Cannabis use in humans is associated with impaired implicit motor learning and supranormal baseline cortical activity

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Abstract

Chronic cannabis use is associated with cognitive impairment, but its impact on implicit motor learning is unclear. Implicit learning of movement sequences (i.e., their specific ordinal and temporal structure) is vital for performing complex motor behavior and lays the foundation for performing daily activities and interacting socially. We collected data from 32 individuals who used cannabis regularly and 30 individuals who did not use cannabis. We utilized the serial reaction time task to assess implicit motor sequence learning and the Corsi block-tapping test to assess visuospatial short-term and working memory. We also recorded resting state electroencephalography (EEG) to measure baseline cortical activity. While implicit motor learning was evident at the group level, cannabis use measures were associated with a smaller index of motor learning and increased activity in beta and gamma EEG frequencies during resting state. The cannabis group also had a significantly shorter Corsi span (in both forward and backward conditions). These findings indicate that chronic cannabis use is associated with impaired implicit motor learning that may be a function of increased baseline neural oscillatory activity, resulting in increased cortical noise, and reduced visuospatial short-term and working memory. These findings suggest that chronic cannabis use may disrupt corticostriatal pathways that underlie implicit motor sequence learning, indicating a more extensive effect of cannabis on the motor system.

Keywords: Cannabis use, Implicit motor learning, Resting state brain activity, EEG, Working memory

Introduction

Recreational cannabis is legal in 23 states in the United States and is widely used around the world [1]. Acute and chronic cannabis use is associated with cognitive impairment, including attention and working memory [2–6]. These cognitive processes underlie motor learning [7–9], which involves combining actions into specific temporal and ordinal structures that form complex motor behaviors important for daily living. These behaviors include communicating with others, operating equipment and software (e.g., driving a car, using a computer), and engaging in activities that improve our health (e.g., physical activity). Thus, motor learning is critical for human behavior throughout the lifespan.

Acute and chronic cannabis use may influence motor learning through movement pathways in the corticostriatal network that are modulated by dopamine. The D1 subtype of dopamine receptors modulates the direct pathway that facilitates movement, while the D2 subtype modulates the indirect pathway that inhibits movement. A careful balance between these pathways is required to perform the desired movement and suppress unnecessary or redundant movements. In addition to these movement pathways, dopamine also regulates the reward circuit from the ventral tegmental area to the nucleus accumbens and prefrontal cortex [10]. Dopamine pathways in the prefrontal cortex integrate rewarded motor behavior that leads to goal-directed actions [11]. Alterations in these pathways are associated with substance use, including cannabis, and are foundational to the development of substance use disorders [12]. For example, chronic cannabis use results in decreased dopamine synthesis in the striatum [13,14], which may impact movement pathways that connect through the striatum via dopamine projections. In addition, cannabis predominantly affects D1 receptors [15] and influences the binding of stimuli-response pairs [16] that are required for integrating task-related

stimuli and appropriate motor responses. Furthermore, endogenous cannabinoids are naturally present throughout the brain and bind with cannabinoid type-1 (CB1) and cannabinoid type-2 (CB2) receptors. Animal studies demonstrate that CB1 receptors are most densely present in the basal ganglia, cerebellum, and hippocampus [17], can alter dopamine, GABA, and glutamate availability [18], and can regulate motor activity [19]. When delta-9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in cannabis, interacts with these receptors, it can inhibit synaptic transmission [20]. Chronic cannabis use was found to reduce CB1 receptor availability in rats [21–24] and humans [25–27]. In rats, acute cannabis activated CB1 receptors in the cerebellum and resulted in impaired motor coordination [28,29]. These findings provide converging evidence that cannabis influences the motor system.

In addition, the effect of cannabis on dopamine and cannabinoid receptors may also alter baseline cortical activity [30,31], which can then impact cognition [32]. Baseline neural oscillations are present during resting state, i.e., when an individual is awake, but not engaged in a task [33,34], and have both spatial and temporal synchrony [35,36]. This neural synchrony can be measured via electroencephalography (EEG), in which neural signals in different frequencies are associated with task-specific cognitive processes. For example, alpha frequencies (8-12 Hz) are synchronized (i.e., they are present with greater power) during resting state, while beta (13-30 Hz) and gamma (30 Hz and above) are synchronized when engaged in a task. Beta frequencies in particular are associated with motor processing [37,38] in the central and parietal areas of the cortex [39,40]. Typically, resting state measured via EEG consists of greater activity in the lower frequencies (i.e., delta, theta, and alpha) and reduced activity in the higher frequencies (i.e., beta and gamma) due to the absence of engagement in a task [35]. Changes in these neural patterns may indicate disruptions in networks underlying

cognition [32]. Prior studies have found that alterations in resting state EEG are associated with chronic cannabis use. For example, Prashad and colleagues reported that individuals who chronically use cannabis exhibited increased beta power and decreased delta (0-4 Hz) and theta (4-7 Hz) activity during resting state compared to controls who do not use cannabis [41]. This altered resting state cortical activity suggests a failure to inhibit excessive cortical noise, which may disrupt cognitive and motor processes. In addition, Böcker and colleagues found greater resting state theta associated with impaired working memory after acute cannabis intoxication. They further demonstrated a dose-dependent effect of THC on beta frequencies, such that individuals who consumed larger doses of THC exhibited greater resting state beta power [42]. These findings indicate that cannabis can disrupt resting state neural oscillations that may be associated with cognitive impairment.

