Resting-state brain connectivity in patients with Parkinson's disease and freezing of gait. Parkinsonism Relat Disord 2012;18(6):781–787. [PubMed: 22510204]

99. Mailly P, Aliane V, Groenewegen HJ, Haber SN, Deniau JM. The rat prefrontostriatal system analyzed in 3D: evidence for multiple interacting functional units. J Neurosci 2013;33(13):5718–5727. [PubMed: 23536085]

100. Averbeck BB, Lehman J, Jacobson M, Haber SN. Estimates of projection overlap and zones of convergence within frontal-striatal circuits. J Neurosci 2014;34(29):9497–9505. [PubMed: 25031393]

101. Sharpe MJ, Stalnaker T, Schuck NW, Killcross S, Schoenbaum G, Niv Y. An integrated model of action selection: distinct modes of cortical control of striatal decision making. Annu Rev Psychol 2019;70:53–76. [PubMed: 30260745]

102. Diaz-Hernandez E, Contreras-Lopez R, Sanchez-Fuentes A, Rodriguez-Sibrian L, Ramirez-Jarquin JO, Tecuapetla F. The Thalamostriatal projections contribute to the initiation and execution of a sequence of movements. Neuron 2018;100(3):739–752. e735. [PubMed: 30344045]

103. Haber SN, Calzavara R. The cortico-basal ganglia integrative network: the role of the thalamus. Brain Res Bull 2009;78(2–3):69–74. [PubMed: 18950692]

104. Bradfield Laura A, Bertran-Gonzalez J, Chieng B, Balleine Bernard W. The thalamostriatal pathway and cholinergic control of goal-directed action: interlacing new with existing learning in the striatum. Neuron 2013;79:153–166. [PubMed: 23770257]

105. Matsumoto N, Minamimoto T, Graybiel AM, Kimura M. Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events. J Neurophysiol 2001;85(2):960–976. [PubMed: 11160526]

106. Mamaligas AA, Barcomb K, Ford CP. Cholinergic transmission at muscarinic synapses in the striatum is driven equally by cortical and thalamic inputs. Cell Rep 2019;28(4):1003–1014 e1003. [PubMed: 31340139]

107. Guo Q, Wang D, He X, et al. Whole-brain mapping of inputs to projection neurons and cholinergic interneurons in the dorsal striatum. PLoS One 2015;10(4):e0123381. [PubMed: 25830919]

108. Hart G, Bradfield LA, Fok SY, Chieng B, Balleine BW. The bilateral Prefronto-striatal pathway is necessary for learning new goal-directed actions. Curr Biol 2018;28(14):2218–2229.e2217. [PubMed: 30056856]

109. Hart G, Bradfield LA, Balleine BW. Prefrontal Corticostriatal disconnection blocks the Acquisition of Goal-Directed Action. J Neurosci 2018;38(5):1311–1322. [PubMed: 29301872]

110. Xiong Q, Znamenskiy P, Zador AM. Selective corticostriatal plasticity during acquisition of an auditory discrimination task. Nature 2015;521(7552):348–351. [PubMed: 25731173]

111. Ma L, Hyman JM, Phillips AG, Seamans JK. Tracking progress toward a goal in corticostriatal ensembles. J Neurosci 2014;34(6):2244–2253. [PubMed: 24501363]

112. Chatham CH, Frank MJ, Badre D. Corticostriatal output gating during selection from working memory. Neuron 2014;81(4):930–942. [PubMed: 24559680]

113. Hascup KN, Hascup ER, Pomerleau F, Huettl P, Gerhardt GA. Second-by-second measures of L-glutamate in the prefrontal cortex and striatum of freely moving mice. J Pharmacol Exp Ther 2008;324(2):725–731. [PubMed: 18024788]

114. Kucinski A, Kim Y, Sarter M. Basal forebrain chemogenetic inhibition disrupts the superior complex movement control of goal-tracking rats. Behav Neurosci 2019;133(1):121–134. [PubMed: 30688488]

