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Cognitive motor deficits in cannabis users

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Cannabis use affects cortico-striatal networks that are essential for producing movement. In this review, we summarize the literature on motor system dysfunction in cannabis users and provide a rationale for why motor learning should be considered an important area in cannabis research. A majority of studies have addressed cognitive impairments in cannabis users and some have focused on driving performance, motor impulsivity, and motor inhibition. Our review of the literature has found that cannabis use is associated with motor performance impairments; however, there is a gap in the literature regarding impairments in motor learning. The involvement of the cortico-striatal network in both cannabis addiction and movement also suggests potential avenues for treatment and rehabilitation via the motor system.

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Introduction

Cannabis abuse has significant implications for both the individual and society. Chronic and acute use of cannabis have been associated with cognitive impairments and mental disorders such as anxiety, depression, schizophrenia, and psychosis, an increased likelihood of using other illicit drugs, and poor educational outcomes [1–4]. As public perception and policy toward cannabis use become more accepting [5], it is critical to investigate the effects of cannabis use.

An important implication to consider is the effect of cannabis use on motor performance and learning. Recent research on impairments in cannabis users has focused on cognitive and motor performance, specifically related to driving. It is unsurprising that cannabis users exhibit impairments in cognition and motor performance given the critical role of cortico-striatal networks and dopamine in both addiction and production of movement. Both cognition and motor performance are required for acquiring new motor skills. However, there is a paucity of studies on the effects of cannabis on motor skill learning. Learning new motor skills is critical for adapting to constantly changing environment, organism, and task constraints throughout the lifespan [6]. Importantly, complex motor behaviors comprise of simpler actions produced in a specific order at a specific time. Playing the piano, speaking, writing, driving, and playing sports are examples of intricate motor skills composed of a sequence of simple actions with important ordinal and temporal components. These important skills are obtained through the process of motor learning, which is integral for conducting activities of daily living, interacting with others and the environment, and having a fulfilling life. It is interesting to note that learning and adaptation via synaptic plasticity is a requirement of living in a dynamic environment and is also the basis of drug addiction. The evidence for impairments in cognition and certain motor tasks in cannabis users taken together with the cognitive resources required in order to learn and perform motor skills suggests a potential for impairments in users of cannabis in motor learning as well.

This review will summarize the literature on cognitive motor deficits in cannabis users and provide a rationale for why motor learning should be considered an important area in cannabis research. Assessing how a capacity of such importance is affected by cannabis is critical in light of the recent changes in public policy and perception.

Cortico-striatal networks play a critical role in both addiction and motor learning

Doyon and Benali [7] have proposed an updated framework for the acquisition of motor skills to five stages from the classic three stages proposed by Fitts and Posner [8]. The early learning stage consists of rapid improvements in performance within a single session, followed by a later learning stage with continuing improvements at slower rates over multiple sessions, a consolidation stage that occurs after a break of 6 h or more in which performance further increases without further practice, an automatization stage during which fewer cognitive resources are required to execute the skill, and lastly a retention stage that does not require any practice to perform the skill even after extended breaks. The neural correlates of the first three stages are contingent on the cognitive processes involved and are thought to include the striatum, cerebellum, motor cortical regions, prefrontal cortex, parietal areas, and limbic areas [7,9•]. As motor learning

approaches automatization, the motor cortical and parietal regions continue to be involved, but the striatal and cerebellar regions are involved depending on whether the learning is of sequential motor actions to perform a complex motor behavior (motor sequence learning) or to adapt to environmental constraints (motor adaptation) and continues through the retention phase.

Dopamine plays a critical role in the control of voluntary movement by modulating two pathways that are critical for voluntary movement. The direct pathway facilitates movement and through D1 receptors, dopamine has an excitatory effect on this pathway. The indirect pathway inhibits movement and dopamine has an inhibitory effect on this pathway via D2 receptors. Changes in dopamine causes an imbalance between these pathways and is the basis for movement disorders, such as Parkinson's disease and Huntington's disease [10,11]. For example, in Parkinson's disease, a depletion of dopamine causes increased inhibitory outflow in the basal ganglia that results in bradykinesia and difficulties initiating movement among other symptoms. Interestingly, when levodopa medication is given to patients with Parkinson's disease to supplement dopamine levels and relieve motor symptoms, a subset of patients exhibit impulse control disorders as well as cognitive impairments. This is consistent with studies that suggest that both insufficient and excessive levels of dopamine impair cognitive performance [12,13]. The relationship between increased dopamine and decreased cognitive performance further provides evidence for cognitive impairments in cannabis users.