Moreover, some studies suggest acute cannabis use impairs motor control. For example, acute cannabis use is typically associated with longer reaction times [43] in a dose-dependent manner [44]. Acute use was also associated with reduced inhibition of ongoing motor responses in the stop signal task [45,46]. Importantly, although there is some evidence that acute cannabis use affects the motor system, no studies to date have examined the impact of chronic cannabis use on implicit motor sequence learning in humans or whether implicit motor learning is associated with baseline cortical activity.

In this study, we examined the effect of chronic cannabis use on implicit motor sequence learning and baseline cortical activity. Implicit motor learning was assessed using the serial reaction time (SRT) task and cortical activity was measured during resting state EEG. We also measured visuospatial short-term and working memory using the Corsi block-tapping test. We predicted that individuals with chronic cannabis use would exhibit increased baseline cortical activity (i.e., greater activity in the beta and

gamma bands and less activity in the delta, theta, and alpha bands) compared to individuals who do not use cannabis. Moreover, we expected that increased years of cannabis use would be associated with increased baseline cortical activity as well as larger declines in implicit motor learning. This prediction is based on prior research that indicates that longer duration of cannabis use is associated with greater neuropsychological decline [47]. Finally, consistent with the current literature [2,4], we expected that chronic cannabis use would be associated with shorter forward and backward Corsi spans (i.e., number of items in memory), indicating reduced short-term and working memory, respectively.

Materials and Methods

Participants

We recruited 72 participants from the Washington State University (Pullman) community. Of these, five participants did not meet the inclusion criteria and five participants did not complete all sessions of the study. Of the remaining 62 participants, 30 participants used cannabis at least four times a week for at least one year (cannabis group; mean age = 20.5 ± 1.7 years; 20 female participants) and 32 participants used cannabis 25 times or fewer in their lifetime (control group; mean age = 20.7 ± 3.0 years; 23 female participants). Participant demographic information is displayed in Table 1. Of the 32 participants in the control group, 16 reported never using cannabis, and the remaining 16 had used cannabis an average of 4.7 ± 7.4 (range: 1-25) times in their lifetime. All participants were right-handed, proficient in English, did not have a history of neurological diagnoses, and provided their informed consent. All procedures were approved by the Institutional Review Board at Washington State University. Participants

were not asked to abstain from cannabis for any session and used cannabis as was typical for them. Participants received Amazon gift cards of $10, $20, and $30 for completing the first, second, and third sessions, respectively.

Procedures

The three sessions were completed within approximately one week. In the first session (45 minutes), participants completed surveys about handedness, cannabis, alcohol, and cigarette use, anxiety, stress, mood, and cognitive function. We assessed handedness using the Edinburgh Handedness Inventory – Short Form [48,49]. To assess cannabis use, we measured: 1) frequency and quantity of use with the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU [50]), 2) cannabis dependence using the Cannabis Use Disorder Identification Test-Revised (CUDIT-R [51]), and 3) the impact of cannabis use on different aspects of daily life using the Marijuana Problem Scale (MPS [52]). We also assessed alcohol and nicotine dependence using the Alcohol Use Disorder Identification Test (AUDIT [53]) and the Fagerstrom Test for Nicotine Dependence (FTND [54]), respectively. To assess anxiety, mood, and stress, we used the Depression, Anxiety, and Stress Scale-21 Items (DASS-21 [55]). Lastly, we assessed self-reported cognitive impairment with the Cognitive Failures Questionnaire (CFQ [56]).

In the second session (90 minutes), we assessed subjective craving using the Marijuana Craving Questionnaire-Short Form (MCQ-SF [57]) following which participants performed two tasks: 1) the serial reaction time (SRT) task [58] to assess implicit motor sequence learning and 2) the Corsi block-tapping test [59] to assess visuospatial short-term and working memory. The SRT task was followed by the NASA Task Load Index (NASA-TLX [60]) to assess the amount of perceived mental and physical demand during

the task. Participants also completed the AX-Continuous Performance Test [61] to assess cognitive control and a water cup transport task [62] to assess physical and cognitive load that will be reported elsewhere.