115. Kucinski A, Lustig C, Sarter M. Addiction vulnerability trait impacts complex movement control: evidence from sign-trackers. Behav Brain Res 2018;350:139–148. [PubMed: 29705686]

116. Avila C, Kucinski A, Sarter M. Complex movement control in a rat model of Parkinsonian falls: bidirectional control by striatal cholinergic interneurons. J Neurosci 2020;40:6049–6067. [PubMed: 32554512]

117. Klug JR, Engelhardt MD, Cadman CN, et al. Differential inputs to striatal cholinergic and parvalbumin interneurons imply functional distinctions. Elife 2018;7:e35657. https://pubmed.ncbi.nlm.nih.gov/29714166/. [PubMed: 29714166]
118. Zucca S, Zucca A, Nakano T, Aoki S, Wickens J. Pauses in cholinergic interneuron firing exert an inhibitory control on striatal output in vivo. Elife 2018;7:e32510. https://pubmed.ncbi.nlm.nih.gov/29578407/. [PubMed: 29578407]
119. Doig NM, Magill PJ, Apicella P, Bolam JP, Sharott A. Cortical and thalamic excitation mediate the multiphasic responses of striatal cholinergic interneurons to motivationally salient stimuli. J Neurosci 2014;34(8):3101–3117. [PubMed: 24553950]
120. Maurice N, Liberge M, Jaouen F, et al. Striatal cholinergic interneurons control motor behavior and basal ganglia function in experimental parkinsonism. Cell Rep 2015;13(4):657–666. [PubMed: 26489458]
121. Chuhma N, Mingote S, Moore H, Rayport S. Dopamine neurons control striatal cholinergic neurons via regionally heterogeneous dopamine and glutamate signaling. Neuron 2014;81(4):901–912. [PubMed: 24559678]
122. Threlfell S, Lalic T, Platt NJ, Jennings KA, Deisseroth K, Cragg SJ. Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. Neuron 2012;75(1):58–64. [PubMed: 22794260]
123. Kosillo P, Zhang YF, Threlfell S, Cragg SJ. Cortical control of striatal dopamine transmission via striatal cholinergic interneurons. Cereb Cortex 2016;26(11):4160–4169. [PubMed: 27566978]
124. Adrover MF, Shin JH, Quiroz C, Ferre S, Lemos JC, Alvarez VA. Prefrontal cortex driven dopamine signals in the striatum show unique spatial and pharmacological properties. J Neurosci 2020;40(39):7510–7522. [PubMed: 32859717]
125. Aoki S, Liu AW, Akamine Y, Zucca A, Zucca S, Wickens JR. Cholinergic interneurons in the rat striatum modulate substitution of habits. Eur J Neurosci 2018;47(10):1194–1205. [PubMed: 29359362]
126. Apicella P The role of the intrinsic cholinergic system of the striatum: what have we learned from TAN recordings in behaving animals? Neuroscience 2017;360:81–94. [PubMed: 28768155]
127. Gritton HJ, Howe WM, Romano MF, et al. Unique contributions of parvalbumin and cholinergic interneurons in organizing striatal networks during movement. Nat Neurosci 2019;22(4):586–597. [PubMed: 30804530]
128. Tanimura A, Pancani T, Lim SAO, et al. Striatal cholinergic interneurons and Parkinson's disease. Eur J Neurosci 2018;47(10):1148–1158. [PubMed: 28677242]
129. Aoki S, Liu AW, Zucca A, Zucca S, Wickens JR. Role of striatal cholinergic interneurons in set-shifting in the rat. J Neurosci 2015;35(25):9424–9431. [PubMed: 26109665]
130. Augustin SM, Chancey JH, Lovinger DM. Dual dopaminergic regulation of Corticostriatal plasticity by cholinergic interneurons and indirect pathway medium spiny neurons. Cell Rep 2018;24(11):2883–2893. [PubMed: 30208314]
131. Aceves Buendia JJ, Tiroshi L, Chiu WH, Goldberg JA. Selective remodeling of glutamatergic transmission to striatal cholinergic interneurons after dopamine depletion. Eur J Neurosci 2019;49(6):824–833. [PubMed: 28922504]
132. Brimblecombe KR, Threlfell S, Dautan D, Kosillo P, Mena-Segovia J, Cragg SJ. Targeted Activation of Cholinergic Interneurons Accounts for the Modulation of Dopamine by Striatal Nicotinic Receptors. eNeuro 2018Oct 30;5(5). 10.1523/ENEURO.0397-17.2018.
133. McKinley JW, Shi Z, Kawikova I, et al. Dopamine deficiency reduces striatal cholinergic interneuron function in models of Parkinson's disease. Neuron 2019;103(6):1056–1072 e1056. [PubMed: 31324539]
134. Kawaguchi Y, Wilson CJ, Augood SJ, Emson PC. Striatal interneurons: chemical, physiological and morphological characterization. Trends Neurosci 1995;18(12):527–535. [PubMed: 8638293]
135. Schulz JM, Reynolds JN. Pause and rebound: sensory control of cholinergic signaling in the striatum. Trends Neurosci 2013;36(1):41–50. [PubMed: 23073210]
136. Wilson CJ, Chang HT, Kitai ST. Firing patterns and synaptic potentials of identified giant aspiny interneurons in the rat neostriatum. J Neurosci 1990;10(2):508–519. [PubMed: 2303856]

