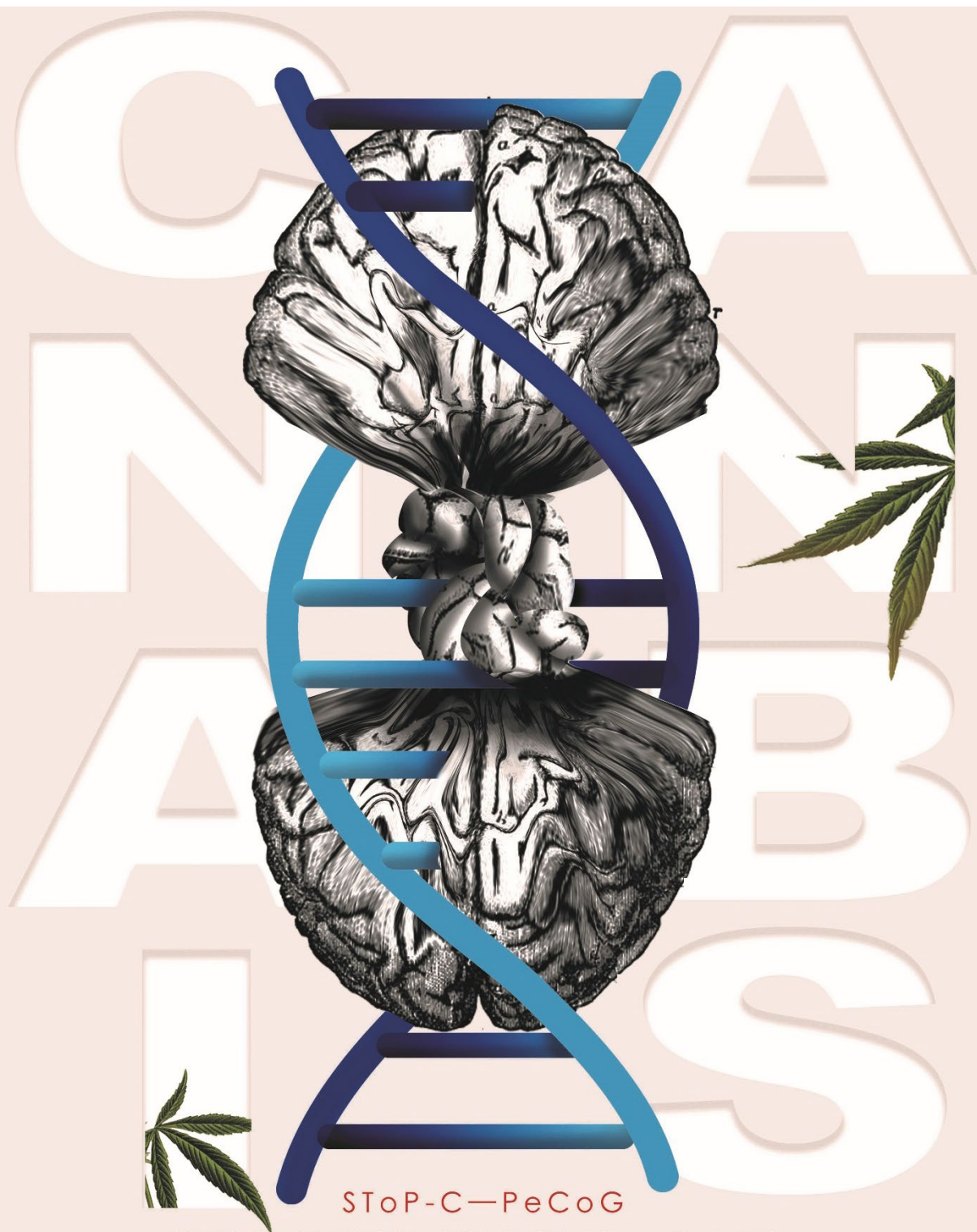




SToP-C—PeCoG

精神物質濫用至精神障礙 - 「大麻」

大麻使用者認知功能及其相關基因遺傳易受性的前瞻性評估研究

Substance misuse To Psychiatric disorders for Cannabis

Prospective evaluation on Cognitive function and its associated Genetic vulnerability
in cannabis users

BDF190050 Final Research Report

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Abstract

Background

Cannabis abuse in Hong Kong has been increasingly popular among drug abusers. Currently, most evidence on neurocognitive impairments resulted from cannabis use are mainly from cross-sectional studies. There is also a lack of study on any common genetic vulnerability of cannabis use disorder (CUD) and its associated neurocognitive functioning among cannabis users, in particular in the Asian population.

Aims

This study aimed to examine the temporal changes in neurocognitive functions from cannabis use, and whether genetic vulnerability might correlate with addiction to cannabis/CUD and the related changes in neurocognitive outcomes, focusing on global cognition, frontal executive function and memory functions.

Methods

The current study employed a prospective, naturalistic, non-interventional longitudinal design that followed up individuals who abused cannabis over an 18-month period. Participants were recruited via community outreach, from the Counselling Centres for Psychotropic Substance Abusers, substance abuse clinics operated under Hospital Authority, and by self-referrals to the research team. Consented participants were assessed at baseline and every three months on various outcomes, including their level of cannabis dependence, severity of CUD, global cognitive function, frontal executive function and memory functions using MoCA, FAB and WMS-III, respectively. Genomic analysis was also performed using venous blood samples

from the consented participants over a predefined panel of SNPs selected *a priori* based on GWAS and candidate-gene studies relevant to CUD and neurocognitive function or disorders.

Results

One hundred and nine participants consented and completed the baseline assessment. Ninety participants (82.57%) constituted the follow-up sample and genome-association analysis. The mean age of the participants was 28.86 years and the majority were male. They were suffering from psychological dependence on cannabis with moderate CUD. Among demographics, including age, gender, years of education, and lifetime duration of cannabis use, only years of formal education appeared to be the most consistent and significant factor positively influencing all three tested neurocognitive functions. Participants with higher educational levels tended to show preserved neurocognitive functioning in MoCA, FAB and all domains of WMS-III in this study. Global cognitive function and frontal executive function from cannabis use remained in the respective normative range within the whole study period, but working memory impairment was noted. Recent cannabis use was the most significant predictive factor on the negative impact on immediate memory and general memory associated with cannabis use. Two cannabis use-related SNPs, rs80030908 on chromosome 13 and rs73229090 on chromosome 8, identified from this study showed preliminary associations with the baseline frontal executive function and general memory, respectively, but did not predict the severity of CUD nor the longitudinal trajectories of the neurocognitive functions associated with cannabis use.

Conclusions

The current 18-month study showed that despite the global cognitive function and executive function might be relatively preserved in adult cannabis users, cannabis use did have

significant impact on different aspects of memory functions, with working memory being the most negatively impacted. Educational level and recency of cannabis use were the two most significant factors predicting the detrimental effects on neurocognitive functions associated with cannabis use. The two SNPs, rs80030908 on chromosome 13 and rs73229090 on chromosome 8, identified from this study are still far from conclusive to be used as biomarkers for predicting the trajectory of neurocognitive changes from cannabis use.

Executive Summary

Cannabis abuse in Hong Kong has been increasingly popular among drug abusers. Currently, most evidence on neurocognitive impairments resulted from cannabis use are mainly from cross-sectional studies. There is also a lack of study on any common genetic vulnerability of cannabis use disorder (CUD) and its associated neurocognitive functioning among cannabis users, in particular in the Asian population.

“Substance misuse To Psychiatric disorders for Cannabis—Prospective evaluation on Cognitive function and its associated Genetic vulnerability in cannabis users” (SToP-C—PeCoG) study here aimed to examine the temporal changes in neurocognitive functions from cannabis use, and whether genetic vulnerability might correlate with addiction to cannabis/CUD and the related changes in neurocognitive outcomes, focusing on global cognition, frontal executive function and memory functions.

This study employed a prospective, naturalistic, non-interventional longitudinal design that followed up individuals who abused cannabis over an 18-month period. Participants were recruited via community outreach, from the Counselling Centres for Psychotropic Substance Abusers, substance abuse clinics operated under Hospital Authority, and by self-referrals to the research team. Consented participants were assessed at baseline and every three months on various outcomes, including their level of cannabis dependence, severity of CUD, global cognitive function, frontal executive function and memory functions using the Severity of Dependence Scale (SDS), Structured Clinical Interview for DSM-5 Disorders–Clinician Version (SCID-5-CV), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB) and Wechsler Memory Scale 3rd edition (WMS-III), respectively. Genomic analysis was

also performed using venous blood samples from the consented participants over a predefined panel of SNPs selected *a priori* based on GWAS and candidate-gene studies relevant to CUD and neurocognitive function or disorders.

One hundred and nine participants consented and completed the baseline assessment. Ninety participants (82.57%) constituted the follow-up sample and genome-association analysis. The mean age of the participants was 28.86 years (SD = 9.65) and the majority were male (58.89%), with an average of 12.25 years of formal education (SD = 2.63). They were suffering from DSM-5 defined CUD with moderate severity ($M = 3.81$, $SD = 2.85$) and were psychologically dependent on cannabis ($M = 4.07$, $SD = 3.48$). Among demographics, including age, gender, years of education, and lifetime duration of cannabis use, only years of formal education appeared to be the most consistent and significant factor positively influencing all three tested neurocognitive functions (B 's = 0.23 – 3.94; all p 's <0.001). Participants with higher educational levels tended to show preserved neurocognitive functioning in MoCA, FAB and all domains of WMS-III in this study. Global cognitive function and frontal executive function from cannabis use remained in the respective normative range within the whole study period, but working memory impairment was noted (Means: 93.89 – 99.54). Recent cannabis use was the most significant predictive factor on the negative impact on immediate memory ($B = -0.82$) and general memory ($B = -0.59$) associated with cannabis use over time. Two cannabis use-related SNPs, rs80030908 on chromosome 13 and rs73229090 on chromosome 8, identified from this study showed preliminary associations with the baseline frontal executive function and general memory, respectively, but did not predict the severity of CUD nor the longitudinal trajectories of the neurocognitive functions associated with cannabis use.

In conclusion, the current 18-month study showed that despite the global cognitive function and executive function might be relatively preserved in adult cannabis users, cannabis use did have significant impact on different aspects of memory functions, with working memory being the most negatively impacted. Educational level and recency of cannabis use were the two most significant factors predicting the detrimental effects on neurocognitive functions associated with cannabis use. The two SNPs, rs80030908 on chromosome 13 and rs73229090 on chromosome 8, identified from this study are still far from conclusive to be used as biomarkers for predicting the trajectory of neurocognitive changes from cannabis use. Clinicians and professionals working in the anti-drug fields should continue educating the public about the “Not Now. Not Ever” principle towards cannabis, especially targeting the evidence-based negative impacts on neurocognitive functions from cannabis use as researched in this study and the existing literature. Vulnerable cannabis users, in particular those with low educational level should have their cognitive functions carefully monitored. Cannabis users and the general public should also be warned about the harms on memory functioning from the recency (acute) effect of cannabis use (“Not Now”). With the extensive literature supporting abstinence on improvements in cognition, long-term abstinence from cannabis use should still be strongly encouraged (“Not Ever”).