In the SRT task, participants responded to stimuli that appeared in one of four squares that were presented horizontally in the middle of the computer screen. Participants pressed the “D” key using their left middle finger for the left-most location, “F” using their left index finger for the second location, “J” using their right index finger for the third location, and “K” using their right middle finger for the right-most location. Participants responded to the stimuli by pressing the corresponding button as quickly and accurately as possible. They had 500 ms to respond to the stimulus and the response-to-stimulus interval was randomly selected between 500-1000 ms. The task consisted of eight blocks of 120 trials each. In the first block (i.e., B0), stimuli appeared in a random order to assess baseline reaction time (RT). In Blocks 1-4 (B1-B4), stimuli appeared in a specific sequential order consisting of 12 items that repeated 10 times in each block. In Block 5 (B5), stimuli appeared in a random order. In Block 6 (B6), stimuli appeared in the same sequence as B1-B4. This task assesses implicit motor sequence learning as participants were not informed that stimuli often appeared in the same sequence [58].

In the Corsi block-tapping test, participants were presented with squares in different locations on the computer screen. In each trial, stimuli appeared in these squares in a specific order. In the forward condition, participants were instructed to click the squares in the same order. In the backward condition, participants were instructed to click the squares in the reverse order. The Corsi span score represented the largest number of items participants were able to remember in the forward condition (i.e., short-term memory) and the backward condition (i.e., working memory). The SRT task and the

Corsi block-tapping test were presented using Presentation software (Neurobehavioral Systems Inc., Berkeley, CA).

Finally, in the third session (75 minutes), we assessed subjective craving again using the MCQ-SF and global cognition using the Montreal Cognitive Assessment [63]. We recorded eyes closed resting state EEG from each participant with a 64-electrode ActiCap with BrainAmp amplifier (Brain Products GmbH, Gilching, Germany) with a sampling frequency of 1000 Hz and referenced to the sensor on the left earlobe. Channel impedances were below 7 kΩ. We collected three trials of two minutes each and instructed participants to close their eyes, relax, and try not to think about anything in particular.

EEG Analysis

We first processed the EEG to reduce the presence of artifacts. To reduce longitudinal drift, EEG data were high-pass filtered with a 4th-order zero-phase Butterworth filter at a cutoff frequency of 0.1 Hz. Brief deflections in the EEG signals, caused by sudden head movements, were reduced with artifact subspace reconstruction [64,65]. This technique removes reconstructed artifacts from time windows that contain unusually high variances in amplitude. We used a time window length of 0.5 seconds and removed artifacts from time windows that had a variance beyond 60 standard deviations compared to other data that had no deflections. Next, we removed artifacts associated with ocular, muscular, and power line activity with Independent Component Analysis (ICA) and the "ICLabel" functions [66] in the EEGLAB toolbox [67]. ICA decomposes the EEG signals into statistically independent components while ICLabel automatically classifies which components are artifacts based on a large freely available database.

Then, we extracted spectral power from the EEG recordings. First, we re-referenced the EEG to the common average reference. Next, we extracted the 90-second epoch that began 15 seconds after the participant was given the cue to close their eyes. Next, the linear trend from the epoch was removed to reduce spectral leakage. The Welch method was used to calculate the power spectral density (PSD), which estimates the PSD based on the average Fast Fourier Transform (FFT) solution from split segments from the epoch. The FFT was calculated in 10-second segments with a 5-second overlap, each of which was multiplied by a Hamming window using an FFT length of 8192 samples. From the PSD, we extracted power from five frequency bands: delta (<4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-50 Hz). We calculated relative spectral power as a percentage of the total power (1-50 Hz) for each frequency band and grouped the EEG sensors into four regions that corresponded to major cortical areas (i.e., frontal, central, parietal, and occipital regions).

Statistical Analyses

To evaluate implicit motor learning, we calculated mean RTs for each block in the SRT task. We excluded incorrect responses and RTs that were greater or less than 2.5 standard deviations from each participant's mean from the analysis [68,69]. We conducted a mixed factorial analysis of variance (ANOVA) on RT with Group (control, cannabis) as the between-subjects factor and Block (B0-6) as the within-subjects factor. As is standard in this task [70,71], we expected RTs to significantly decrease in the last learning block (i.e., B4) compared to the first learning block (i.e., B1) as participants learned the sequence and could respond faster by anticipating the response to the upcoming stimulus before it appeared. Since B5 contained randomly ordered stimuli, we expected mean RTs to significantly increase in B5 compared to B4 as participants could

no longer anticipate the next stimulus. This increase in RT in response to random stimuli compared to the sequenced stimuli is an index of motor learning [72]. We also expected a significant decrease in RT in B6, where the stimuli appeared in the same sequence as that in the learning blocks, compared to B5.

To assess differences in short-term and working memory, we performed independent *t*-tests on the forward and backward Corsi span, respectively.

To assess differences in resting state EEG, we conducted a 2 x 4 mixed-design ANOVA with the between-subjects factor of Group (control, cannabis) and the within-subject factor of Region (frontal, central, parietal, and occipital) on relative spectral power for each frequency band.

