

Review

**Make a left turn: Cortico-striatal circuitry mediating the attentional control of complex movements**

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**Abstract**

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. 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. Here we describe the cortico-striatal 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. Evidence from parkinsonian fallers and from a rodent model reproducing the dual cholinergic-dopaminergic losses seen in these patients, support the main hypotheses derived from this neuronal circuitry-guided conceptualization of parkinsonian falls. Furthermore, in the striatum, cholinergic interneurons constitute a particularly critical node for the integration of cortical with midbrain dopaminergic afferents, and thus for cues to control movements. Pro-cholinergic 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.

**Key Words:** cortex, striatum, acetylcholine, dopamine, attention, gait, balance falls, Parkinson's disease

## Attentional control of movements

As a healthy person, you rarely think much about your every-day movements. Getting up, going up or down the stairs, 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 (e.g., 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:<sup>1</sup> The attentional shift is triggered by a mismatch between pre-programmed 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.<sup>2-</sup>

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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 (e.g., stair height and tread dimensions), programmed movements (e.g., lower limb cyclic pattern <sup>7</sup>), and interoceptive cues indicating, for example, reduced gait rhythmicity and poor trunk orientation. <sup>8</sup> As a result, movement errors can rapidly accumulate, thereby increasing the risk for a fall. <sup>9-19</sup>

This review will evaluate the evidence supporting an essential neuronal circuit for complex movement control (see Footnote<sup>1</sup>) 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 (depicted in Figure 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, also exhibit gait dysfunction and a propensity for

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<sup>1</sup>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 defines 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.

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 (e.g., <sup>20</sup>). 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, e.g., <sup>12, 21, 22</sup>). However, it also needs to be noted that overtly kinematic risk factors for falls, such as reduced step lengths prior to turning, freezing of gate (FOG), and alterations in trunk control <sup>23-27</sup> can reflect the breakdown of cognitive-motor interactions, <sup>28, 29</sup> 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, e.g., <sup>30</sup>). 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 (below).

#### **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. <sup>31-34</sup> 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 neuro-behavioral model of complex movement control (Figure 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. <sup>35</sup> 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, 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).<sup>36, 37</sup> As illustrated in Fig. 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.<sup>38-42</sup> However, the cortical circuitry and the synaptic mechanisms responsible for cues failing to generate, or suppressing, cholinergic transients, and thus yielding misses, has yet to be explained (but see **Cholinergic top-down control**, below).

Consistent with the demonstration that cholinergic transients are evoked by detected cues, removal of cholinergic inputs to the cortex,<sup>43-45</sup> or optogenetic suppression of cholinergic transients,<sup>46</sup> reduces detection rates. Moreover, optogenetic generation of transients enhances detection rates (Figure 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.<sup>46</sup> 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.<sup>47</sup> 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 complex, cue-oriented behavior. Stimulation of M1 muscarinic acetylcholine receptors (mAChRs) is essential for such effects of ACh. These receptors are expressed by cortical interneurons<sup>48</sup> and cortical output neurons<sup>49</sup> (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,<sup>34, 47, 50-52</sup> administration of a M1 positive allosteric modulator (PAM) partly rescued the detection rates of rats with partial removal of cholinergic inputs to the cortex<sup>53</sup> and, in a rodent model of parkinsonian falls (see below), reduced the rates of falls.<sup>54</sup>

**Cholinergic top-down control.** Above, 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.<sup>55-60</sup> 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 than wild type (WT) humans.<sup>61-64</sup> Rats performing a sustained attention task (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.<sup>65, 66</sup>

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 above. However, cholinergic transients produce relatively lasting post-synaptic neurophysiological effects, mentioned above, 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.<sup>52</sup> Thus, the postsynaptic effects of cholinergic transients may sufficiently explain the cholinergic mediation of attentional control.<sup>33</sup> 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,<sup>64, 67-69</sup> differ from non-fallers by showing impairments in cued turning behavior.<sup>11, 70-72</sup> 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.<sup>73</sup> 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<sup>74-76</sup>).