研究摘要

在香港，大麻濫用在毒品濫用者中越來越普遍。目前，關於大麻導致神經認知障礙的證據主要來自橫斷面研究。同時，針對亞洲人口中大麻使用障礙（CUD）與其相關神經認知功能的共同遺傳易感性研究亦較為缺乏。

「精神物質濫用至精神障礙—大麻 —大麻使用者認知功能及其相關基因遺傳易受性的前瞻性評估研究」(SToP-C –PeCoG)旨在探討濫用大麻對神經認知功能的時間性變化，以及遺傳易受性是否與大麻成癮/ 大麻使用障礙及相關神經認知變化，包括整體認知功能、前額執行功能及記憶功能相關。

本研究採用前瞻性、非干預的縱向研究設計，追蹤濫用大麻的參與者在 18 個月內神經認知功能的變化。參與者透過社區外展、濫用精神藥物者輔導中心、醫院管理局轄下的藥物濫用診所，以及自我推薦加入研究。在獲得同意後，參與者於基線及每三個月進行多項評估，包括使用大麻依賴嚴重度量表(SDS)、DSM-5 定式檢查臨床第(SCID-5-CV)、蒙特利爾認知評估(MoCA)、額葉評估量表(FAB)，以及魏氏記憶量表第三版（WMS-III），以分別測量並跟進參與者的大麻依賴程度、大麻使用障礙嚴重程度、整體認知功能、前額執行功能及記憶功能。同時，也利用參與者的靜脈血樣進行基因組分析，針對根據全基因組關聯分析(GWAS) 和候選基因與大麻使用障礙及神經認知功能相關研究，預先篩選的一組單核苷酸多態性(SNPs)進行分析。

一百零九位同意參與本研究的參與者完成了基線評估。追蹤樣本包括九十位參與者（82.57%），他們的靜脈血樣同樣用於基因關聯分析。本研究參與者的平均年齡為 28.86 歲（標準差 = 9.65），大多數為男性（58.89%），平均受教育年數為 12.25 年（標準差 = 2.63）。他們符合 DSM-5 定義的中度 CUD（平均值 = 3.81，標準差 = 2.85），並對大麻具有心理依賴（平均值 = 4.07，標準差 = 3.48）。在包括年齡、性別、教育年數及一生大麻使用時長等人口統計變數中，只有受教育年數顯示出與所有三項神經認知功能的正向顯著相關（回歸係數 B 's = 0.23 – 3.94；所有 p 值 <0.001）。教育程度較高的參與者在 MoCA、FAB 及 WMS-III 所有測域的神經認知功能表現均能維持完整性。整個研究期間，參與者的整體認知功能與前額執行功能均維持在正常範圍內，但工作記憶則出現損傷（平均值：93.89 – 99.54）。短期內的大麻使用是預測對立即記憶（ $B = -0.82$ ）及一般記憶（ $B = -0.59$ ）負面影響的最重要因素。研究亦發現兩個與大麻使用相關的單核苷酸多態性，分別是染色體 13 上的 rs80030908 和染色體 8 上的 rs73229090，與基線的前額執行功能及一般記憶呈初步相關，但未能預測 CUD 嚴重程度或神經認知功能的長期變化軌跡。

總結來說，這項為期 18 個月的研究顯示，儘管成人大麻使用者的整體認知功能及前額執行功能大致維持在正常範圍，但大麻使用對不同記憶功能產生了顯著的負面影響，其中工作記憶受到的影響最為嚴重。教育程度與短期內的大麻使用是預測神經認知功能受損的兩個最重要因素。研究中發現的兩個單核苷酸多態性（rs80030908 與 rs73229090）目前尚未能作為預測大麻使用引起的神經認知變化的生物標記。從事禁毒工作的臨床醫生和專業人士應特別針對大麻的負面影響，包括本研究及相關文獻所揭示的神經認知損害，持續向社會大眾宣傳「不可一·不可再」的原則。對於高危群體，

尤其是教育程度較低的大麻濫用者，應密切監測其認知功能。大麻濫用者及公眾亦應警惕短期（急性）大麻使用對記憶功能的傷害（「不可一」）。基於大量文獻支持戒除大麻有助於改善認知功能，長期戒除大麻亦應被強烈鼓勵推廣（「不可再」）。

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Glossary of Acronyms

17q24	17q24.2 microdeletion syndrome
ABS	days of abstinence
AD	auditory delayed index (memory)
AI	auditory immediate index (memory)
ARD	auditory recognition delayed index (memory)
ATP10A-DT	ATP10A divergent transcript
ATP2A1	ATPase sarcoplasmic/endoplasmic reticulum Ca^{2+} transporting 1
B	regression coefficient
BDF-Q6	Beat Drugs Fund Evaluation Question Set No. 6
BPTF	bromodomain PHD finger transcription factor
C17orf58	chromosome 17 open reading frame 58
CADM2	cell adhesion molecule 2
CB1	cannabinoid receptor 1
CHRNA2	cholinergic receptor nicotinic $\alpha 2$ subunit
CI	confidence interval
CSMD1	CUB and sushi multiple domains 1
CUB	complement C1r/C1s, Uegf, Bmp1 domain
CUD	cannabis use disorder
DAILY	daily use status
DLPC	dorsolateral prefrontal cortex
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5 th edition)
DSM-III	Diagnostic and Statistical Manual of Mental Disorders (3 rd edition)
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4 th edition)

EDTA	ethylenediaminetetraacetic acid
EDU	years of education
EPHX2	epoxide hydrolase 2
FAB	Frontal Assessment Battery
FDR	false discovery rate
FOXP2	forkhead box P2
FREQ	frequency of cannabis use
GABA	γ-aminobutyric acid
GM	general memory
GULOP	gulonolactone (L-) oxidase, pseudogene
GWAS	genome-wide association studies
HC3	heteroskedasticity-consistent 3
ICC	intraclass correlation coefficient
IM	immediate memory
IRB	institutional review board
LIFETIME	lifetime duration of cannabis use
LMM	linear mixed-effects model
LSD	lysergic acid diethylamide
M	mean
MAC	minor allele count
MAF	minor allele frequency
MC	mental control
MDMA	3,4-methylenedioxymethamphetamine
MED21	mediator complex subunit 21
MoCA	Montreal Cognitive Assessment

MTF	Monitoring the Future
N	number of participants
NCAM1	neural cell adhesion molecule 1
PPM1D	protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1D
PTPRM	protein tyrosine phosphatase receptor type M
RABEP2	rabaptin, RAB GTPase binding effector protein 2
SCID-5-CV	Structured Clinical Interview for DSM-5 Disorders—Clinician Version
SD	standard deviation
SDK1	sidekick cell adhesion molecule 1
SDS	Severity of Dependence Scale
SLC35G1	solute carrier family 35 member G1
SMG6	suppressor with morphological effect on genitalia-6
SNP	single nucleotide polymorphism
SToP-C—PeCoG	Substance misuse To Psychiatric disorders for Cannabis—Prospective evaluation on Cognitive function and its associated Genetic vulnerability in cannabis users
SYNCAM2	synaptic cell adhesion molecule 2
THC	tetrahydrocannabinol
TOMM40	translocase of outer mitochondrial membrane 40
VD	visual delayed index (memory)
VI	visual immediate index (memory)
VIF	variance inflation factor
WM	working memory
WMS	Wechsler Memory Scale
WMS-III	Wechsler Memory Scale, 3 rd edition
ZNF704	zinc finger protein 704

Introduction

Over the past decade, cannabis abuse in Hong Kong has been increasingly popular among drug abusers. According to the Central Registry of Drug Abuse, the number of reported cannabis abusers nearly doubled between 2015 and 2024. The figure registered amongst those newly reported cannabis abusers aged below 21 years is especially worrying. Between 2015 and 2024, there was a four-fold surge from 14.0% to 40.5% in reported use of cannabis among these young psychotropic substance abusers (Narcotics Division, 2025a).

It is estimated that around 2.7% of Hong Kong student ever taken drugs. Overall, 56.7% of drug-taking students who participated in the “2023/24 Survey of Drug Use among Students” reported cannabis ever-use, throning cannabis as their commonest psychotropic substance of abuse. By education level, 50.4% of ever drug-taking secondary school students and 84.0% of ever drug-taking post-secondary school students were cannabis ever-users (Narcotics Division, 2025b), giving the estimated lifetime prevalence of 1.4% and 2.3%, respectively. Though these figures are still far lower than the lifetime prevalence at 14.3% - 34.4% of cannabis ever-use reported in the US Monitoring the Future (MTF) national survey on adolescence (Miech et al., 2026), the high prevalence of lifetime cannabis ever-use amongst students in Hong Kong remains alarming.

Cannabis use can predispose at-risk individuals to severe psychiatric disorders. The prevalence of psychosis in DSM-III defined cannabis dependence users can be as high as 64% (Smith et al., 2009). As compared to the never-users, there is an associated five-fold increased risk for first-episode psychosis development for cannabis abusers. Such risk is also proportional to their overall exposure to cannabis and to the potency of the cannabis being used (Di Forti et

al., 2019; Pierre, 2017). Apart from the heightened risk in developing psychosis, lifetime prevalence for DSM-IV defined major depressive disorder and anxiety disorders in individuals with cannabis use disorder are as high as 20.9% and 30.5%, respectively (Stinson et al., 2006). Early adolescence cannabis use also correlates to the significantly increased risks in developing depression, suicidal ideation, and suicidal attempts in their early adulthood (Gobbi et al., 2019), as well as harboring a higher risk of addiction to other illicit substances (Volkow et al., 2014).

For cannabis users not suffering any psychiatric co-morbidity or cannabis use disorder (CUD), cannabis use might worsen their neurocognitive functions as compared to non-users, in particular on executive function, attention, memory, and learning (Duperrouzel et al., 2020), though preliminary evidence also suggests that these deteriorations are reversible after 25 days of abstinence (Schreiner & Dunn, 2012). In contrast, data elucidating poorer neurocognitive outcomes in adolescent-onset users are still equivocal (Duperrouzel et al., 2020; Meier et al., 2018). A recent population-based analysis from a four-year longitudinal study on secondary school students shows that a past use of cannabis might lead to poorer performance in working memory, delayed memory recall and perceptual reasoning (Morin et al., 2019).

Structural neuroimaging studies fail to show any consistent findings on brain regions accountable for either CUD or cannabis use-related neurocognitive changes (Duperrouzel et al., 2020). A small-scale magnetic resonance imaging study in older cannabis users who had an average of 23 years of cannabis use cannot find any significant difference in cortical volume or in cognitive performance as compared to the non-user controls (Thayer et al., 2019). Despite lacking the consistency on topographical evidence on which brain region is specifically affected, most functional neuroimaging studies demonstrate that the frontal and prefrontal cortices, limbic areas, cingulate gyrus, and cerebellum might be involved. These regions are high in

endocannabinoid CB1 receptors, where the Δ^9 -tetrahydrocannabinol (THC) in cannabis binds as agonist, might contribute to the development of CUD and/or cannabis use-related decline in neurocognitive function (Bloomfield et al., 2019; Duperrouzel et al., 2020; Sneider et al., 2013).