We also calculated Pearson's correlations between variables related to cannabis use (i.e., CUDIT-R, MPS, MCQ-Session 2, MCQ-Session 3, cannabis use in the prior 30 days, years of cannabis use, age at onset of cannabis use, and lifetime cannabis use), mood, anxiety, stress, cognition, index of motor learning from the SRT task, forward and backward Corsi span, and spectral power in the cannabis group.

For all analyses, we used Bonferroni *post hoc* tests to account for multiple comparisons in significant effects. Any significant differences between groups on other variables such as age, education, alcohol use, or nicotine use, were included as covariates in the analyses. Statistical significance was defined at $p < 0.05$. We analyzed the data using custom scripts in MATLAB (MathWorks, Natick, MA) and SPSS (IBM, Armonk, NY).

Results

Demographics, Cognitive-Emotional Assessments, and Cannabis Use Measures

Differences in demographic, cognitive-emotional assessments, and cannabis use measures for the two groups are reported in Table 1. There were no significant differences between the groups in age ($t(60) = 0.30$, $p = 0.77$, $d = 2.4$), gender ($t(60) = -0.44$, $p = 0.66$, $d = 0.47$), education ($t(60) = 1.5$, $p = 0.14$, $d = 0.81$), or nicotine use (no participants reported nicotine use). The cannabis group reported significantly higher alcohol use ($t(60) = -2.7$, $p = 0.010$, $d = 4.9$) compared to the control group, so alcohol use was included as a covariate in subsequent analyses. For cognitive-emotional assessments, there were no differences in self-reported anxiety ($t(60) = -1.3$, $p = 0.21$, $d = 3.2$), mood ($t(60) = 0.019$, $p = 0.99$, $d = 3.5$), or stress ($t(60) = 0.56$, $p = 0.58$, $d = 3.5$). There were also no differences in global cognition ($t(60) = -0.61$, $p = 0.55$, $d = 1.9$) or self-reported cognitive impairment ($t(60) = 1.8$, $p = 0.081$, $d = 20.9$).

The cannabis group used cannabis on significantly more days in the prior 30 days ($t(60) = -40.8$, $p < 0.001$, $d = 2.5$), for significantly more years ($t(60) = -11.6$, $p < 0.001$, $d = 1.1$), and had significantly greater lifetime cannabis use ($t(60) = -5.2$, $p < 0.001$, $d = 19.6$) compared to the control group. In addition, the cannabis group had higher MPS ($t(60) = -5.2$, $p = 0.001$, $d = 2.7$) and CUDIT-R ($t(60) = -16.1$, $p < 0.001$, $d = 3.2$) scores than the control group. Moreover, the cannabis group had significantly higher MCQ-SF scores compared to the control group (Session 2, $t(60) = -7.0$, $p < 0.001$, $d = 10.9$ and Session 3, $t(60) = -7.8$, $p < 0.001$, $d = 9.4$; the MCQ-SF was not collected in the first session).

There was a significant positive partial correlation (controlled for alcohol use) between the MPS score and anxiety ($r = 0.30$, $p = 0.047$) as well as self-reported cognitive impairment ($r = 0.30$, $p = 0.043$) in the cannabis group. In addition, age at onset of cannabis use was positively partially correlated with global cognition ($r = 0.37$, $p = 0.013$). Other correlations are included in Table S1 in the supplemental materials.

Table 1. Participant demographics (mean ± SD)

	Control Group	Cannabis Group	*p*-value
N	32	30	-
Age (years)	20.7 ± 3.0	20.5 ± 1.7	0.77
Gender (M/F)	9/23	10/20	0.66
Years of education	14.4 ± 1.1	14.1 ± 0.37	0.14
Cannabis use days in prior 30 days	0.0 ± 0.0	25.4 ± 4.2	< 0.001*
Years of cannabis use	0.0 ± 0.0	3.3 ± 1.6	< 0.001*
Age at cannabis use onset (years)	-	16.4 ± 2.1	-
Lifetime cannabis use	4.7 ± 7.4	2518.8 ± 2758.3	< 0.001*
MPS	1.0 ± 1.7	4.6 ± 3.5	< 0.001*
CUDIT-R	1.1 ± 1.6	14.1 ± 4.3	< 0.001*
AUDIT	3.8 ± 4.8	7.0 ± 4.9	0.010*
FTND	0.0 ± 0.0	0.0 ± 0.0	1.0
DASS-21	10.5 ± 8.1	11.1 ± 9.3	0.81
DASS-21 Depression score	3.8 ± 3.2	3.7 ± 3.8	0.99
DASS-21 Anxiety score	2.7 ± 3.1	3.7 ± 3.4	0.21
DASS-21 Stress score	4.1 ± 3.3	3.6 ± 3.7	0.58
Cognitive Failures Questionnaire	59.4 ± 18.6	50.0 ± 23.0	0.081
MCQ-SF (Session 2)	18.7 ± 8.0	38.1 ± 13.3	< 0.001*
MCQ-SF (Session 3)	16.3 ± 6.8	34.8 ± 11.5	< 0.001*
MoCA	26.9 ± 2.2	27.2 ± 1.5	0.55

Abbreviations: M/F, male/female; MPS, Marijuana Problem Scale; CUDIT-R, Cannabis Use Disorder Identification Test-Revised; AUDIT, Alcohol Use Disorder Identification Test; FTND, Fagerstrom Test for Nicotine Dependence; DASS-21, Depression, Anxiety, and Stress Scale – 21 Items; MCQ-SF, Marijuana Craving Questionnaire-Short Form (not assessed in Session 1); MoCA, Montreal Cognitive Assessment.