137. Aosaki T, Kimura M, Graybiel AM. Temporal and spatial characteristics of Tonically active neurons of the Primate's striatum. J Neurophysiol 1995;73:1234–1252. [PubMed: 7608768]

138. Aldrin-Kirk P, Heuer A, Rylander Ottosson D, Davidsson M, Mattsson B, Bjorklund T. Chemogenetic modulation of cholinergic interneurons reveals their regulating role on the direct and indirect output pathways from the striatum. Neurobiol Dis 2018;109(Pt A):148–162. [PubMed: 29037828]

139. Kharkwal G, Brami-Cherrier K, Lizardi-Ortiz JE, et al. Parkinsonism driven by antipsychotics originates from dopaminergic control of striatal cholinergic interneurons. Neuron 2016;91(1):67–78. [PubMed: 27387649]

140. Faust TW, Assous M, Tepper JM, Koos T. Neostriatal GABAergic interneurons mediate cholinergic inhibition of spiny projection neurons. J Neurosci 2016;36(36):9505–9511. [PubMed: 27605623]

141. Sciamanna G, Ponterio G, Mandolesi G, Bonsi P, Pisani A. Optogenetic stimulation reveals distinct modulatory properties of thalamostriatal vs corticostriatal glutamatergic inputs to fast-spiking interneurons. Sci Rep 2015;5:16742. [PubMed: 26572101]

142. Lemos JC, Friend DM, Kaplan AR, et al. Enhanced GABA transmission drives Bradykinesia following loss of dopamine D2 receptor signaling. Neuron 2016;90(4):824–838. [PubMed: 27196975]

143. Matamales M, McGovern AE, Mi JD, Mazzone SB, Balleine BW, Bertran-Gonzalez J. Local D2- to D1-neuron transmodulation updates goal-directed learning in the striatum. Science 2020;367 (6477):549–555. [PubMed: 32001651]

144. Yttri EA, Dudman JT. Opponent and bidirectional control of movement velocity in the basal ganglia. Nature 2016;533(7603):402–406. [PubMed: 27135927]

145. Howe M, Ridouh I, Allegra Mascaro AL, Larios A, Azcorra M, Dombeck DA. Coordination of rapid cholinergic and dopaminergic signaling in striatum during spontaneous movement. Elife 2019;8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6457892/pdf/elife-44903.pdf.