Several genome-wide association studies (GWAS) have tried to correlate CUD or cannabis dependence, neurocognitive function deterioration, and risk-taking behaviors in cannabis users as phenotypic phenomena to their underlying genetic predispositions. GWAS revealed several genes or single nucleotide polymorphisms (SNPs) that might ascend users' vulnerability. These genes or SNPs include those located on: i) chromosome 17q24 for C17orf58, PPM1D and BPTF for CUD, of which BPTF has also been identified from deceased Alzheimer's subjects that is worth considering for its association with the cognitive decline in susceptible cannabis users (Agrawal et al., 2014); ii) chromosome 10 with SNP rs1409568 associating with DSM-IV cannabis dependence that plays the role as enhancer in addiction-relevant regions, such as the dorsolateral prefrontal cortex (DLPC), angular and cingulate gyri, which are also involved in neurocognitive performance disruptions in cannabis users (Agrawal et al., 2018); iii) chromosome 8 with SNP rs77378271 in the CUB and Sushi multiple domains 1 gene (CSMD1) correlating with the severity of cannabis dependence (Sherva et al., 2016), and various SNPs, such as rs73229090 from the cholinergic receptor nicotinic $\alpha 2$ subunit (CHRNA2) that its under-expression in cerebellum (and potentially at the DLPC) might contribute to CUD and/or the lowered intelligence in cannabis users (Demontis et al., 2019); and iv) chromosome 3 for the gene cell adhesion molecule 2 (CADM2) that overlaps cannabis use and risk- or novelty- seeking behaviors (Pasman et al., 2018). CADM2 is worth investigating for its cognitive effect on cannabis users. CADM2 has demonstrated relevance to the prolongation of information processing speed in older individuals due to its involvement in the glutamate and γ -aminobutyric acid (GABA) neuro-signaling (Ibrahim-Verbaas et al.,

2016). An activation of the endocannabinoid pathway by THC can cause a retrograde signaling for both glutamatergic and GABAergic pathways (Bloomfield et al., 2019). Other potential genes and lead-SNPs based on GWAS and candidate-gene studies relevant to cannabis use disorder and neurocognitive function or disorders are listed in Tables 4 and 5 (Agrawal et al., 2018; Agrawal et al., 2014; Cao et al., 2023; Deak & Johnson, 2021; Demontis et al., 2019; Hatoum et al., 2023; Ibrahim-Verbaas et al., 2016; Johnson et al., 2020; Levey et al., 2023; Pasman et al., 2018; Phan et al., 2025; Sherva et al., 2016; Thorpe et al., 2021).

Nevertheless, most of these studies assessing CUD and neurocognitive functions are cross-sectional without examining the longitudinal changes in neurocognitive function at a within-subject level with respect to the continuum of cannabis use behavior, or mainly studying on the acute cannabis effect on neurocognitive function. Also, the GWAS population analyzed for addressing the underlying genetic susceptibility between neurocognitive functions and/or cannabis use or CUD are almost exclusively based on African-, European- or American samples, their generalizability to Chinese or to the non-Caucasian population remains limited.

With the upsweeping statistical figures of cannabis abuse in Hong Kong, the substantial reduction in the perceived risks and personal disapproval from using cannabis among young people (Miech et al., 2025; Narcotics Division, 2025b), the global advocacy of de-criminalizing cannabis, and the increased availability of recreational cannabis worldwide, it is reasonable to predict that there will be a further upsurge in numbers of all aged cannabis users in Hong Kong as in the other parts of the world (United Nations Office on Drugs and Crime, 2025). The “Substance misuse To Psychiatric disorders for Cannabis—Prospective evaluation on Cognitive function and its associated Genetic vulnerability in cannabis users” (SToP-C—PeCoG) study here therefore examined the prospective, long-term changes in neurocognitive

functions and the associated genetic risks for those repeated and active cannabis users without psychiatric co-morbidity, in particular in the Asian minority and Chinese in Hong Kong, on CUD and neurocognitive outcomes.

Methods

Study Design and Participants

This prospective, naturalistic, non-interventional longitudinal study followed up individuals who abused cannabis over an 18-month period to examine the temporal changes in their neurocognitive functions, and whether genetic vulnerability might correlate with their addiction to cannabis and the related changes in neurocognitive outcomes.

Participants were recruited via community outreach, from the Counselling Centres for Psychotropic Substance Abusers, substance abuse clinics operated under Hospital Authority, and by self-referrals to the research team. Tables 1 and 2 outlined the inclusion and exclusion criteria for cannabis abusers to be eligible to participate in this study, respectively.

Participants would receive a total of HK\$500 as travel allowances after completing all the outcome assessments and provided biological (blood) samples for genomic testing in this 18-month follow-up study. This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB reference: UW 20-189), and all procedures adhered to the Declaration of Helsinki.

Study Objectives and Study Hypothesis

The primary objective of this study was to evaluate the long-term changes in neurocognitive functions for cannabis abusers over the 18-month period. The secondary objectives were to determine if genetic vulnerability associated with cannabis use would predispose cannabis abusers to have more severe CUD and poorer neurocognitive outcomes.

This study hypothesized that:

1. *Neurocognitive function*-H₀: cannabis use causes no neurocognitive function decline over time.
2. *Genetic vulnerability* on
 - a. *severity of CUD*-H₀: no genetic vulnerability is associated with the severity of CUD.
 - b. *neurocognitive function*-H₀: no genetic vulnerability is associated with the decline in neurocognitive function.

Incidence and Sample Size

The total number of newly reported cannabis abusers for all ages and genders from the Central Registry of Drug Abuse between 2014 and 2018 was 1180 (mean = 236), and the total number of newly reported psychotropic substance abusers within the same timeframe was 8368 (mean = 1673.6). Hence, the 5-year incidence rate was 14.1%. Meier et al. (2022) demonstrated that individuals with long-term cannabis use would have poorer neurocognitive functions with significant deteriorations in intelligence quotient (mean -5.50; SD = 8.88) and Wechsler Memory Scale (WMS) scores (standardized mean -0.48; SD = 1). Previous meta-analyses and reviews (Deak & Johnson, 2021; Johnson et al., 2020; Thorpe et al., 2021) had located several important genes with minor allele frequency (MAF) for cannabis use and dependence. These genes include CHRNA2, EPHX2 and GULO1 (lead SNP rs4732724) on Chromosome 8, and FOXP2 (lead SNP rs7783012) on Chromosome 7. Their MAFs ranged from 0.32 to 0.43 on Chromosome 8, and from 0.38 to 0.48 for Chromosome 7. Taking into the account that Chromosome 8 is associated with both cannabis dependence/ CUD and neurocognitive performances, and the use of WMS in assessing the neurocognitive functions for cannabis abusers in the current study, we estimated that a sample size of at least 101 participants were

needed with the corresponding genetic variance, in order to obtain a power level (β) of 0.8 and a confidence level (α) of 0.05.

Outcome Measures

Demographic characteristics including age, gender, education, marital status, past psychiatric history and comprehensive history of substance use were collected at baseline assessment, including whether they were daily (DAILY) or non-daily cannabis users. Highest educational attainment was converted into approximate years of education. Lifetime duration of cannabis use was calculated as the difference between current age and self-reported age of first use. Severity of CUD and neurocognitive functioning were assessed at baseline and longitudinally every 3 months over the subsequent 18 months. Diagnostic assessments were conducted by board-certified psychiatrists (AKKC, CKL & NC), and neurocognitive and questionnaire-based measures were administered by the psychiatrists and/or trained research staff. Table 3 detailed the study timeline for all the outcome assessments.

Genomic testing

One-time peripheral blood samples were obtained from consented participants for genomic analyses. A total of 12 mL of whole blood was collected via venipuncture. Genomic DNA was extracted from EDTA-venous blood samples using standard methodology. The SNP genotyping used the Agena Bioscience MassARRAY Analyzer 4 384-well configuration (San Diego, CA, USA). Genotyping assays were designed using Typer software version 4.1 (Agena Bioscience). Quality control included the exclusion of SNPs with genotype call rates <95%. In this study, a predefined panel of 73 SNPs was selected *a priori* based on GWAS and candidate-gene studies relevant to cannabis use disorder and neurocognitive function or disorders (Tables 4 and 5) (Agrawal et al., 2018; Agrawal et al., 2014; Cao et al., 2023; Deak & Johnson, 2021;

Demontis et al., 2019; Hatoum et al., 2023; Ibrahim-Verbaas et al., 2016; Johnson et al., 2020; Levey et al., 2023; Pasman et al., 2018; Phan et al., 2025; Sherva et al., 2016; Thorpe et al., 2021). Genotype data were coded at the allele level, and standard quality-control procedures were applied, including checks for call rate and allele frequency distributions.

Urine drug test

At the beginning of each assessment, participants completed a urine drug screening test using rapid immunoassay test kits (Multi Drug Screen Dip Panel, Ulti med Products, Germany) to detect THC, the primary psychoactive substance from cannabis. The result of the urine drug test was coded in binary format (positive = 1, negative = 0) to reflect the presence of THC.

DSM-5 assessment

DSM-5-defined CUD severity was evaluated using the SCID-5-CV administered by board-certified psychiatrists. The interview assessed 11 diagnostic criteria including impaired control over cannabis use, related social impairment, risky use, and pharmacological dependence. Categorical severity was classified as no CUD (0–1 criterion), mild (2–3 criteria), moderate (4–5 criteria), or severe (≥ 6 criteria).

Beat Drugs Fund Evaluation Question Set No. 6 (BDF-Q6)

Participants reported their estimated frequency of cannabis use using the standardized BDF Drug Use Frequency Questionnaire No. 6. The frequency variable (FREQ) was manually transformed into approximate times per month, with a maximum of 30 times per month. They were then categorized into 3 pattern of use groups: i) “irregular” use [FREQ (irregular)] with cannabis use frequency ≤ 30 times per 3 months; ii) “regular” use [FREQ (regular)] with use

frequency 31 times to ≤ 90 times per 3 months; and iii) “heavy” use [FREQ (heavy)] with use frequency >90 times per 3 months.

Also, the same questionnaire was used to probe recent drug use history between each assessment interval. The timing and frequency of the most recent cannabis use were on an ordinal scale ranging from today/yesterday to abstinence for more than one year. Responses were converted into approximate days of abstinence (ABS) using midpoint estimates.

Severity of Dependence Scale (SDS)

Psychological dependence on cannabis was measured using the self-administered SDS (Gossop et al., 1995), which assesses perceived control, anxiety, worry, desire, and difficulty in stopping use. Items were rated on a 4-point Likert scale (never = 0 to always = 3) with total scores ranging from 0 to 15. A diagnostic cut-off SDS score ≥ 3 indicates moderate-to-severe CUD or clinical dependence on cannabis for both Chinese- and English-speaking populations (Chung & Tse, 2025; Swift et al., 1998).