Implicit Motor Sequence Learning

As we found significantly higher alcohol use in the cannabis group, we included the AUDIT score as a covariate and conducted a mixed factorial ANCOVA on RT from the SRT task. We found a main effect of Block, $F(6,354) = 22.7$, $p < 0.001$, partial $\eta^2 = 0.28$, but no main effect of Group, $F(1,59) = 0.13$, $p = 0.72$, partial $\eta^2 = 0.002$ or AUDIT score, $F(1,59) = 0.23$, $p = 0.63$, partial $\eta^2 = 0.004$. There were also no significant interactions between Block and Group, $F(6,354) = 0.41$, $p = 0.88$, partial $\eta^2 = 0.007$ or Block and AUDIT score, $F(6,354) = 0.92$, $p = 0.48$, partial $\eta^2 = 0.015$. Figure 1A shows mean RTs for each block of the SRT task for both groups. *Post hoc* analyses corrected for multiple

comparisons revealed a significant decrease in RT from B1 to B4 for both groups (control group, $p = 0.001$, $d = 0.79$; cannabis group, $p < 0.001$, $d = 0.88$), a significant increase in B5 compared to B4 (i.e., index of motor learning, control group, $p < 0.001$, $d = 1.1$; cannabis group, $p = 0.008$, $d = 0.76$), and a significant decrease from B5 to B6 (control group, $p < 0.001$, $d = 1.3$; cannabis group, $p < 0.001$, $d = 0.96$).

Although there were no significant group differences in the SRT task, there was a significant negative partial correlation between years of cannabis use and the index of motor learning ($r = -0.55$, $p = 0.002$) in the cannabis group, shown in Figure 1B.

To evaluate perceived mental and physical demand of the SRT task, we compared ratings on the NASA-Task Load Index, shown in Figure 1C. The cannabis group reported exerting significantly greater effort ($t(60) = -2.0$, $p = 0.025$, $d = 4.8$) and feeling more rushed ($t(60) = -1.7$, $p = 0.046$, $d = 5.0$) during the task compared to the control group. There were no significant differences in perceived mental demand ($t(60) = -1.2$, $p = 0.12$, $d = 4.9$), physical demand ($t(60) = -0.42$, $p = 0.34$, $d = 2.5$), successful performance ($t(60) = -0.64$, $p = 0.26$, $d = 3.9$), or frustration ($t(60) = -0.34$, $p = 0.37$, $d = 4.5$).