146. Crittenden JR, Tillberg PW, Riad MH, et al. Striosome-dendron bouquets highlight a unique striatonigral circuit targeting dopamine-containing neurons. Proc Natl Acad Sci U S A 2016;113(40):11318–11323. [PubMed: 27647894]

147. Berke JD. What does dopamine mean? Nat Neurosci 2018;21(6):787–793. [PubMed: 29760524]

148. Bohnen NI, Kanel P, Zhou Z, et al. Cholinergic system changes of falls and freezing of gait in Parkinson's disease. Ann Neurol 2019;85(4):538–549. [PubMed: 30720884]

149. Parent MJ, Cyr M, Aliaga A, et al. Concordance between in vivo and postmortem measurements of cholinergic denervation in rats using PET with [18F]FEOBV and choline acetyltransferase immunochemistry. EJNMMI Res 2013;3(1):70. [PubMed: 24103360]

150. Parent M, Bedard MA, Aliaga A, et al. PET imaging of cholinergic deficits in rats using [18F]fluoroethoxybenzovesamicol ([18F]FEOBV). Neuroimage 2012;62(1):555–561. [PubMed: 22555071]

151. Aghourian M, Legault-Denis C, Soucy JP, et al. Quantification of brain cholinergic denervation in Alzheimer's disease using PET imaging with [18F]-FEOBV. Mol Psychiatry 2017;22(11):1531–1538. [PubMed: 28894304]

152. Ruberg M, Mayo W, Brice A, et al. Choline acetyltransferase activity and [3H]vesamicol binding in the temporal cortex of patients with Alzheimer's disease, Parkinson's disease, and rats with basal forebrain lesions. Neuroscience 1990;35(2):327–333. [PubMed: 2166243]

153. Pisani A, Bernardi G, Ding J, Surmeier DJ. Re-emergence of striatal cholinergic interneurons in movement disorders. Trends Neurosci 2007;30(10):545–553. [PubMed: 17904652]

154. Dubois B, Danze F, Pillon B, Cusimano G, Lhermitte F, Agid Y. Cholinergic-dependent cognitive deficits in Parkinson's disease. Ann Neurol 1987;22(1):26–30. [PubMed: 3631918]

155. Praamstra P, Stegeman DF, Cools AR, Horstink MW. Reliance on external cues for movement initiation in Parkinson's disease. Evidence from movement-related potentials. Brain 1998;121(Pt 1):167–177. [PubMed: 9549497]

156. Sarter M Behavioral-cognitive targets for cholinergic enhancement. Curr Opin Behav Sci 2015;4:22–26. [PubMed: 28607947]