Montreal Cognitive Assessment (MoCA)

Global cognitive functioning was assessed using the paper-based MoCA in Chinese (Hong Kong versions 7.1 and 7.2) or English (version 7.1) (Nasreddine et al., 2005). MoCA had been previously validated as a quick screening tool for identifying gross cognitive impairment in individuals with substance use disorders with high sensitivity and specificity (Copersino et al., 2009). A score below 26 represents the clinical threshold for potential global cognitive impairment.

Frontal Assessment Battery (FAB)

Frontal executive functioning was evaluated using the FAB (Dubois et al., 2000), which has been used previously in individuals with substance dependence (Cunha et al., 2010; Nakamura-Palacios et al., 2014). FAB consists of six items probing distinct domains in executive function from the frontal networks: conceptualization to dorsolateral frontal areas, mental flexibility to the prefrontal dorsolateral cortex and medial frontotemporal cortex, motor programming with the right prefrontal dorsolateral cortex and basal ganglia, and inhibition, interference control and autonomy with orbitomedial areas (Appollonio et al., 2005; Climent-Martinez et al., 2014; Hurtado-Pomares et al., 2018). The validated Chinese version was used for non-native English population in this study (Wang et al., 2016). A cut-off score of ≤ 12 indicates potential frontal lobe dysfunction (Slachevsky et al., 2004).

Wechsler Memory Scale (WMS)

Memory functions and mental control were assessed using the WMS, 3rd edition (WMS-III). In WMS-III, standardized indices of mnemonic functioning across immediate memory (IM), general memory (GM) and working memory (WM) are derived. Both the immediate and general memory indices consist of the visual and auditory components.

Immediate memory refers to the ability to rapidly encode and recall information over a very short period, typically a few seconds to minutes. For example, when a person is remembering a phone number just long enough to dial it after hearing the number once. Whilst general memory refers to the ability to store, retain and retrieve information over longer periods, encompassing longer-term memory. For example, when one is recalling a phone number for dialing the same number after a few minutes or even after a month. In contrast, working memory focuses more on the memory process and refers to one's capacity to temporarily hold, update

and actively manipulate information during cognitive tasks. For example, when a person is keeping or recalling the phone number in his or her mind while dialing, he or she is actively maintaining that information in the immediate or short-term memory and possibly manipulating it, like repeating it to oneself or chunking digits, to complete the task. Lastly, mental control refers to the cognitive ability to intentionally regulate, suppress, or manipulate thoughts, feelings, and impulses. It involves processes like attention regulation, inhibiting automatic responses, and maintaining goal-directed behavior. Imagine when a person hears a new phone number, but he or she realizes it's similar to another number and needs to avoid dialing the wrong one. The person must consciously suppress the automatic response to dial the familiar number and instead recall and dial the new, correct number. This requires mental control to override automatic tendencies and focus on the task.

In the current study, we tested our participants by WMS-III on: i) immediate memory index with both visual immediate and auditory immediate components, ii) general memory index with visual delayed, auditory delayed and auditory recognition delayed components after a delayed of around 30 minutes from the first presentation of the testing materials, iii) working memory index, and iv) mental control (MC). All indices except for MC are norm-referenced (mean = 100, SD = 15) and 1 SD below the mean was used as a threshold for potential memory functioning impairment in clinical settings (Brooks et al., 2008; Gonzalez et al., 2017; Lange et al., 2006; Meier et al., 2022). GM was specified as the primary memory outcome, while other domain-specific indices were modelled in secondary analyses to characterize modality-specific memory functioning.

Statistical analysis

Demographic characteristics were summarized using means (M) and standard deviations (SD) for continuous variables and frequencies with percentages for categorical variables. Longitudinal changes in cognitive functioning were examined using linear mixed-effects models (LMMs). Three neurocognitive outcomes of main interests were global cognition (MoCA), frontal executive functioning (FAB), and the GM index derived from WMS-III. A common LMM specification was applied to each cognitive outcome: $\text{COGNITION} \sim 1 + \text{MONTH} \times (\text{SDS} + \text{THC} + \text{ABS} + \text{DAILY} + \text{FREQ}) + \text{AGE} + \text{SEX} + \text{EDU} + \text{LIFETIME} + (1 + \text{MONTH} \mid \text{ID})$.

Fixed effects were specified for time (month), psychological dependence, urine drug test results for THC, (log-transformed) days of abstinence, status of daily use, frequency of cannabis use, and their interactions with time. Additional baseline covariates included age, sex, years of education, and lifetime duration of cannabis use. Random intercepts and random slopes for month were included at the participant level to accommodate individual differences in cognitive performance at baseline and distinct trajectories over time. Month was modeled as a continuous variable (range = 0-18), with baseline (Month 0) as the reference. Binary predictors for urine THC status (negative = -0.5, positive = 0.5), status of daily use (no = -0.5, yes = 0.5), and sex (female = -0.5, male = 0.5) were contrast-coded, while continuous covariates (log-transformed abstinence days, age, years of education, and lifetime use) were mean-centered. The categorical variable frequency of use was modelled with orthogonal effect-coded contrasts to independent test the difference in cognition between regular use group vs. the other two groups, and heavy use group vs. the other two groups. Thus, the model intercept represented the grand mean of cognitive score for a statistical average participant at baseline.

SNPs failing genotyping call-rate ($<95\%$) were removed, and remaining panel variants were screened for allele validity and only biallelic SNPs retained for subsequent analyses. Genotypes were encoded as minor-allele dosages (0, 1, or 2). Variants with more than 10% missing dosage were excluded. Remaining missing dosages were imputed using the SNP-wise mean, and near-invariant variants (variance $\leq 1 \times 10^{-8}$) were removed. Baseline associations with DSM-5 defined number of symptoms, MoCA, FAB, and GM were examined using ordinary least squares regression and modelled with the main effect of additive SNPs with adjustments for age (mean-centered), years of education (mean-centered), and gender (effect-coded). Heteroskedasticity-robust (HC3) standard errors were used. Multiple testing was controlled separately for each outcome using the Benjamini–Hochberg false discovery rate (FDR). Variants surviving FDR correction were subsequently evaluated in LMM using all available follow-up data, with fixed effects for time, SNP, their interaction, and adjustments for age, education, and gender. Subject-specific random intercepts and random slopes for time were specified.

Participants who did not return for assessment in any subsequent follow-up session would have their observations of that specific timepoint considered as missing data. These missing data were not imputed in this study because LMMs provide unbiased estimates under the assumption of missing at random (Bates et al., 2015). All models converged successfully, and model diagnostics were inspected visually. Analyses were conducted in R (v4.4.1) using the lme4 (v1.1-35.5) and lmerTest (v3.1-3) packages.

All statistical tests were two-tailed with a significance threshold of $\alpha = 0.05$, and no corrections for multiple comparisons were applied.

Results

This study started in September 2020 with the last participants recruited in June 2024. The original target sample was 101 participants but eventually 110 (108.91%) cannabis users consented to participate. One consented participant (subject code *PeCoG011*) did not complete the assessment at baseline and never attended the other follow-up assessments. Hence, 109 (99.09%) consented participants who had performed the baseline assessment were followed-up.

At the end of the study, nineteen (17.43%) participants only performed their baseline assessments with no subsequent attendance to the rest of the follow-up timepoints. Therefore, 90 participants constituted the sample of LMM analysis for the temporal trajectory of changes in neurocognitive functioning in the current study. The completion rates for follow-up assessments declined over time: 83 (92.22%) out of the 90 participants returned for assessment at Month 3, 64 (71.11%) at Month 6, 60 (66.67%) at Month 9, 56 (62.22%) at Month 12, and 54 (60.00%) at the final assessment Month 18.

Upon the completion of the study, two participants (subject codes *PeCoG098* and *PeCoG110*) never provided the blood sample for genomic analysis, and another 4 participants' blood samples failed the initial quality control for further genomic analysis. Therefore, a total of 104 (94.55%) participants' blood samples were available for genome analysis with 103 participants' samples (after excluding subject code *PeCoG011*; 94.50%) being available for further analyzed in this study.

At baseline, DSM-5 CUD and SDS were tested for collinearity and were strongly correlated (Pearson's $r = 0.65$; Spearman's $\rho = 0.63$; both p 's < 0.001). Variance inflation factor

diagnostics indicated low-to-moderate collinearity ($VIF = 1.75$); therefore, DSM-5 CUD and SDS were not entered simultaneously into multivariable models for neurocognitive functions.

Demographics and Drug Use History at Baseline

Baseline demographics and history of drug use were summarized in Table 6. Participants had an average age of 28.86 years ($SD = 9.65$), 53 out of 90 participants (58.89%) were male, and the majority were single (83.33%), with an average of 12.25 years of formal education ($SD = 2.63$). Tobacco smoking and alcohol use were common, and lifetime use of other illicit substances was frequently reported. The majority of the participants (94.44%) smoked cannabis as the only major routine of administration, with the remaining reported edible use or both. At baseline, participants on average met the clinical threshold for DSM-5 defined CUD with moderate severity ($M = 3.81$, $SD = 2.85$; Figure 1A) and were psychologically dependent on cannabis (SDS: $M = 4.07$, $SD = 3.48$; Figure 1B). Most of the participants were regular-to-heavy users (51.11%) with an average of 46 times of cannabis use in 3 months (Figure 1C). Their abstinence period from cannabis use was less than a month on average (days of abstinence, $M = 25.10$, $SD = 48.64$; Figure 1D). About 39% of participants had recent cannabis use with urine tested positive for THC on urine drug screening test (Figure 1E).

Temporal trajectory of neurocognitive functions (Supplementary Table 1)

Baseline neurocognitive performances for the participants were within the normative range for the general population across global cognition (MoCA: $M = 26.10$, $SD = 2.29$), frontal executive functioning (FAB: $M = 16.20$, $SD = 1.84$) and mental control ($M = 13.39$, $SD = 3.07$). However, major memory function, including immediate memory, general memory and working memory were all below -0.2 to -0.5 SD of the index means (WMS-IM: $M = 92.07$, $SD = 16.73$;

WMS-GM: $M = 91.23$, $SD = 16.73$; WMS-WM: $M = 93.89$, $SD = 15.47$) (Figures 2 and 3; Table 6).

Significant main effects of time were observed across all three primary neurocognitive outcomes. Global cognition, indexed by the MoCA, showed a trend with very modest increase in scorings (mean <1 point) over time ($B = 0.08$, 95% CI = $[0.03, 0.13]$, $p = 0.001$; Figure 2A and Table 7). Similarly, a trend with a very small magnitude of increase in FAB scorings (mean <1 point) was observed over the study period ($B = 0.04$, 95% CI = $[0.00, 0.08]$, $p = 0.043$; Figure 2B and Table 7). A longitudinal improvement from below normative range at baseline back to the normal range was observed for general memory over the study period (WMS-GM: $B = 1.43$, 95% CI = $[1.10, 1.75]$, $p < 0.001$; Figure 2C and Table 7). Random-effects estimates indicated substantial between-participant variability in baseline cognitive performance (ICC range = 0.44 – 0.68), whereas variability in individual rates of change over time was minimal (random-slope variance for month τ_{11} range = 0.00 – 0.13), suggesting largely homogeneous cognitive trajectories across participants despite marked differences in baseline performance.