Dopamine projections from the substantia nigra to the striatum form only a part of the dopamine projections from subcortical regions. Additional projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex contribute to the reward system and play a central role in addiction [14]. Interestingly, dopamine projections from the substantia nigra also aid in consolidating the motor repertoire required to obtain rewards [14,15], suggesting an intersection of the motor and reward systems. Furthermore, the presence of dopamine projections to the prefrontal cortex and its role in working memory [16] suggests a central role in integrating reward and motor repertoires to generate goal-direction actions to pursue the reward (in this case cannabis seeking behavior) [17]. A recent neuroimaging study has suggested that chronic long-term cannabis use is associated with a decrease in striatal dopamine synthesis. This reduction may be related to amotivation and account for the disconnect between the addictive behavior and its negative consequence [18].

Through the reinforcing effects of cannabis and other drugs of abuse, a transformation for the acquisition of cannabis occurs from a voluntary goal-directed action to a habitual response. This transformation has been suggested to involve the basal ganglia with the shift of the cannabis seeking behavior from the prefrontal cortex to the dorsal striatum [19••,20]. Central to this theory is the requirement of cortical plasticity to support these transitions and is supported by several animal models that have found cortical plasticity as a result of exposure to cocaine and alcohol [21–23]. Indeed, interactions between corticostriatal networks resulting in behavioral changes are also the basis of motor learning and adaptation [7,9•]. Thus, motor learning is reliant on cortical plasticity in corticostriatal networks and addiction alters this plasticity.

Endogenous cannabinoids are involved in processes related to motor learning: learning, memory, and motor activity

Endogenous cannabinoids are present in both the central and peripheral nervous system. They act through the CB1 and CB2 receptors that are present in abundance in the brain. In fact, rodent models indicate that the basal ganglia (substantia nigra, globus pallidus), cerebellum, and hippocampus have the greatest densities of CB1 receptors [24•,25]. Animal studies have indicated that CB1 cannabinoid receptors can modify dopamine, GABA, and glutamate activity in the basal ganglia [26]. These findings are consistent with the suggestion that endogenous cannabinoids are involved in learning and memory (along with reward-motivation processes) through synaptic plasticity [27••,28]. Both of these play crucial roles in both motor learning and the development of substance use disorders. Learning and memory formation are reliant on long-term potentiation (LTP) and long-term depression (LTD) and have been shown to be negatively affected by Δ^9-tetrahydrocannabinol (THC), the most prominent cannabinoid in the cannabis plant [30]. Additionally, single cell recordings indicate that CB1 activation can stimulate release of dopamine or inhibit dopamine reuptake in the nucleus accumbens [29], producing a similar effect as other drugs of abuse. In addition to cognitive processing, animal models suggest that the endogenous cannabinoid system plays a role in modulating motor activity [25,26]. The presence of endogenous cannabinoids in the basal ganglia and cerebellum and the interaction of CB1 receptors with dopamine supports their role in motor activity. Taken together, endogenous cannabinoids are not only involved in the reward pathway, but also in learning, memory, and motor processes, providing an additional prospect of overlap between the cannabis addiction and motor activity.

Cannabis users exhibit cognitive and motor performance deficits

A number of studies provide evidence for cognitive deficits in both chronic and acute users of cannabis. Cannabis use has been reported to impair memory, associative learning, abstraction, and vocabulary [31–33]. Additional studies have found impairments in episodic memory [34],

Table 1

Studies of motor function in cannabis users.

Authors	Participants	Cannabis intoxication state	Motor assessment(s)	Motor deficits
Block *et al*. [31]	48 non-users 18–42 years old	Acute	Discriminant reaction time task	Participants who smoked a marijuana cigarette exhibited slower reaction time (RT) compared to placebo
Block and Ghoneim [32]	144 users separated into: - Heavy (7+ uses per week) - Intermediate (5–6 uses per week) - Light (1–4 uses per week) 72 non-users 18–42 years old	Abstinent	Discriminant reaction time task	No deficits reported
Hart *et al*. [38]	18 users (10 males, 8 females) Mean use: 24 marijuana cigarettes per week Mean age: 21.5 years	Acute	Reaction time task	No deficits reported
Curran *et al*. [33]	15 infrequent male users Mean use: 1 use per week (only 1 participant had prior experience with cannabis) Mean age: 24.2 $\pm$ 2.1 years	Acute	Choice reaction time task	No deficits reported in RT, but participants given THC exhibited a greater number of errors
D'Souza *et al*.* [37]	11 frequent users Lifetimes uses $\geq$ 100, last use within a week, and recent uses $>$ 10 per month 17 non-users Mean age of both groups: 24.9 $\pm$ 7.0 years	Acute	Motor screening task (reaction time task)	No deficits reported
Wilson *et al*. [40]	10 male users Mean age: 30.3 $\pm$ 7.5 years	Acute	Reaction time task, Critical tracking task	No deficits reported for critical tracking task. Slower RT exhibited by participants given THC 30 min later, but not 90 or 150 min later
Hunault *et al*. [35]	23 users Mean use: 7.7 $\pm$ 3.7 per month in past year Mean age: 24.1 $\pm$ 4.0 years	Acute	Reaction time task, Critical tracking task	Impairments in both tasks linearly correlated with THC dose
Desrosiers *et al*. [42]	14 frequent users (10 males, 4 females) Mean use: $\geq$ 4 uses per week in past 3 months Mean age: 25.7 $\pm$ 4.6 years 11 occasional users (8 males, 3 females) Mean use: $<$ 2 uses per week in past 3 months Mean age: 31.4 $\pm$ 6.3 years	Acute	Critical tracking task	No deficits reported
Ramaekers *et al*. [41]	20 users (14 males, 6 females) 19–29 years old	Acute	Critical tracking task, Stop signal task	Impaired performance in critical tracking task and stop-signal task (participants receiving THC exhibited slower RT in stop trials and greater omission and commission errors)
Ramaekers *et al*.# [39]	21 heavy users (15 males, 6 females) Mean use: 373.7 $\pm$ 101.6 uses per year for 9.0 $\pm$ 5.5 years Mean age: 23.2 $\pm$ 8.4 years	Acute	Critical tracking task Stop signal task	No deficits reported