Despite the finding that, in parkinsonian fallers, cholinergic-attentional losses, but not striatal DA losses, are associated with higher fall rates,<sup>68</sup> 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,<sup>77</sup> the age-related decline in cholinergic function and associated limitations of attentional capacities<sup>17-19, 78, 79</sup> likely interact with age-related losses of basal ganglia DA<sup>80</sup> 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 seen in parkinsonian fallers, exhibit heightened fall rates while traversing dynamic surfaces and fail to execute cued turns. In contrast, rats with only cholinergic losses<sup>45, 81, 82</sup> or only with dorsomedial striatal DA losses do not produce elevated fall rates.<sup>83</sup> 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.<sup>84</sup> Such falls belong to a category separate from our focus on the impact of disruption of the cognitive-motor interface.

In DL rats, 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.<sup>45</sup> 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 below). 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 thought to be drastically slower and less effective, owing to striatal DA loss,<sup>85-88</sup> 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 interaction 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 visuo-spatial attention network. However, frontal activation was insufficient to fully compensate for the impaired gait control in PD patients.<sup>89, 90</sup> Assuming that a portion of the right frontal activation reflects cholinergic signaling,<sup>62</sup> these findings support the interpretation of the cortico-striatal interactions derived from the rodent model above.

Specifically, 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 of 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.<sup>91-94</sup> In PD patients with a history of freezing of gait, which is major risk factor for falls and potentially a behavioral expression of disrupted cortico-striatal control,<sup>29, 95</sup> attenuated functional connectivity within the right-hemispheric attention network may in part reflect loss of cortical cholinergic mediation of attentional control.<sup>96</sup>

### **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<sup>97, 98</sup> are a major constituent of the fronto-striatal cognitive loop.<sup>99</sup> 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<sup>100, 101</sup> and equally influencing striatal cholinergic interneurons (ChIs).<sup>102, 103</sup> ChIs will be discussed below as essential attentional-motor integrators.<sup>104, 105</sup>

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.<sup>91, 106-110</sup> However, exactly what aspects of movement-related cues are imported into striatal circuitry awaits to be addressed by, for example, recording glutamate signaling<sup>111</sup> in rats performing complex movements and committing errors, such as while traversing complex beams or executing cued turns.<sup>45, 112-114</sup> 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<sup>29</sup> 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).<sup>104, 105, 115</sup> ChI-derived cholinergic signaling in turn modulates the activity of these glutamatergic inputs and



enforces inhibitory control on striatal output neurons.<sup>116</sup> 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.<sup>117</sup> Moreover, the interactions between ChIs, cortico, thalamo- and nigro-striatal afferents appear to be reciprocal (Fig. 1),<sup>118-122</sup> further supporting the view that ChIs serve as an essential striatal integrator that orchestrates complex movements and error-triggered corrections.<sup>123-126</sup>

A recent series of experiments was designed to test the general hypothesis that ChIs are essential attentional-motor integrators.<sup>114</sup> 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.<sup>70, 71</sup> 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 dopamine 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,<sup>45</sup> This finding again supports the view that 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 upon inhibition of these neurons, cue-guided modification of behavior was disrupted,<sup>127</sup> 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, 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<sup>128, 129</sup> and to suppress the regulation of striatal DA.<sup>120, 130</sup> Furthermore, striatal DA denervation causes diminished ChI function.<sup>131</sup> 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.<sup>120, 121, 130</sup> Furthermore, ChIs are characterized by relatively large dendritic and axonal spaces<sup>132</sup> and broad responsiveness to sensory cues.<sup>133</sup> Therefore, the specific region in which stimulation of striatal ChIs produce beneficial performance effects may be less crucial than preservation of their connectivity, particularly with midbrain DA neurons.

These experiments<sup>114</sup> did not speak to the important question as to how chemogenetic inhibition or stimulation of ChIs modify their neurophysiological characteristics during complex movements. ChIs typically exhibit autonomous, tonic firing patterns interspersed with pauses.<sup>126, 133-135</sup> Following striatal DA loss, ChI firing rates are reduced and the firing and pausing patterns become uncorrelated.<sup>131</sup> Chemogenetic inhibition may likewise have suppressed these patterns of ChI activity (see also<sup>116</sup>). 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.<sup>123, 136</sup> 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<sup>137</sup>).