Among demographic, years of formal education showed consistent positive associations with all three primary cognitive outcomes, with preserved normative scores attained for those with higher education (MoCA: $B = 0.38$, FAB: $B = 0.23$, WMS-GM: $B = 3.94$; all p 's < 0.001). In contrast, age and gender were not reliably associated with cognitive performance in any domains (all p 's > 0.05) (Table 7).

With respect to cannabis use-related variables, no significant main effects of lifetime duration of cannabis use, psychological dependence (SDS), urine positive THC status, days of abstinence, daily use status, or frequency of use were observed on any primary cognitive

outcomes from baseline (all p 's > 0.05 ; Table 7). However, several statistically significant time-dependent associations emerged. For MoCA, a statistically significant positive interaction between time and heavy cannabis use was observed, indicating a small longitudinal improvement in MoCA scores among participants in the heavy use group relative to the other two groups (MONTH $\times$ FREQ (heavy): $B = 0.17$, 95% CI = [0.03, 0.32], $p = 0.020$). For WMS-GM, a negative interaction between time and urine positive THC status was observed, indicating that participants who were THC-positive exhibited attenuated longitudinal gains in general memory relative to THC-negative participants (MONTH $\times$ THC: $B = -0.59$, 95% CI = [-1.17, -0.01], $p = 0.047$). In contrast, a statistically significant positive interaction between time and regular cannabis use was noted, suggesting that there could be a modest improvement in general memory over time compared with the participants from other groups (MONTH $\times$ FREQ (regular): $B = 0.87$, 95% CI = [0.29, 1.45], $p = 0.003$).

Secondary analysis on other WMS indices (Figure 3 and Supplementary Table 2A-2C)

Secondary analyses confirmed that time and educational attainment were consistently and positively associated with performance across nearly all memory modalities (p 's ≤ 0.001 for all subdomain measures), with the exception of mental control, for which time effect was not observed. Longitudinal improvement from below normative range at baseline back to the normal range was also observed for immediate memory over the study period (WMS-IM: $B = 1.39$, 95% CI = [1.07, 1.71], $p < 0.001$). Despite an improving trend was noted for working memory over the study period (WMS-WM: $B = 0.44$, 95% CI = [0.19, 0.69], $p = 0.001$), its means at various follow-up timepoints remained below the normative mean ($M = 100$).

Cannabis use-related effects were more selective and domain specific. Greater psychological dependence was associated with poorer baseline working memory performance

(main effect of SDS on WM: $B = -0.82$, 95% CI = $[-1.37, -0.28]$, $p = 0.003$) but was not related to other memory domains. However, the associated negative impact from dependence to working memory diminished over time ($\text{MONTH} \times \text{SDS}$: $B = 0.05$, 95% CI = $[0.00, 0.09]$, $p = 0.042$).

Regular cannabis use was associated with modest longitudinal improvements ($\text{MONTH} \times \text{FREQ}$ [regular]) across almost all domains as compared to irregular and heavy users: AI ($B = 0.66$, 95% CI = $[0.10, 1.21]$), VI ($B = 0.76$, 95% CI = $[0.10, 1.41]$), IM ($B = 0.80$, 95% CI = $[0.23, 1.37]$), AD ($B = 0.65$, 95% CI = $[0.10, 1.21]$), VD ($B = 0.72$, 95% CI = $[0.01, 1.44]$), ARD ($B = 0.95$, 95% CI = $[0.30, 1.61]$), GM ($B = 0.87$, 95% CI = $[0.29, 1.45]$), and MC ($B = 0.10$, 95% CI = $[0.01, 0.18]$).

A urine THC positivity was associated with higher baseline performance in visual immediate memory (VI: $B = 8.23$, 95% CI = $[2.39, 14.07]$, $p = 0.006$) and immediate memory (IM: $B = 5.60$, 95% CI = $[0.51, 10.69]$, $p = 0.031$). But, urine THC-positive status was associated with attenuated performances over time across multiple memory subdomains, including auditory immediate memory (AI: $\text{MONTH} \times \text{THC}$, $B = -0.58$, 95% CI = $[-1.13, -0.02]$, $p = 0.041$), visual immediate memory (VI: $B = -0.86$, 95% CI = $[-1.51, -0.22]$, $p = 0.009$), immediate memory (IM: $B = -0.82$, 95% CI = $[-1.38, -0.25]$, $p = 0.005$), auditory delayed memory (AD: $B = -0.58$, 95% CI = $[-1.13, -0.02]$, $p = 0.042$), and general memory (GM: $B = -0.59$, 95% CI = $[-1.17, -0.01]$, $p = 0.047$).

Abstinence duration also moderated longitudinal trajectories, such that longer abstinence was associated with attenuated gains in auditory immediate memory (AI: $\text{MONTH} \times \text{ABS}$, $B = -0.16$, 95% CI = $[-0.33, -0.00]$, $p = 0.047$) and auditory delayed memory (AD: B

= -0.16, 95% CI = [-0.33, -0.00], $p = 0.048$). However, it did not exert significant effect on visual immediate memory, visual delayed memory, auditory recognition delayed memory, and the overall indices on immediate memory, general memory, working memory or mental control (all p 's > 0.05).

Subgroup analyses

Cognitive changes in early drop-out participants (Supplementary Table 3)

Comparisons on the baseline differences among participants who attended baseline assessment only ($N = 19$) or one subsequent follow-up assessment at any timepoint ($N = 14$) [low attendance rate group ($N = 33$)] with those who attended ≥ 4 follow-up assessments at any timepoint out of the six total assessments [high attendance rate group ($N = 55$)] found no statistical differences between participants across demographics, nor on their scorings of MoCA, FAB and all WMS-III memory indices.

Comparison of participants with and without negative trajectory in neurocognitive functions (Supplementary Table 4)

Using LMMs, individually fitted random slopes over time (MONTH) from the three primary outcome measures of cognition, i.e., MoCA, FAB, and WMS-GM were extracted. Nine participants presented negative slopes (i.e., temporal trajectory of cognitive decline [the negative trajectory group]), with four in MoCA and five in FAB assessments. Comparisons of the baseline characteristics of these nine participants with the rest of 81 analyzed participants revealed that these nine participants reported higher frequency of use ($p = 0.01$), presented greater number of positive urine tests for THC ($p = 0.03$), and with higher psychological dependence by SDS ($p = 0.02$). They also scored lower in a variety of baseline cognitive measures, including MoCA, general memory (GM), working memory (WM), immediate

memory (IM), auditory memory (AI, AD) and mental control (MC) (all p s < 0.05), but not FAB. In particular, their mean scores on MoCA, GM, WM and IM all fell below the normative clinical cut-off (i.e., MoCA < 26 ; GM, WM and IM < 1 SD of respective normative means) at baseline.

Genomic analysis

After quality control, 101 genotyped participants (98.06%) out of the 103 participants' blood samples with aligned baseline phenotypic data were retained for further analysis (Supplementary Table 5). 79 participants (78.22%) were East Asian (with 72.28% were Chinese), 7 (6.93%) were South Asians, 7 (6.93%) Caucasians, 2 were Middle Eastern (1.98%), 1 were Southeast Asians (0.99%), and 5 (4.95%) having their ethnicity not stated. Out of the 73 predefined panel SNPs, 69 SNPs (94.52%) passed call-rate filtering. Of these, 55 SNPs (75.34%) were biallelic, and 54 SNPs (73.97%) remained after exclusion of one near-constant variant (Table 8). Baseline association testing (216 tests across four outcomes) identified two FDR-significant associations: rs80030908 was negatively associated with FAB performance ($B = -1.00$, 95% CI $[-1.56, -0.43]$, $q = 0.03$; minor allele count (MAC) = 1; one carrier from Caucasian ethnicity), and rs73229090 was positively associated with WMS-GM performance ($B = 8.64$, 95% CI $[4.14, 13.14]$, $q = 0.01$; MAC = 4; three carriers with two of Caucasian ethnicity and one of South Asian ethnicity). When these variants were examined in LMM for the 90 genotyped participants having subsequent follow-up assessments, no reliable SNP-by-time interactions were observed for either FAB or GM (both p 's > 0.05), indicating that baseline associations did not extend to differential trajectories over time.

Discussions

To the best of our knowledge, the current study is one of the few prospective longitudinal cohort studies targeting the neurocognitive function among cannabis users in Asia. It takes the merits for its 18-month follow-up assessment period, its sampled population with predominant Asian ethnicity, and its genomic association analysis. Our study demonstrated that: i) cannabis use in adults might have differential effects on the three neurocognitive functions, namely global cognitive function, frontal executive function, and memory function, measured by MoCA, FAB and the WMS-III, respectively; ii) potential genomic variants might exist in cannabis dependent users with memory impairments.

Cannabis users in our sample population were predominantly males, in their young adulthood with a mean age of 29 years and Asian (86.14%). They maintained mild-to-moderate CUD and suffered psychological dependence to cannabis throughout the study period. Among demographics, including age, gender and years of education, and lifetime duration of cannabis use, only years of formal education appeared to be the most consistent and significant factor positively influencing all three tested neurocognitive functions. Participants with higher educational level tended to have performances in MoCA, FAB and all domains from WMS more likely to be preserved within the normative ranges in this study, which findings are compatible with current literature investigating neurocognitive functions in both clinical and non-clinical adult samples using MoCA (Li et al., 2024), FAB (Aiello et al., 2022; Beato et al., 2012; Coen et al., 2016) and WMS-III (Brooks et al., 2008; Walker et al., 2009). Cautious interpretations are mandatory as such findings from educational level only reflect the trends that it might inaptly inflate the scorings in these scales in the serial follow-up assessments, it

should never signify more educated people using cannabis will not have their neurocognitive functioning affected.