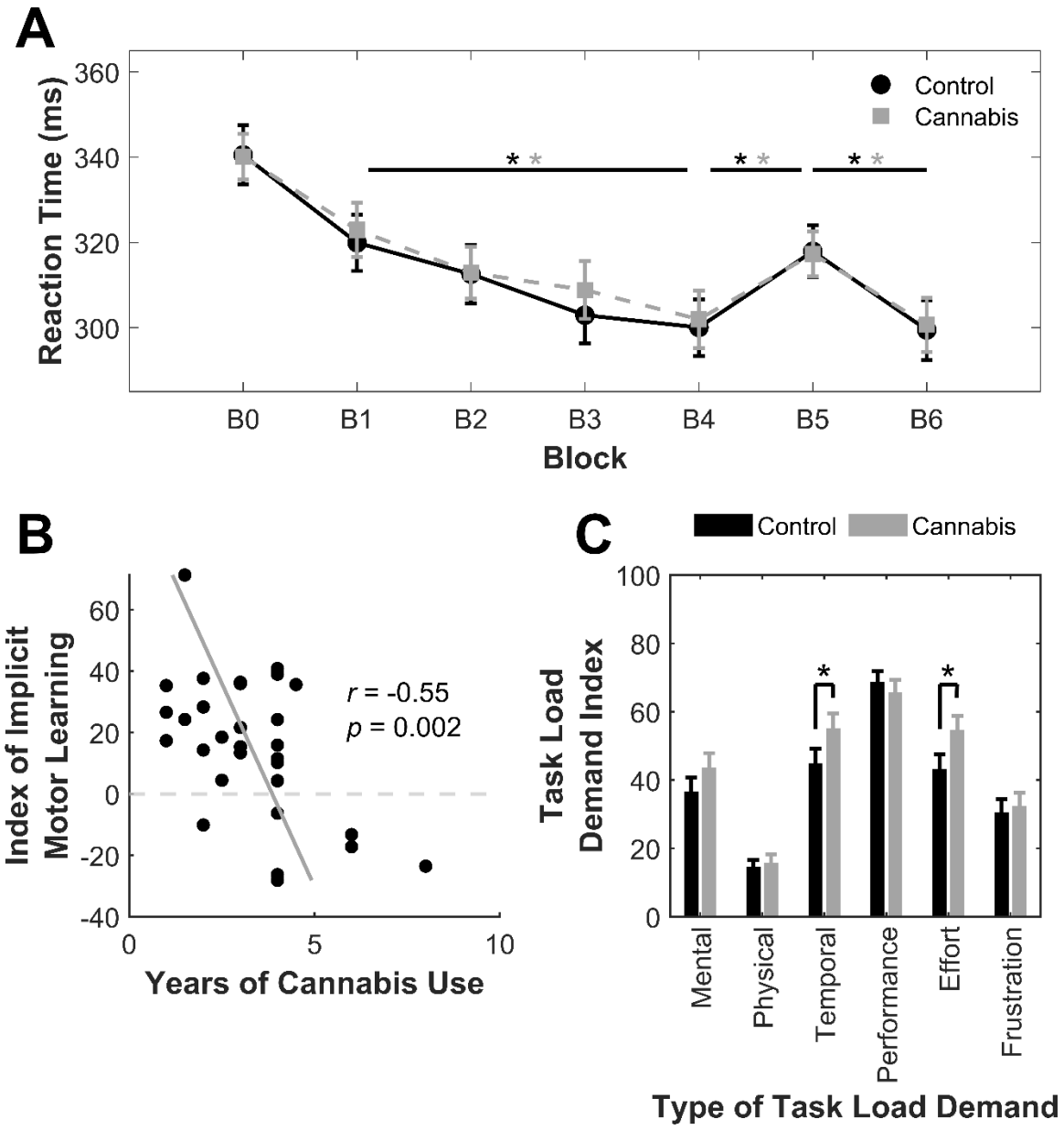

Figure 1. Implicit motor learning. A) Mean reaction times for correct responses in each block for the control group and the cannabis group in the serial reaction time (SRT) task. B) Individuals with more years of cannabis use showed a smaller index of implicit motor learning in the SRT task. The index of implicit motor learning in the SRT task is the difference in reaction time between Block 5 and Block 4 (i.e., a greater positive difference indicates a greater amount of learning, while a negative difference indicates no learning). The horizontal line at 0 represents a 0 ms difference between these blocks. C) The cannabis group reported feeling significantly greater temporal demand (i.e., feeling more rushed) and exerting greater effort compared to the control group when performing the SRT task. Higher task load demand index scores represent subjective reports of higher demand. The performance task load was reverse coded to match the other types of task load. Error bars indicate standard error. *Significance level of $p < 0.05$.

Resting State EEG

In the delta, theta, alpha, and beta bands, there was a significant main effect of Region (delta, $F(3,177) = 103.0$, $p < 0.001$, partial $\eta^2 = 0.64$, theta, $F(3,177) = 14.3$, $p < 0.001$, partial $\eta^2 = 0.20$, alpha, $F(3,177) = 81.8$, $p < 0.001$, partial $\eta^2 = 0.58$, beta, $F(3,177) = 12.8$, $p < 0.001$, partial $\eta^2 = 0.18$), but no significant main effect of Group and no significant interactions. In the gamma band, there were no significant main effects in the gamma band, but there was a significant interaction between Region x Group, $F(3,177) = 4.2$, $p = 0.007$, partial $\eta^2 = 0.066$. *Post hoc* analyses indicated no significant differences between regions in the control group, but in the cannabis group, there was significantly higher gamma power in the central region compared to the frontal ($p < 0.001$, $d = 1.3$), parietal ($p < 0.001$, $d = 1.1$), and occipital ($p = 0.004$, $d = 1.2$) regions.

Figure 2 shows the significant correlations between cannabis use measures and EEG activity. Consistent with our prediction that cannabis use would be associated with supranormal EEG activity, we found significant correlations between cannabis use measures and beta, gamma, and delta frequencies. Specifically, age at onset of cannabis use was negatively partially correlated with beta activity in the central ($r = -0.43$, $p = 0.014$) and the parietal ($r = -0.37$, $p = 0.047$) regions. In addition, cannabis use in the prior 30 days was positively partially correlated with gamma activity in the frontal ($r = 0.62$, $p < 0.001$), central ($r = 0.43$, $p = 0.019$), and occipital ($r = 0.48$, $p = 0.008$) regions. Finally, subjective craving assessed during the third session was negatively partially correlated with delta activity in the parietal ($r = -0.37$, $p = 0.049$) and occipital ($r = -0.38$, $p = 0.041$) regions, positively partially correlated with beta activity in the frontal region ($r = 0.48$, $p = 0.007$), and positively partially correlated with gamma activity in the frontal ($r = 0.45$, $p = 0.014$) and occipital ($r = 0.51$, $p = 0.005$) regions.