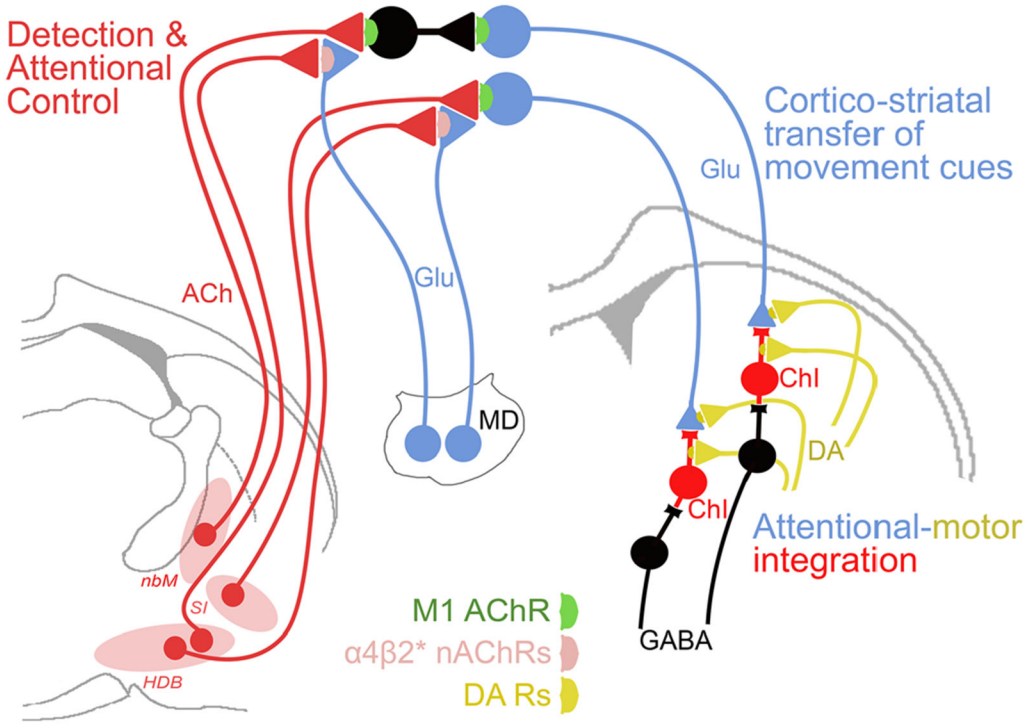

FIG. 1.

Basal forebrain cholinergic cortical and cortico-striatal circuitry essential for integrating attentional and motor functions. This circuitry diagram reflects the main framework and concepts discussed in this review and is not intended to describe comprehensively the circuitry and synaptic connectivity mediating cortico-striatal interactions essential for complex movement control (for key references, see main text). Basal forebrain (nbM, nucleus basalis of Meynert; SI, substantia inominata; HDB, horizontal nucleus of the diagonal band) cholinergic projections to cortex (red), and phasic cholinergic signaling in cortex, are necessary for the detection of task and movement cues. Postsensory information about cues is inserted into the frontal cortex via dorsomedial thalamic (MD) glutamatergic (Glu) inputs (blue). Cholinergic stimulation of a4ß2* nicotinic acetylcholine receptors (nAChRs, pink symbols) on these inputs amplifies cue-evoked Glu responses that are necessary to evoke cholinergic signaling and cortical gamma oscillations. These oscillations mediate the broadcasting cue information across cortical and subcortical regions. Moreover, postsynaptic muscarinic receptors, particularly M1 AChR subtypes (green symbols) on cortical interneurons (black) and output cells, contribute to the cortico-striatal glutamatergic transfer of information about cues (blue). Silencing or generating cortical cholinergic activity disrupts and benefits, respectively, the processing of task- and movement cues, thereby influencing complex movement control. In addition to the essential role of cholinergic transients for the detection of movement-related cues, cholinergic signaling maintains top-down, or goal-directed, attention over complex movements, specifically in response to gait errors and imbalance (see main text for discussion). As a result of loss of cholinergic input to the cortex, as is the case in parkinsonian fallers, the detection of movement cues is impaired, and thus the cortico-striatal glutamatergic transfer of information about movement cues is disrupted. In interaction with slowing and de-

energizing effects of striatal dopamine loss (DA, yellow), impaired cortico-striatal transfer fails to guide movement selection and correction of movement errors, thereby yielding gait dysfunction and increasing the risk for falls. Striatal cholinergic interneurons (ChIs) are positioned to integrate cortico-striatal signaling with dopaminergic (DA) modulation. ChIs are lost or are hypoactive in PD fallers, and inhibition of ChIs in rodents causes falls and related movement deficits.