The findings about our participants not being negatively impacted on their global cognitive function and frontal executive function from their cannabis use warrant careful elucidation. Both functions in the current study remained in the respective normative range within the whole study period after adjusting for the participants' demographics and lifetime duration of cannabis use. Their psychological dependence, recent cannabis use, days of abstinence or daily use status did not predict any significant temporal changes for these two cognitive functions, except frequency of use that influences global cognitive function but not frontal executive function. Unlike earlier study showing impaired global cognitive function measured by MoCA in young adult cannabis users (Goud et al., 2022), Bruijnen et al. (2019) found that cannabis use only had marginal significant negative correlation ($p = 0.05$) with MoCA scores. Hence, MoCA itself might possess suboptimal sensitivity to detect global cognitive dysfunction when used alone in the substance use disorder population (Bruijnen, Jansen, et al., 2019). Also, in our study, none of the participants suffered from dysexecutive syndrome as assessed by FAB. Fontes et al. (2011) illustrated that even dependent cannabis users might perform poorer than non-users in FAB, their total FAB scores could still be well above the diagnostic cut-off commonly validated for organic neurodegenerative disorders. The significant effect from heavy cannabis uses positively modulating MoCA performances over time as compared to recreational or regular use in this study was rather unexpected as abundant evidences supported the contrary with heavy cannabis use significantly impairing cognition (Bourque & Potvin, 2021; Gonzalez et al., 2017; Gowin et al., 2025). In fact, Ellingson et al. (2021) and Bourque & Potvin (2021) pointed out that heavy cannabis users might develop tolerance to the acute cannabis effects on cognitive tasks as compared to occasional users. Thus,

this might explain why the same positive modulatory effect from heavy cannabis use did not present at baseline comparison but only happened over time. Furthermore, even though minute improvements in both MoCA and FAB scorings were observed from baseline over time in our participants, these were likely major pitfalls resulted from practice effects after repeated measurements by using only one alternate forms for MoCA and none for FAB every 3 months over the long follow-up duration in this study (Chung et al., 2025; Cooley et al., 2015; Sakai et al., 2024).

A more diverse effects from cannabis use over different memory functions were observed among the participants. Cannabis use was associated with their poorer immediate memory, general (delayed) memory and working memory than the normal population at baseline, but with mental control relatively preserved. Except from hindering any improvement in working memory, it did not cause further persistent deterioration on immediate or general memory functioning over the rest of the study period. A trend of recovery from their deteriorations was noted for immediate and general memory over time, independent to the demographics, lifetime duration of cannabis use, days of abstinence or daily use status. Such isolated improvements in immediate memory and general delayed memory but not in working memory over time, however, might also be related to the practice effects on WMS-III after repeated measurements. Lo et al. (2012) demonstrated that significant large practice effects (Cohen's $d = 0.67\text{--}0.98$) for immediate and general memory, but to a much smaller extent for working memory (Cohen's $d = 0.19\text{--}0.22$), could occur even when WMS-III was repeated in every 3-year period. Our findings also suggested that cannabis dependence particularly impaired working memory irrespective to the frequency of cannabis use, and heavy cannabis use might impair potential recovery from all memory domains under tests. These findings accord with Pilon et al. (2025) who showed that working memory impairment was significant

in users with cannabis use disorder and such impairment was independent to the frequency of cannabis use. Also, preclinical study demonstrated that cannabis withdrawal could precipitate memory impairment and heavy cannabis users could be in particular prone to withdrawal syndrome (Bahji et al., 2020; Wise et al., 2011).

Nonetheless, the subgroup analysis comparing the baseline characteristics of those participants who had their neurocognitive scores declined with those who did not over the 18-month period of this study shed lights on the plausibility that cannabis users who had higher frequency of use and with higher psychological dependence at baseline might suffer from cognitive impairments over time.

Recent cannabis use, proxied by the positive urine THC, was only associated with higher scorings on immediate memory and immediate visual memory at baseline. Over time, it had significant negative impacts to immediate memory, immediate visual and auditory memory and general memory as compared to those with no recent cannabis use. These findings follow the current evidence that recent cannabis use causes significant impairments to verbal memory functioning and verbal learning (Bourque & Potvin, 2021; Gowin et al., 2025).

In this study, duration of abstinence did not predict significant positive changes on the overall immediate memory, general memory, working memory or mental control over the 18 months follow-up period. Previous studies demonstrated that residual cognitive impairments from cannabis use can last for at least 3 days and up to 90 days (Burke et al., 2025; Schuster et al., 2018; Scott et al., 2018; Wallace et al., 2020). As the mean duration of abstinence of our participants ranged from 25.10 to 99.44 days with most assessment time points below 90 days, the lack of positive predictive relation between duration of abstinence and neurocognitive

functions in our participants might therefore merely reflect the inadequate duration of abstinence instead.

The current study postulated that common genetic risk factors might contribute to the vulnerability to cannabis use and cognitive deficits and predispose our participants to cannabis dependence (or worse CUD) and its associated cognitive deficits according to the antecedent (vulnerability) hypothesis (Bourque & Potvin, 2021). Two cannabis use-related SNPs, rs80030908 on chromosome 13 and rs73229090 on CHRNA2 (a gene encoding the alpha-2 subunit of neuronal nicotinic acetylcholine receptors) of chromosome 8, identified from both Caucasian and South Asian ethnicities in this study showed preliminary association to the baseline frontal executive function and general memory, respectively. Nevertheless, both SNPs did not predict the severity of CUD or the longitudinal trajectories of the neurocognitive functions associated with cannabis use. While the mechanistic pathway about how rs80030908, an intron variant, being associated the vulnerability to CUD remains unknown (Levey et al., 2023), the effect from rs73229090 on CHRNA2 to cannabis use is likely related to the nicotinic acetylcholine receptors. Nicotinic acetylcholine receptors have crucial roles in modulating presynaptic, postsynaptic, and extrasynaptic signalling, and are involved in a wide range of neurocognitive disorders (Posadas et al., 2013) and the dopaminergic rewards pathway in addiction (Valles & Barrantes, 2023). It is hypothesized that cannabis might interact with the alpha-2 subunit containing nicotinic acetylcholine receptors and the THC in cannabis can affect the release of acetylcholine in various brain regions. The resulted depolarization after binding of acetylcholine to these nicotinic acetylcholine receptors can lead to the release of dopamine, thus potentiating cannabis use and addiction (Demontis et al., 2019). Given the low minor allele counts, these two novel SNPs identified in this study might, at best, provide a hypothesis-generating basis for future large-scale genome association study, especially if the SNP

rs73229090 on CHRNA2 can serve as a potential biomarker to identify Asian cannabis users susceptible to (general) memory impairments.

Limitations

There are several limitations need to be carefully considered for this study. First, the small sample size with cannabis users predominantly in their young adulthood might limit the generalizability of the results to older adults. Second, most of the participants in this study had only mild-to-moderate CUD or relatively mild psychological dependence at baseline which might have obscured the plausibility of continual cognitive impairments among cannabis users with more severe CUD or higher psychological dependence. Third, recall biases on the frequency of cannabis use and its last use might exist and lead the results on duration of abstinence in this study diverging from the current literature. Fourth, the current study did not assess the method of cannabis use, effect from potency or “dosage” of THC that previously shown to have association with cognitive impairments (Behzad et al., 2025). Moreover, the absence of a non-using control group restricts the ability to make definitive conclusions about the extent of cognitive impairment attributable to cannabis use. Also, the suboptimal sensitivity of MoCA and FAB, and the practice effects from repeated assessments over the 18-month period and years of formal education might have inflated the follow-up scores, particularly for clinical screening tools like MoCA, FAB and WMS-III which are all rely on paper-based static item formats. Furthermore, the current study lacks the premorbid (before cannabis use) cognitive data from our participants. Comparing their scores to normative data may be problematic as many participants might already exhibit cognitive deficits or long-term impairments prior to the study. Another key limitation lies in the potential selection bias between treatment-seeking and non-treatment-seeking individuals, though there was a roughly equal ratio of life-time outpatient clinic attendance to non-attendance in our participants. Treatment-seeking individuals may represent a subgroup with greater cognitive function and higher motivation to quit cannabis, while non-treatment-seeking cannabis users may show more

persistent cognitive decline over time that could not be realistically captured inherent to their attrition. Finally, due to the low minor alleles counts, the genomic results identified in this study should be interpreted with cautions, and should be regarded as exploratory for hypothesis testing.

Conclusions and Implications

The current 18-month study showed that despite the global cognitive function and executive function might be relatively preserved in adult cannabis users, cannabis use did have significant impact on different aspects of memory function, with working memory being the most negatively impacted. Educational level and recency of cannabis use were the two most significant factors predicting the detrimental effects on neurocognitive functions associated with cannabis use. The two SNPs, rs80030908 on chromosome 13 and rs73229090 on chromosome 8, identified from this study are yet far from conclusive to be used as biomarkers for predicting the trajectory of neurocognitive changes from cannabis use, especially among the Asian population.

Future study investigating the effects of cannabis use on neurocognitive functions can consider: i) sampling cannabis users with more severe CUD or higher psychological dependence as target population, ii) using more than two alternative versions of MoCA to limit practice effects, iii) employing more sensitive task-specific assessment tools, such as N-back task (Cousijin et al., 2014; Huang et al., 2025) and Wisconsin Card Sorting Test (Queiroz et al., 2025) for executive function, iv) a larger sample size focusing on Han Chinese or Asian sample population to further confirm their vulnerability from candidate genes or SNPs identified in the current study, v) the epigenetic approach to explain the diversity in neurocognitive performances, vi) the use of task-based neuroimaging technique to dismantle the most susceptible brain regions and the underlying neurocircuits involved in cannabis-related changes on neurocognitive functions, and vii) correlating the trajectory changes in cognitive functions to the cannabis users' academic and/ or occupational functioning. All these will provide a personalized approach in the treatment and rehabilitation of cannabis addiction and related neurocognitive changes.

Meanwhile, clinicians and professionals working on the anti-drug fields should continue educating the public about the “Not Now. Not Ever” principle to cannabis, especially targeting the evidence-based negative impacts on neurocognitive functions from cannabis use as researched in this study and the existing literature (Queiroz et al., 2025). Vulnerable cannabis users, for example those with low educational level should have their cognitive functions carefully monitored. Cannabis users and the general public should also be warned about the harms on memory functioning from the recency (acute) effect of cannabis use (“Not Now”). Even though our current study did not show any positive trajectory from the duration of abstinence to neurocognitive functioning, with the extensive literature supporting abstinence on improvements on cognition, long-term abstinence from cannabis use should still be strongly encouraged (“Not Ever”).

Tables

Table 1. Inclusion criteria for SToP-C—PeCoG study.

<i>Inclusion Criteria</i>
• Age: 16-60 years old at the time of enrollment
• Using cannabis or “marijuana” as the <i>primary</i> psychoactive substance of abuse
• “Repeated” and/or “Active” cannabis users as defined by the Structured Clinical Interview for DSM-5 Disorders – Clinician Version (SCID-5-CV): ⇒ “Repeated”: ≥ 6 times of cannabis use in 12 months ⇒ “Active”: using cannabis within the past month at the time of enrollment
• Able to read and communicate in English and/or Chinese
• Able to give informed consent ⇒ For individual ≥ 16 years old but < 18 years old, guardian’s consent would also be sought

Table 2. Exclusion criteria for SToP-C—PeCoG study.