Table 1 (*Continued*)

Authors	Participants	Cannabis intoxication state	Motor assessment(s)	Motor deficits
Grant *et al*. [37]	16 users (10 males, 6 females) Mean use: 3.1 ± 2.2 uses per week Mean age: 21.8 ± 2.9 years 214 non-users (153 males, 61 females) Mean age: 21.2 ± 3.2 years	Abstinent	Stop signal task	No deficits reported
McDonald *et al*. [43]	37 users (19 males, 18 females) Mean age: 23.0 ± 4.5 years	Acute	Stop signal task, Go/no-go task	No deficits reported in go/no-go task. Impairments found in stop signal task with participants receiving THC exhibited slower RT in stop trials
Hester *et al*. [44]	16 users Mean lifetime use: 11 626.8 ± 5993.4 Mean age: 24.6 ± 1.5 years 16 non-users Mean lifetime use: 3.0 ± 0.6 Mean age: 25.2 ± 1.3	Abstinent	Go/no-go task	No deficits reported
King *et al*. [53]	30 users (16 males, 14 females) Mean use: 6.5 uses per week) Mean age: 21.8 years 30 non-users (16 males, 14 females) Mean age: 23.8 years	Abstinent	Pegboard task, Finger sequencing task	No deficits reported in pegboard, no behavioral results reported for finger sequencing task

* This study investigated the effects of haloperidol on THC and participants were tested on two sessions where they received either haloperidol or a placebo. The results reported here are from the placebo session.
# This study investigated separate and combined effects of THC and alcohol in which participants received placebo or two dosages of alcohol in conjunction with THC. The results reported here are from the alcohol placebo condition with only THC.

attention [35], cognitive flexibility (task switching) [36], and immediate and delayed recall [37]. It is important to note that there are several inconsistencies regarding the deficits in acute and chronic users and some studies have found no deficits in chronic users [38,39]. Given that various cognitive processes play a critical role in motor performance, it is likely that cannabis use impacts motor control and learning.

Surprisingly, few studies have investigated motor deficits in cannabis users (see Table 1 for studies reporting motor assessments). Some studies have reported slower reaction times in cannabis users [31,35,40], but others have not reported impairments in reaction time [32,33,37,38]. Hunault and colleagues examined cognitive and motor deficits in non-daily cannabis users exposed to different dosages of THC (0.003, 9.8, 16.4, or 23.1%) over four sessions with each session separated by at least seven days [35]. Along with cognitive assessments, they used the critical tracking task (CTT) in which participants used a joystick to counteract movements of a vertical bar on the screen to keep it in the central position. They found that THC dosage was correlated with impairments in attention, short-term memory, reaction time, as well as the CTT. Impairments in the CTT were also seen in an additional study on recreational users of cannabis [41], but others have not reported impairments [39,40,42].