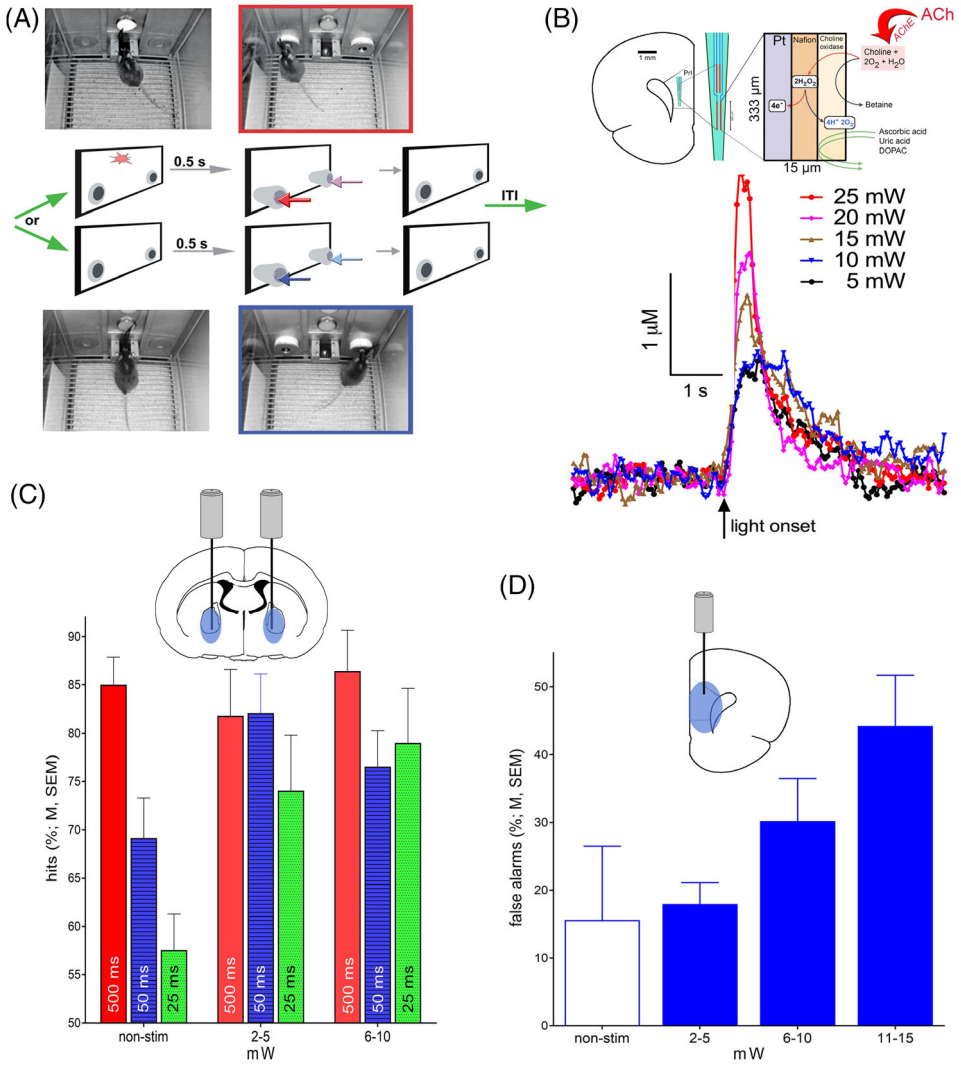

FIG. 2.

Cortical cholinergic transients cause the detection of cues. (**A**) The signal detection task used for these experiments consisted of a random order of visually cued and non-cued trials (middle schematic illustration). Following either event, 2 nose-poke devices extended into the chambers and were retracted on a nose-poke or following 4 seconds (schematic illustration in the middle). Hits and correct rejections (dark-red and dark-blue arrows) were correct responses in cued and non-cued trials, respectively, and rewarded with water, whereas misses and false alarms (pink and light-blue arrows) were incorrect responses and not rewarded. Following an intertrial interval of 12 ± 3 seconds, the next cue or non-cue event commenced. The photographic inserts show a cue presentation with a mouse orienting toward the intelligence panel while positioned at the water port (upper row, left), a subsequent hit (upper row, right), a non-cue event (lower row, left), and a subsequent correct rejection (lower row, right). (**B**) Prefrontal choline currents as a function of laser stimulation power in mice expressing channelrhodopsin-2 (ChR2) in basal forebrain cholinergic neurons. Top insert: real-time currents indicating newly released acetylcholine (ACh) were recorded amperometrically and using choline-sensitive microelectrodes. The