<i>Exclusion Criteria</i>
• Age <16 years old at the time of enrollment
• Unable to read English or Chinese
• Unable to give informed consent
• Had been diagnosed with other DSM-5 defined Substance Use and Related Disorders ⇒ <i>except</i> for Tobacco Use Disorders due to the known frequent comorbid use for cannabis users
• Had been diagnosed with other DSM-5 defined psychiatric disorders including: ⇒ Neurodevelopmental Disorders ⇒ Schizophrenia Spectrum and Other Psychotic Disorders ⇒ Bipolar and Related Disorders ⇒ Depressive Disorders and Anxiety Disorders ⇒ Obsessive-Compulsive and Related Disorders ⇒ Dissociative Disorders, Somatic Symptoms and Related Disorders ⇒ Feeding and Eating Disorders ⇒ Sleep-wake Disorders ⇒ Neurocognitive Disorders
• Currently taking <u>regular</u> prescribed psychiatric medications, including antipsychotics, antidepressants, mood stabilizers, anti-epileptics, benzodiazepines, hypnotics, and anti-cholinergic medications.

Table 3. Study timeline for outcome assessments. *Note:* DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th edition), SCID-5-CV: Structured Clinical Interview for DSM-5 Disorders–Clinician Version, SDS: Severity of Dependence Scale.

	Baseline visit	3-month follow-up	6-month follow-up	9-month follow-up	12-month follow-up	18-month follow-up (End of study)
Informed consent	X					
Blood taking for Genome Test	X ONCE at <i>any time</i> during the study period					
Urine test	X	X	X	X	X	X
Assessment on:						
1) SCID-5-CV	X	X	X	X	X	X
2) BDF Evaluation Question Set No. 6	X	X	X	X	X	X
3) SDS	X	X	X	X	X	X
Neuro-cognitive Function assessment:						
1) Montreal Cognitive Assessment	X	X	X	X	X	X
2) Frontal Assessment Battery	X	X	X	X	X	X
3) Wechsler Memory Scale	X	X	X	X	X	X
Travel Allowances to Participants	\$100	\$100	\$100	\$100	\$100	\$100

Table 4. Genes and lead SNPs (N = 60) identified from literature that have been associated with CUD or cannabis use. *Note:* SNPs: single nucleotide polymorphisms, [#] only in African-American cohort, (+): significant effect, (+/-): equivocal.

Chromosome	Gene (SNPs)	Allele (++)	Minor Allele Frequency
1	rs7519259	A	
	rs6690119	T	
	rs1526480	T	
2	rs719504	A	
3	rs143244591	G	0.96 [#]
	rs184064410	T	
	rs3774800	A	
	rs17007864	T	
	rs726610	T	
	rs9815757	T	
	CAMD2 (rs17518584) Also known as <i>SYNCAM2</i>	T	0.64
	CAMD2 (rs1448602)	A	0.756
	CAMD2 ▪ rs2875907	A	0.352
	▪ rs7651996	T	0.477
4	rs201175241	G	
5	rs56070621	A	
	rs159365	A	
	rs574008891	T	
	rs573117193	A	
6	rs9344740	T	
7	FOXP2 (rs7783012)	A	0.38-0.48
	SDK1 (rs10085617)		
	rs62461183	T	
	rs2189010	A	
8	CSMD1 (rs77378271)	A	0.94-0.96
	CHRNA2 ▪ GULOP rs73229093	T	0.06/0.15
	▪ GULOP rs7838316	A	0.12/0.16
	▪ GULOP rs56372821	A	0.09-0.163
	▪ GULOP rs73229090	A	0.04-0.11
	▪ GULOP rs4732724	C	0.32-0.43
	▪ GULOP rs6558008	A	0.24-0.25
	▪ rs11783092		
	EPHX2 (rs4732723)	T	0.41-0.49
	ZNF704 (rs9773390)		
9	rs545943750	A	
	rs10986600	T	
10	rs77300175	T	
	rs200595759	T	
	SLC35G1 (rs146091982)		
	rs1409568	T	
(continued)			

Table 4. (*continued*) Genes and lead SNPs (N = 60) identified from literature that have been associated with CUD or cannabis use. *Note:* SNPs: single nucleotide polymorphisms, [#]only in African-American cohort, (+): significant effect, (+/-): equivocal.

Chromosome	Gene (SNPs)	Allele (++)	Minor Allele Frequency
11	rs34554234	G	
	NCAM1 (rs9919557)		
13	rs6484345	A	
	rs80030908	A	
15	rs78561048	A	
16	RABEP2, ATP2A1 (rs10499)		
	rs62051488	A	
17	BPTF (rs6504555)	A	0.22
	BPTF (rs9897982)	T	0.22
	BPTF (rs2365468)	T	0.22
	BPTF (rs9890629)	A	0.22
	BPTF (rs11870068)	C (+/-)	0.22
	C17orf58 (rs9891146)	T	0.28
	PPM1D		
	BPTF (rs8071463)	G	0.22
	BPTF (rs3935969)	C	0.22
	BPTF (rs8074078)	G	0.22
	BPTF (rs6504548)	C	0.22
	BPTF (rs7208663)	C	0.22
	SMG6 (rs17761723)		
21	rs186825689	A	0.96 [#]

■ : significant liability only in East-Asian Ancestry

■ : Gene/ SNPs associated with *reduced* liability of CUD/ cannabis lifetime use

Table 5. Genes and significant SNPs (N = 13) identified from literature that have been associated with dementia and neurodevelopmental disorders. *Note:* SNPs: single nucleotide polymorphisms.

Chromosome	Gene	SNPs
6	LOC101927293	rs10458022
12	MED21	rs144822097
15	ATP10A-DT	rs72689267 rs7178765
16	LOC101927605	rs4785108 rs9888985
18	PTPRM	rs668168 rs670305
19	TOMM40	rs11556505 rs2075650 rs34404554 rs71352238 rs34095326

Table 6. Participant (N = 90) demographics and history of drug use at baseline in the trajectory analysis. *Note:* BDF-Q6: Beat Drugs Fund Evaluation Question Set No. 6, CUD: cannabis use disorder, FAB: Frontal Assessment Battery, LSD: lysergic acid diethylamide, MDMA: 3,4-methylenedioxymethamphetamine, MoCA: Montreal Cognitive Assessment, SCID-5-CV: Structured Clinical Interview for DSM-5 Disorders–Clinician Version, SD: standard deviation, SDS: Severity of Dependence Scale, THC: tetrahydrocannabinol, WMS: Wechsler Memory Scale, *: lifetime history.

	Total (N = 90)
Male, Count (%)	53 (58.89%)
Age, Mean (SD)	28.86 (9.65)
Education (years), Mean (SD)	12.25 (2.63)
Single, Count (%)	75 (83.33%)
Forensic history, Count (%)	22 (24.44%)
Tobacco smoker, Count (%)	63 (70.00%)
Alcohol drinker, Count (%)	74 (82.22%)
Drinking years, Mean (SD)	11.61 (9.12)
In-patient psychiatric admission*, Count (%)	27 (30.00%)
Out-patient psychiatric care*, Count (%)	47 (52.22%)
Detox center admission*, Count (%)	15 (16.67%)
Cannabis use	
Age of first use, Mean (SD)	18.18 (4.72)
Abstinence (days since last use), Mean (SD)	25.10 (48.64)
Lifetime duration of use (in years), Mean (SD)	10.68 (10.79)
Method of use: smoke, Count (%)	85 (94.44%)
Daily Use, Count (%)	29 (32.22%)
BDF-Q6 Frequency of Use, Mean (SD):	46.41 (64.75)
▪ Irregular Use, Count (%)	44 (48.89%)
▪ Regular Use, Count (%)	40 (44.44%)
▪ Heavy Use, Count (%)	6 (6.67%)
Lifetime use of other substance (Counts [%])	
Cocaine	39 (43.33%)
Ketamine	35 (38.89%)
LSD	26 (28.89%)
Heroin	13 (14.44%)
Magic Mushroom	10 (11.11%)
MDMA	35 (38.89%)
Methamphetamine	35 (38.89%)
Baseline measures	
Positive urine test for THC, Count (%)	35 (38.89%)
SCID-5-CV CUD Severity, Mean (SD)	3.81 (2.85)
SDS, Mean (SD)	4.07 (3.48)
MoCA, Mean (SD)	26.10 (2.29)
FAB, Mean (SD)	16.20 (1.84)
WMS:	
▪ Immediate Memory, Mean (SD)	92.07 (16.73)
▪ General Memory, Mean (SD)	91.23 (16.73)
▪ Working Memory, Mean (SD)	93.89 (15.47)
▪ Mental Control, Mean (SD)	13.39 (3.07)

Table 7. Results of linear mixed-effects model for longitudinal (temporal) changes in three primary neurocognitive outcomes. *Note:* ABS: days of abstinence, DAILY: daily use status, EDU: years of education, FAB: Frontal Assessment Battery, FREQ: frequency of cannabis use, MoCA: Montreal Cognitive Assessment, SDS: Severity of Dependence Scale, THC: tetrahydrocannabinol, WMS: Wechsler Memory Scale.

	MoCA			FAB			WMS-GM		
	B	95%CI	<i>p</i>	B	95%CI	<i>p</i>	B	95%CI	<i>p</i>
(Intercept)	26.23	25.74 – 26.73	<0.001	16.29	15.90 – 16.67	<0.001	95.21	91.12 – 99.31	<0.001
MONTH	0.08	0.03 – 0.13	0.001	0.04	0.00 – 0.08	0.043	1.43	1.10 – 1.75	<0.001
AGE	0.01	-0.07 – 0.09	0.834	-0.04	-0.09 – 0.01	0.153	0.28	-0.43 – 1.00	0.440
SEX	0.12	-0.57 – 0.80	0.737	-0.24	-0.67 – 0.20	0.290	-5.53	-11.69 – 0.62	0.078
EDU	0.38	0.23 – 0.53	<0.001	0.23	0.13 – 0.32	<0.001	3.94	2.61 – 5.28	<0.001
LIFETIME (cannabis)	-0.02	-0.10 – 0.05	0.537	0.00	-0.05 – 0.05	0.986	-0.01	-0.68 – 0.67	0.983
SDS	-0.02	-0.11 – 0.06	0.585	-0.01	-0.08 – 0.06	0.722	0.12	-0.53 – 0.78	0.708
Urine test (THC)	0.33	-0.41 – 1.07	0.380	0.46	-0.12 – 1.03	0.118	3.47	-1.84 – 8.78	0.200
ABS (log)	-0.06	-0.30 – 0.18	0.629	-0.11	-0.29 – 0.08	0.264	0.28	-1.43 – 1.98	0.748
DAILY	0.32	-0.56 – 1.20	0.476	-0.42	-1.10 – 0.25	0.219	-2.86	-8.95 – 3.24	0.357
FREQ (regular)	-0.43	-1.09 – 0.23	0.202	-0.27	-0.78 – 0.24	0.295	-4.13	-8.79 – 0.53	0.083
FREQ (heavy)	-0.70	-2.01 – 0.60	0.288	-0.27	-1.30 – 0.77	0.609	-2.98	-12.17 – 6.21	0.524
MONTH × SDS	0.01	-0.00 – 0.02	0.080	0.00	-0.00 – 0.01	0.284	-0.04	-0.10 – 0.02	0.189
MONTH × THC	-0.06	-0.15 – 0.03	0.167	-0.05	-0.12 – 0.02	0.156	-0.59	-1.17 – -0.01	0.047
MONTH × ABS	-0.01	-0.03 – 0.02	0.620	0.00	-0.02 – 0.02	0.988	-0.16	-0.32 – 0.01	0.071
MONTH × DAILY	-0.08	-0.18 – 0.02	0.134	-0.02	-0.09 – 0.06	0.703	-0.05	-0.72 – 0.63	0.889
MONTH × FREQ (regular)	0.07	-0.02 – 0.16	0.127	0.03	-0.03 – 0.10	0.324	0.87	0.29 – 1.45	0.003
MONTH × FREQ (heavy)	0.17	0.03 – 0.32	0.020	0.03	-0.08 – 0.15	0.561	0.40	-0.57 – 1.37	0.422
Random Effects									
σ^2	2.06			1.09			88.20		
τ_{00}	1.35	Code		0.82	Code		173.28	Code	
τ_{11}	0.01	Code.MONTH		0.00	Code.MONTH		0.13	Code.MONTH	
ρ_{01}	0.66	Code		-0.38	Code		0.07	Code	
ICC	0.56			0.44			0.68		
N	90	Code		90	Code		90	Code	
Observations	397			397			394		
Marginal R ² / Conditional R ²	0.222 / 0.656			0.265 / 0.588			0.355 / 0.794		