Our focus on the role of ChIs in integrating cortico-striatal with nigro-striatal input does not account for a role of non-cholinergic populations of striatal interneurons,<sup>115, 138-140</sup> or additional complexities within circuitry linking cortico-striatal with nigro-striatal input to multiple types of striatal output neurons.<sup>128, 141, 142</sup> 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.<sup>88</sup>

<sup>143-145</sup> 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 above, the precise impact of DA losses on the 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.** Above, ChIs are 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 above). However, ChI function may independently decline in parkinsonian fallers as well. Using a PET ligand ([<sup>18</sup>F]FEOBV) to visualize the Vesicular Acetylcholine Transporter (VAChT), lower striatal FEOBV binding was observed in parkinsonian fallers showing freezing of gait when compared with fallers not showing freezing of gait. <sup>146</sup> Loss of striatal FEOBV binding was also observed in healthy, aged controls. <sup>78</sup> Loss of FEOBV binding may indicate a loss of cholinergic neurons <sup>147-149</sup> or reflect compensatory effects in neurons with elevated firing rates <sup>150</sup> which, in the striatum, have been thought to result from DA loss. <sup>151</sup> 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 not only be 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 (Figure 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 <sup>114</sup> 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. <sup>17, 18, 94, 152, 153</sup> 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, <sup>154</sup> such signaling may be more effectively enhanced or restored by modulating postsynaptic, specifically M1-mediated mechanisms. As already mentioned, we found that an M1 PAM improved the attentional performance of rats with partial losses of the cortical cholinergic input system. <sup>53</sup> More recently, we also observed that such a treatment benefits the complex movement control of DL rats (see above for a description of these rats as a model of the dual cortical cholinergic – striatal dopaminergic losses which 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 re-programming of gait and balance. <sup>54</sup> 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 de-prioritized over walking even in healthy people <sup>2, 6</sup> 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, <sup>81, 82</sup> particularly Ch1 function, although the latter target involves neurophysiological complexities that require careful evaluation to avoid worsening of the primary motor symptoms of PD. <sup>118</sup>

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## Figure Legends

### Figure 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. Post-sensory information about cues is inserted into the frontal cortex via dorsomedial thalamic (MD) glutamatergic (GLU) inputs (blue). Cholinergic stimulation of  $\alpha 4\beta 2^*$  nicotinic acetylcholine receptors (nAChRs; pink symbols) on these inputs amplify cue-evoked GLU responses which 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 disrupt and benefit, 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 also 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.

### Figure 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, two nose-poke devices extended into the chambers and were retracted upon a nose-poke or following 4 s (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  $12 \pm 3$  s, 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 release 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 out of 4 Pt sites and all sites were equipped with a Nafion layer to repel ascorbic acid and other electroactive interferences. 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 were used for self-referencing (for more details see, e.g., <sup>36, 155, 156</sup>). Bottom insert: The traces depict currents evoked by blue laser stimulation (5–25 mW; 1,000 ms). Increasing stimulation power resulted in higher transient amplitudes, with 10-15 mW-evoked currents mimicking the choline currents measured in rats in cued trials yielding hits. <sup>36</sup> **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. <sup>37</sup> Therefore, cholinergic transients generated optogenetically during these trials caused an increase in false alarms (that is, 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 <sup>46</sup>).