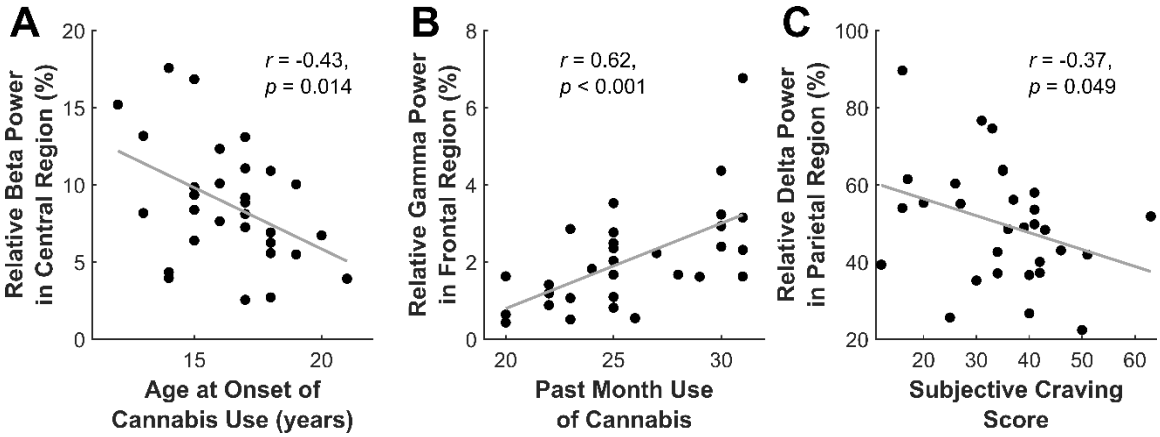

Figure 2: Correlation between cannabis use measures and cortical activity. A) Individuals who started using cannabis at an earlier age exhibited higher beta activity in the central (shown) and parietal (not shown) regions. B) Individuals who used more cannabis in the prior 30 days exhibited higher gamma activity in the frontal (shown), central (not shown), and occipital (not shown) regions. C) Individuals who reported higher subjective craving of cannabis (measured via the Marijuana Craving Questionnaire-Short Form; MCQ-SF) exhibited lower delta activity in the parietal (shown) and occipital (not shown) regions.

Corsi Block-Tapping Test

The cannabis group had a significantly shorter forward (i.e., short-term memory, $t(60) = 2.5$, $p = 0.017$, $d = 1.2$) and backward (i.e., working memory, $t(60) = 2.9$, $p = 0.006$, $d = 1.5$) span compared to the control group (see Figure 3). Additionally, subjective craving assessed in the second session was negatively partially correlated with the backward Corsi span ($r = -0.37$, $p = 0.049$) in the cannabis group.

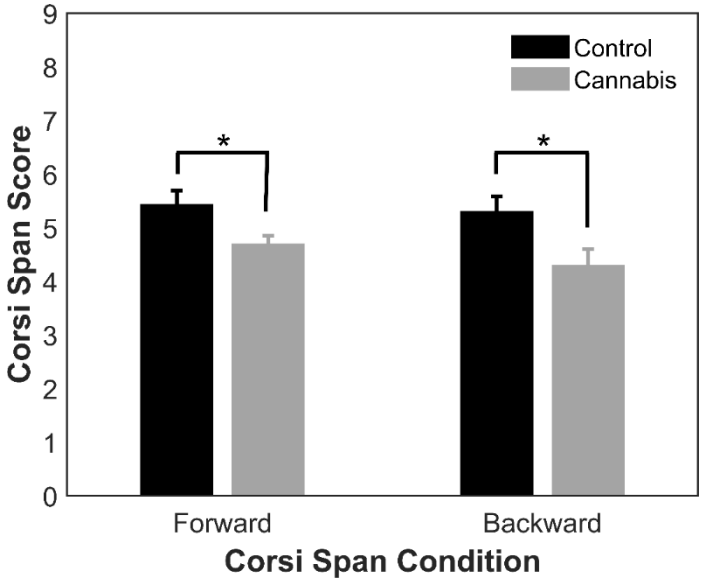

Figure 3. Memory span in the control and cannabis groups measured by the Corsi block-tapping test. The cannabis group had significantly lower Corsi span scores in both the forward (i.e., short-term memory) and backward (working memory) conditions. *Significance level of $p < 0.05$.

Discussion

We examined the effect of chronic cannabis use on implicit motor learning, baseline cortical activity, and visuospatial short-term and working memory. Our results indicate that cannabis use was associated with a smaller index of motor learning and altered baseline neural oscillations. In addition, we found a significantly reduced short-term and working memory span in the cannabis group. These findings suggest that disrupted resting state may increase cortical noise, interfere with cognition, and affect motor processes. The cannabis group reported exerting greater effort during the implicit motor learning task, which may have contributed to their performance being comparable to the control group and may have been necessary to compensate for the increased baseline cortical noise.