insert depicts the 4 platinum (Pt) recoding sites fabricated onto ceramic bases and the approximate placement of the recording sites in the prelimbic (Prl) cortex. Choline oxidase was immobilized onto 2 of 4 Pt sites, and all sites were equipped with a Nafion layer to repel ascorbic acid and other electroactive interferents. Newly released ACh is hydrolyzed by endogenous acetylcholinesterase (AChE), and the resulting choline is oxidized by immobilized choline oxidase on the electrode. The resulting hydrogen peroxide is then detected amperometrically. Current from sites not equipped with choline oxidase was used for self-referencing (for more details, see, eg, Parikh et al.[36,37] and Giuliano et al.[38]). Bottom insert: the traces depict currents evoked by blue laser stimulation (5–25 mW; 1000 ms). Increasing stimulation power resulted in higher transient amplitudes, with 10- to 15-mW-evoked currents mimicking the choline currents measured in rats in cued trials yielding hits.[36] (**C**) Optogenetic generation of cholinergic transients (bilateral illumination of the basal forebrain; see insert) during cued trials increased hit rates, particularly the hit rates to shortest cues when compared to the absence of photostimulation (non-stim). (**D**) In non-cue trials, cholinergic transients normally are not observed.[39] Therefore, cholinergic transients generated optogenetically during these trials caused an increase in false alarms (ie, false reports of cues). Bilateral stimulation of the basal forebrain (not shown) or generation of cholinergic transients in the right prefrontal cortex more than doubled the rate of false alarms (adapted from Gritton et al.[40]).

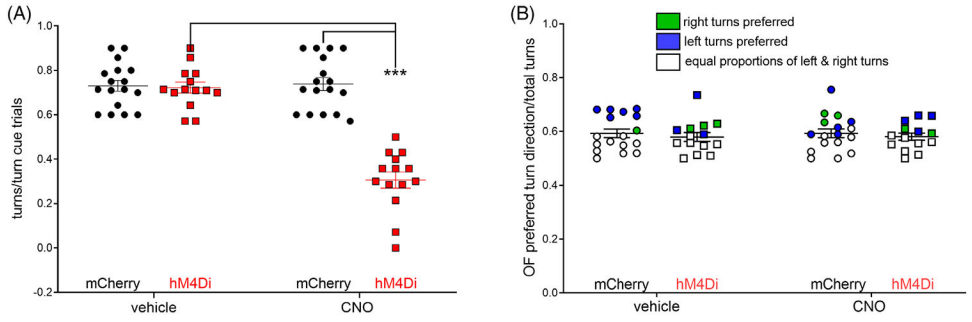

FIG. 3.

Chemogenetic inhibition of dorsomedial striatal cholinergic interneurons (ChIs) impairs cued-turning behavior in otherwise-intact rats (adapted from Avila et al.[116]). The task used to train and test cued-turning behavior in rats was inspired by evidence indicating that parkinsonian fallers also exhibit turning deficiencies, considered to reflect a disrupted cognitive–motor interface (references in text). Rats were trained to walk on a treadmill and detect cues requiring either to turn (as the treadmill would stop and restart in reverse) or to merely stop (as the treadmill would restart in the same direction). ChIs were then transfected with either an inhibitory DREADD (designer receptor exclusively activated by designer drugs, hM4Di) or a reporter molecule-expressing control construct (mCherry). To activate the inhibitory DREADD, clozapine-*N*-oxide (CNO) was administered. The effects of DREADD expression per se were controlled by assessing the effects of the vehicle for CNO. As illustrated in part figure **A**, turning rates remained unaffected in mCherry and hM4Di-expressing rats after the administration of vehicle (left). CNO, however, robustly reduced turning rates in rats expressing the inhibitory DREADD (right). (**B**) Results from an important control experiment that addressed the possibility that DREADD-induced inhibition of ChIs interfered with the rats' turning ability per se rather than with their ability to utilize the turn cue to execute a turn. Rats explored an open field, and the effects of CNO on the rats' preferred turning direction were determined. The color-coded symbols in part figure **B** indicate rats with a significant preference. The results rejected the possibility that the effects of CNO on turning performance were due in part to disruption of their spontaneous and preferred turning behavior (for details see Avila et al.[116]). Together, these results indicate that dorsomedial ChIs are an essential node in circuitry mediating the cognitive–motor integration necessary from complex movement control.