### Figure 3

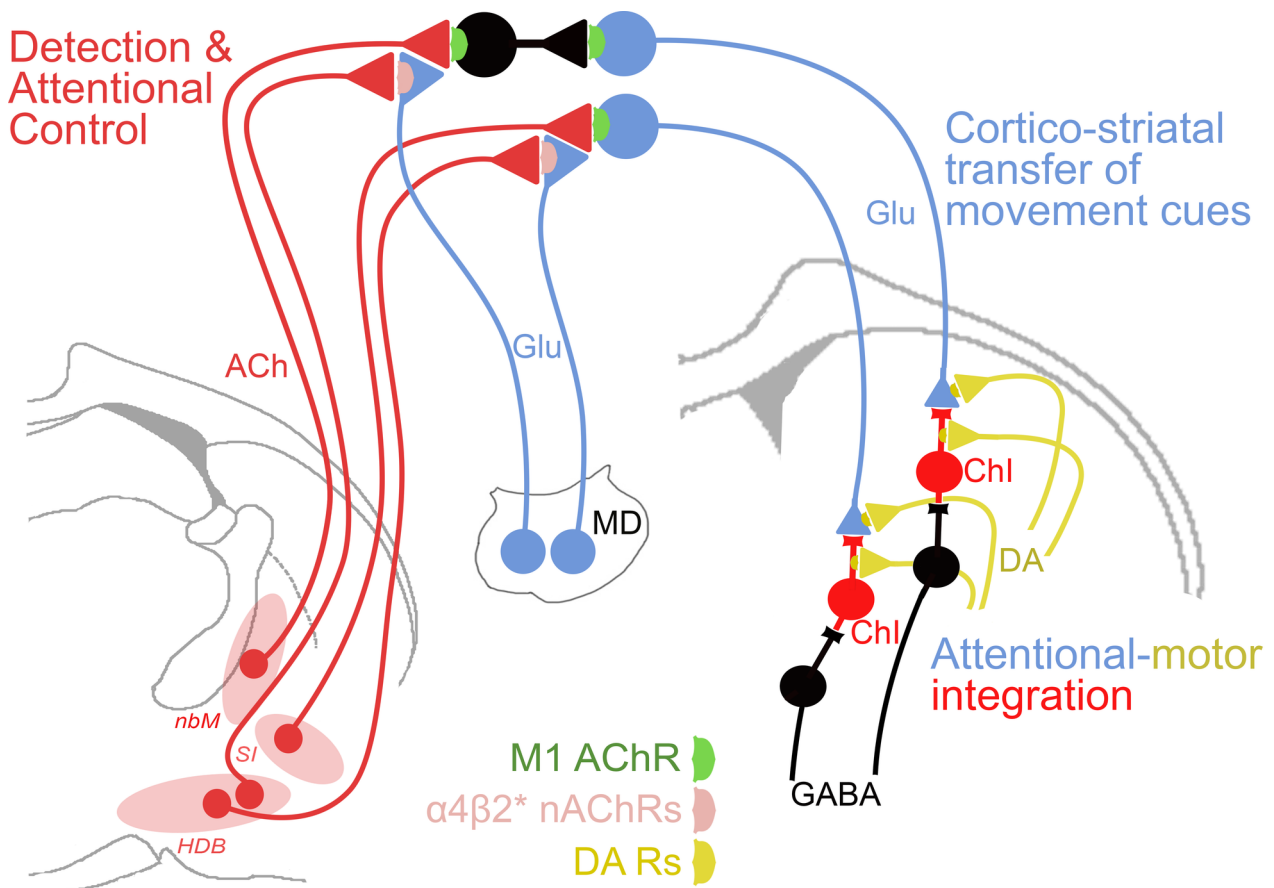
Chemogenetic inhibition of dorsomedial striatal cholinergic interneurons (ChIs) impairs cued turning behavior in otherwise intact rats (adapted from <sup>114</sup>). The task used to train and test cued-turning behavior in rats was inspired by evidence indicating that parkinsonian fallers also exhibit

turning deficiencies, thought 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 re-start in the same direction). ChIs were then transfected either with an inhibitory DREADD (Designer Receptors 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 a, turning rates remained unaffected in mCherry and hM4Di-expressing rats following the administration of vehicle (left). CNO, however, robustly reduced turning rates in rats expressing the inhibitory DREADD (right). b shows 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 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 <sup>114</sup>). Together, these results indicate that dorsomedial ChIs are an essential node in circuitry mediating the cognitive-motor integration necessary for complex movement control.