Implicit motor learning was impaired in individuals with longer cannabis use

While at the group level, we observed intact implicit motor sequence learning, there were individual differences within the cannabis group. Those who used cannabis for more years demonstrated a smaller index of motor learning, indicating impaired implicit motor learning in these individuals. This finding suggests that chronic cannabis use may impact the corticostriatal pathway that plays a critical role in motor learning [73,74]. These results complement recent evidence demonstrating that chronic cannabis use impairs visuomotor adaptation (i.e., successful application of previously well-learned motor skills to new contexts) [75,76]. However, motor adaptation is reliant on the corticocerebellar circuit, as opposed to the corticostriatal circuit that serves motor sequence learning [73]. This novel result suggests that the corticostriatal pathway is also likely impaired by chronic cannabis use, advocating a more widespread impact of chronic cannabis use on the motor system.

Supranormal resting state EEG may underlie implicit motor learning impairment

We found that the cannabis group exhibited supranormal resting state neural oscillations that was correlated with cannabis use measures. Specifically, individuals who started using cannabis at a younger age exhibited higher beta activity, and those who used cannabis for more days in the prior 30 days exhibited higher gamma activity. The shift in cortical activity may be due to the interaction between THC and CB1 receptors that can modulate the balance between excitatory and inhibitory postsynaptic activity and regulate local cortical excitability [77]. Specific to gamma activity, THC exposure can decrease the release of GABA in the prefrontal cortex and disrupt cortical gamma activity in adolescents [78]. Furthermore, another study reported that individuals who use cannabis chronically exhibited increased resting state beta activity [41], which is also consistent with our results. Tempel and colleagues found that when retrieving motor

sequences from memory, increased beta power predicted motor forgetting [79]. Importantly, we found increased beta activity in the central and parietal areas—regions that are critical for motor control [80–82]. While our results only reflect changes in resting state, the effect cannabis use has on resting beta activity should be considered in future studies that examine task-related activity.

Our finding of supranormal cortical activity during resting state may reflect increased cortical noise in the baseline functional organization of the brain. Prior studies have found that increased cortical noise during the baseline period before stimulus presentation in an oddball task was associated with acute THC use [83] and cannabis dependence [84]. Our findings suggest that increased cortical noise may extend beyond acute effects and underlie impaired cognition and implicit motor learning. It is unclear whether these effects persist with abstinence from cannabis or if they endure long-term. Future studies may consider a longitudinal approach to understand the directionality of these effects and parse whether short-term or long-term abstinence allows for recovery of motor learning.

Lower visuospatial short-term and working memory capacity in the cannabis group

A critical aspect of motor learning is the ordering of action sequences; this acquisition requires short-term and working memory to combine these individual actions into complex motor behavior [8]. Visuospatial working memory, in particular, is critical for optimum motor control [85] and is positively correlated with the rate of motor learning [86]. We found that individuals in the cannabis group had significantly reduced forward and backward Corsi spans compared to those in the control group. This is consistent with prior studies that have found poorer working memory and reduced hippocampal volume associated with more frequent cannabis use [87]. Furthermore, animal studies

have directly demonstrated the impact of THC on spatial working memory. Rats given THC exhibited dose-dependent impaired short-term and working memory in a water maze task [88,89]. In addition, D1 receptors in the prefrontal cortex are involved in working memory and are stimulated by cannabis [15,90]. When D1 receptors were activated at a higher level than is typical, spatial working memory was impaired in rhesus monkeys [91] and rodents [92]. This evidence is consistent with our findings that there was significantly reduced visuospatial short-term and working memory in the cannabis group.

Conclusion

We found that longer chronic cannabis use was associated with impaired implicit motor learning, increased baseline cortical activity, and a decline in visuospatial short-term and working memory. This increase in neural oscillations may lead to increased cortical noise that may disrupt cognitive and motor processing. These findings indicate that chronic cannabis use may affect the corticostriatal network that plays an important role in implicit motor learning, revealing a more widespread impact of chronic cannabis use on the motor system. Our findings highlight the complex nature of the effect of chronic cannabis use on cortical activity, cognition, and implicit motor learning that presents important considerations for understanding the full impact of cannabis on brain health, instrumental activities of daily living, and the consequent impact on public health.

Author Contributions

SP and LRF designed the study. SP and AYP analyzed the data. SP lead the writing of the manuscript. All authors collected data and reviewed/contributed to ideas contained in the manuscript.

Funding

This investigation was supported in part by funds provided for medical and biological research by the State of Washington Initiative Measure No. 171 to SP. This work was also supported by the National Science Foundation under Grant # EEC-2127509 administrated by the American Society for Engineering Education (ASEE) to AYP.

Competing Interests

The authors have nothing to disclose.

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