Studies have also assessed motor impulsivity through the stop signal task in which participants respond as quickly as possible to a stimulus; however, in a small subset of trials, the stimulus is followed by an additional signal and participants must inhibit their response in those trials (stop trials). Ramaekers and colleagues reported that cannabis users who smoked 250 or 500 μg/kg THC exhibited slower reaction time in stop trials and made greater omission (no response in a trial) and commission (response in a stop trial) errors compared to users who smoked a placebo cigarette [41], suggesting that cannabis users exhibit greater motor impulsivity. These differences were most pronounced 30 min to 3.5 h after smoking, but disappeared 5.5 h after smoking, suggesting that the deficits are temporary. The declining of deficits was also reported in [40], where slower reaction time was exhibited 30 min after smoking a 3.55% THC cigarette, but not 90 or 150 min later. Impairments in the stop signal task have been reported by McDonald and colleagues as well [43], but other studies have reported no impairments [36,39]. In contrast to the stop signal task, in the go/no-go task, participants make a decision to initiate a response

(go trials) or to inhibit a response (no-go trials) in each trial, thus measuring motor inhibition. No impairments have been reported in this task in cannabis users [43,44].

Neuroimaging studies have reported changes in brain networks related to cannabis use [45•]. For example, Filbey and colleagues found that users of cannabis exhibited greater functional connectivity between cortical (prefrontal cortex) and subcortical (substantia nigra and subthalamic nucleus) during the stop signal task, suggesting that cannabis users exerted greater effort to inhibit an ongoing response [46]. This inhibitory control supported by prefrontal cortex and basal ganglia activation has also been reported to play an important role in motor adaptation [47], suggesting that cannabis use reduces the neural efficiency required in motor adaptation. Similar changes in activations during inhibitory control (Stroop task or go/no-go response inhibition task) were reported by [44,48] in which abstinent chronic cannabis users exhibited decreased anterior cingulate activity. Additionally, Block and colleagues [34] reported impairments in episodic memory in cannabis users who were required to abstain from cannabis for at least 26 h. PET imaging disclosed that the impairment was accompanied by a reduced activation in the prefrontal cortex as well as regions of the cerebellum that are involved in memory.

In light of the shift in public policy, a number of recent studies have focused on the effects of cannabis use on driving (please see [49] for in-depth reviews). These studies are primarily conducted using simulations, but some have been conducted on the road though they are limited in their interpretation [49]. Preliminary results from the most recent study investigating the influence of an acute bout of cannabis in chronic users between the ages of 19–25 years found reduced speeds in a driving simulator in a dual-task condition as well as impairments in a pegboard test [50]. Additional studies have reported deficits in driving performance including when cannabis is consumed in conjunction with alcohol [49,51•].

While there are some inconsistencies regarding effects of cannabis use on cognition, the general consensus supports impairments in both short-term and long-term use [45•,52•]. As seen in Table 1, these inconsistencies may stem from small sample sizes, sample biases, large variation in usage and categorization of heavy/light or frequent/infrequent users, as well as the possibility of the abuse of multiple drugs, confounding the effects of cannabis. Thus, the studies that have explored motor deficits have been limited to reaction time, tracking, motor impulsivity, and response inhibition. Only one study included an explicit motor sequence learning task, but did not report any behavioral measures (reaction time or accuracy) and thus learning could not be assessed [53]. Animal models indicate that drugs of abuse, such as cocaine [54] and nicotine [55], can impair motor learning. It is important that future studies close this knowledge gap by investigating motor learning (e.g., serial reaction time task, motor adaptation) in cannabis users.

Conclusion

In this review, we describe the intersection of movement and addiction via cortico-striatal pathways and the critical role of dopamine in both motor and reward pathways. The literature on deficits in motor performance in cannabis users has predominantly focused on applications to driving. While the focus on cannabis' effects on driving performance is important given recent changes in policy, a clear knowledge gap exists in the literature regarding deficits in motor learning. The literature indicates that users of cannabis exhibit cognitive impairments and the few existing studies show evidence of motor deficits. Together with the evidence that cognitive processes are critical for motor learning, it is probable that cannabis users also exhibit deficits in motor learning.

Studies demonstrating alterations in neural pathways causing goal-direction actions to be transformed into habits [20,56••] suggest that addiction has a considerable effect on the motor system. Addiction can be viewed as a problem of the motor system in that it is the selection and generation of sequences of actions that result in negative consequences [23]. Thus, it is critical to investigate how these actions are selected, connect with existing literature on reward-guided action selection, and explore whether this selection can be altered as an intervention to addiction.

Evaluating how the motor system is affected in cannabis use will provide novel insights into the neural mechanisms of addiction as well as answer important questions about the societal impact of potential policy changes. Importantly, despite the view that cannabis is relatively innocuous, it is critical to assess deficits as a result of cannabis use on this important ability required for all activities of daily living. Furthermore, given the overlap between the motor and reward systems, there may be potential avenues for treatment and rehabilitation via the motor system.

Conflict of interest statement

Nothing declared.

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This paper provides an excellent framework for the hierarchical structure required to construct goal-directed actions and the role of the cortico-striatal loop. This is important for understanding the role of the cortico-striatal networks in action generation and selection and its application to addiction.