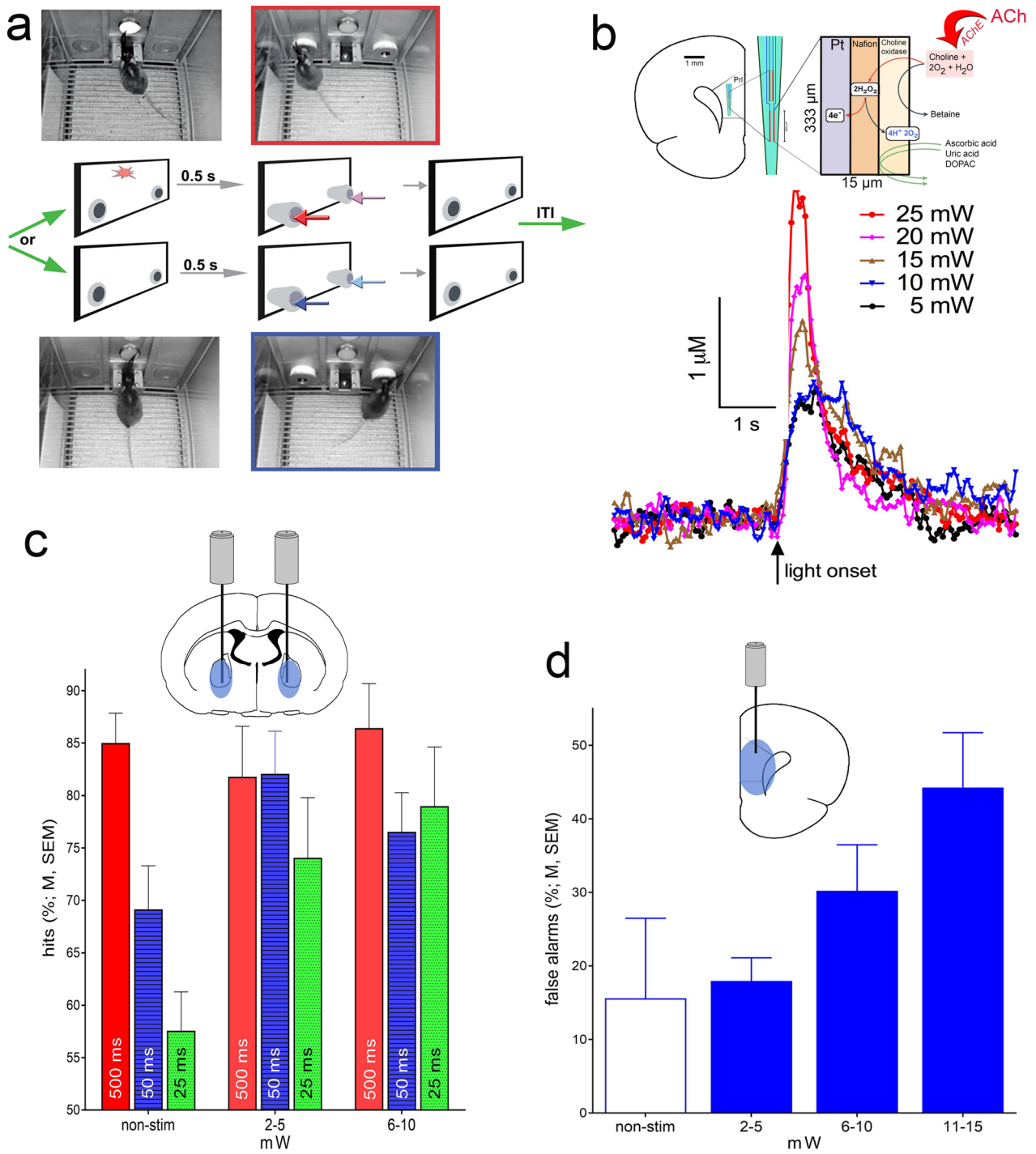
**Authorship contributions:**

MS, CA, AK, and ED made substantial contribution to the conception of this article, and they participated in drafting and revising this article. All co-authors approved the submitted version of this article, and they agree to be accountable for all aspects of the work.

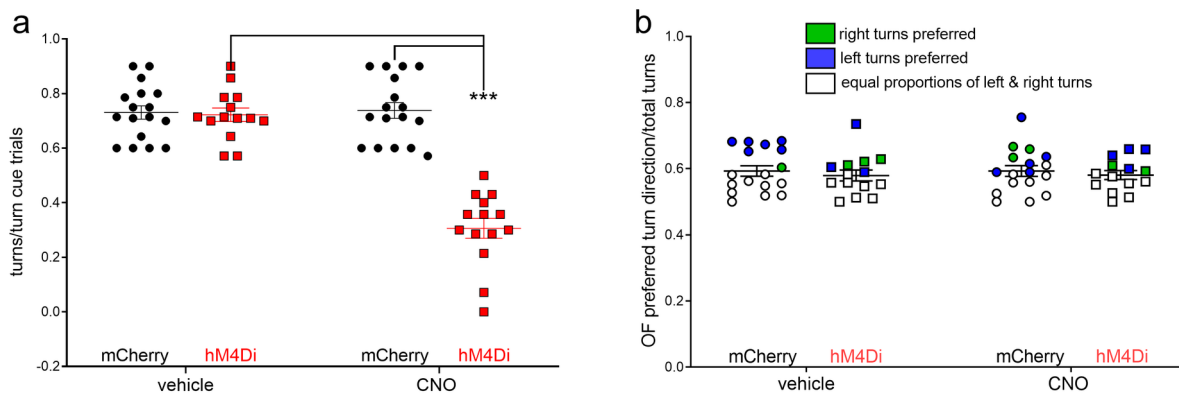




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