Table 8. Allele frequencies of 54 biallelic SNPs included in the genome analyses. *Note:* bold SNPs refer to significant variants.

count	rsID	Major allele	Minor allele	Minor count	Total count	MAF
1	rs10499	A	G	15	202	0.07
2	rs159365	G	A	41	202	0.2
3	rs668168	T	G	71	202	0.35
4	rs670305	G	A	41	200	0.2
5	rs719504	G	A	64	202	0.32
6	rs726610	T	C	31	200	0.16
7	rs1409568	T	C	32	200	0.16
8	rs1448602	A	G	17	202	0.08
9	rs1526480	T	C	89	200	0.44
10	rs2075650	A	G	15	202	0.07
11	rs2189010	G	A	95	202	0.47
12	rs2365468	T	C	79	202	0.39
13	rs2875907	G	A	32	202	0.16
14	rs3774800	A	G	14	202	0.07
15	rs3935969	G	A	82	202	0.41
16	rs4732724	G	C	94	200	0.47
17	rs4785108	A	T	60	202	0.3
18	rs6504548	C	T	79	202	0.39
19	rs6504555	A	G	75	202	0.37
20	rs6558008	A	C	34	194	0.18
21	rs7178765	G	A	35	202	0.17
22	rs7208663	C	T	82	202	0.41
23	rs7519259	G	A	57	202	0.28
24	rs7651996	G	T	73	202	0.36
25	rs7783012	G	A	95	202	0.47
26	rs7838316	G	A	7	202	0.03
27	rs8071463	G	A	78	202	0.39
28	rs8074078	G	T	81	202	0.4
29	rs9344740	G	T	82	202	0.41
30	rs9888985	G	A	30	202	0.15
31	rs9890629	G	A	77	202	0.38
32	rs9891146	T	C	64	202	0.32
33	rs9897982	T	G	79	202	0.39
34	rs9919557	C	T	49	202	0.24
35	rs10085617	T	A	81	202	0.4
36	rs10458022	C	T	93	200	0.46
37	rs10986600	T	C	49	188	0.26
38	rs11556505	C	T	15	202	0.07
39	rs11783092	A	G	66	202	0.33
40	rs11870068	C	A	78	202	0.39

Table 8. *(continued)* Allele frequencies of 54 biallelic SNPs included in the genome analyses.
Note: bold SNPs refer to significant variants.

41	rs17007864	T	C	14	202	0.07
42	rs17518584	T	C	45	202	0.22
43	rs17761723	C	T	17	202	0.08
44	rs34095326	G	A	1	202	0
45	rs34404554	C	G	15	202	0.07
46	rs56070621	T	A	40	202	0.2
47	rs62051488	C	A	40	202	0.2
48	rs71352238	T	C	15	202	0.07
49	rs72689267	C	T	18	202	0.09
50	rs73229090	C	A	4	202	0.02
51	rs73229093	C	T	6	202	0.03
52	rs77300175	C	T	32	202	0.16
53	rs78561048	G	A	9	202	0.04
54	rs80030908	G	A	1	202	0

Figures

Figure 1. Temporal changes of (A) DSM-5 CUD severity, (B) cannabis dependence, and (C-E) cannabis use habits. *Note:* DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th edition), SDS: Severity of Dependence Scale, THC: tetrahydrocannabinol

Figure 2. Temporal trajectories of the three neurocognitive measures over the 18-month study period. *Note:* MoCA: Montreal Cognitive Assessment, FAB: Frontal Assessment Battery, WMS-GM: Wechsler Memory Scale-General Memory. Error bars denote 95% confidence intervals.

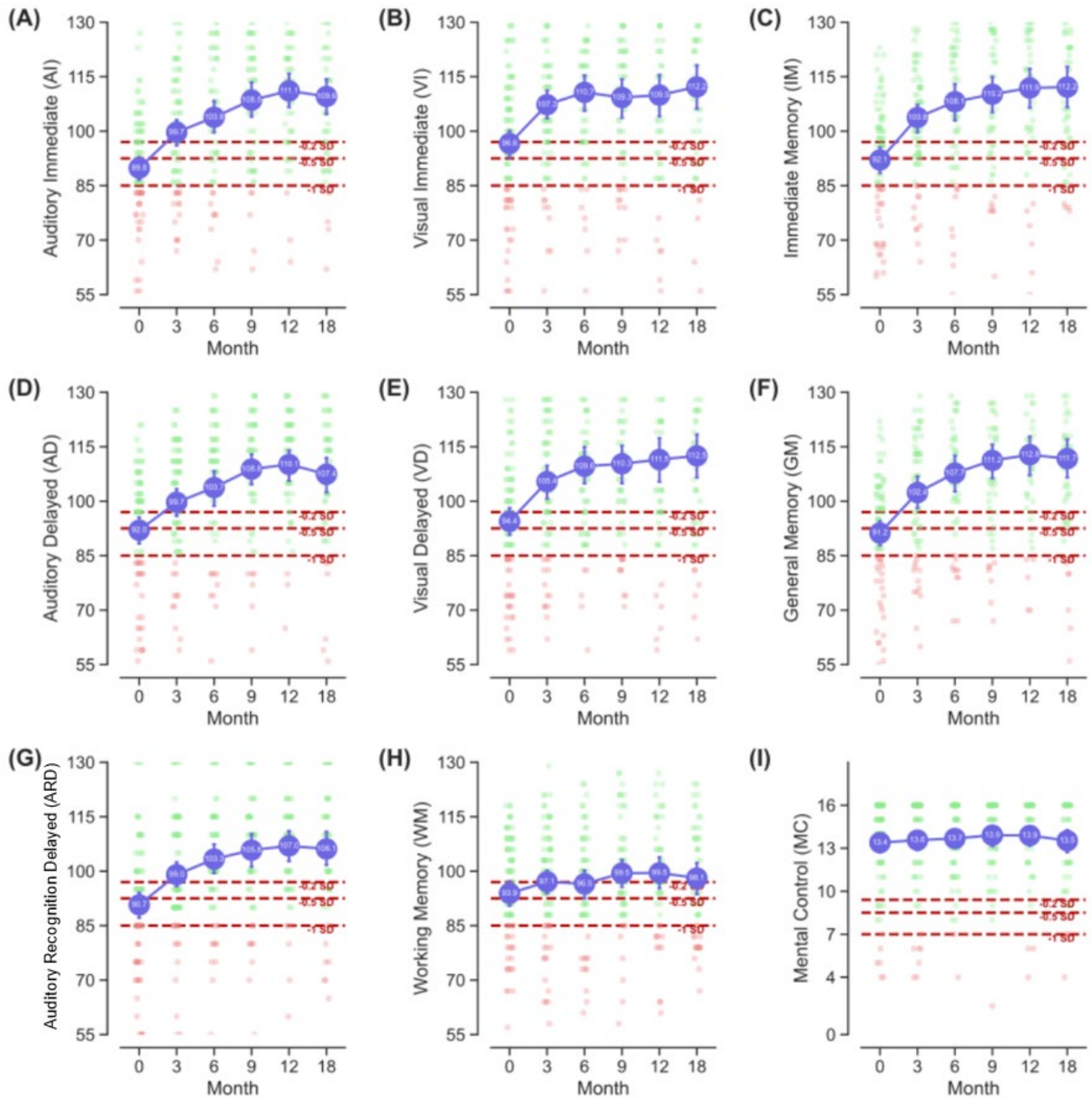


Figure 3. Temporal trajectories of all memory indices measured from Wechsler Memory Scale over the 18-month study period. *Note.* Error bars denote 95% confidence intervals.

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Supplementary Materials

Supplementary Table 1. Descriptive statistics for cannabis use, dependence severity, and cognitive performance over 18-month observation period (N = 90).

	Month 0	Month 3	Month 6	Month 9	Month 12	Month 18
N	90	83	64	60	56	54
ABS	25.10 (48.64)	49.58 (82.08)	67.84 (91.31)	52.10 (83.33)	77.40 (110.05)	99.44 (129.38)
DAILY	29 (32.22%)	20 (24.10%)	17 (26.56%)	16 (26.67%)	12 (21.43%)	12 (22.22%)
DSM-5	3.81 (2.85)	2.90 (2.73)	2.78 (2.81)	2.72 (2.62)	2.59 (2.83)	2.83 (2.76)
FAB	16.20 (1.84)	16.69 (1.28)	16.73 (1.66)	16.76 (1.45)	16.91 (1.43)	16.61 (1.96)
FREQ	46.41 (64.75)	32.07 (59.39)	41.40 (77.04)	28.77 (40.27)	27.89 (54.94)	28.35 (55.40)
FREQ-Heavy	6 (6.67%)	3 (3.61%)	5 (7.81%)	1 (1.67%)	3 (5.36%)	3 (5.56%)
FREQ-Irregular	44 (48.89%)	58 (69.88%)	40 (62.50%)	39 (65.00%)	42 (75.00%)	40 (74.07%)
FREQ-Regular	40 (44.44%)	22 (26.51%)	18 (28.12%)	20 (33.33%)	11 (19.64%)	11 (20.37%)
WMS-GM	91.23 (16.73)	102.37 (19.26)	107.73 (19.90)	111.21 (19.23)	112.79 (20.17)	111.72 (20.86)
WMS-IM	92.07 (16.73)	103.76 (18.13)	108.11 (20.02)	110.18 (19.81)	111.89 (20.81)	112.15 (20.86)
WMS-MC	13.39 (3.07)	13.57 (3.10)	13.68 (2.69)	13.91 (2.73)	13.89 (2.70)	13.53 (2.84)
WMS-WM	93.89 (15.47)	97.08 (15.43)	96.51 (15.38)	99.46 (15.58)	99.54 (16.54)	98.09 (16.34)
MoCA	26.10 (2.29)	26.67 (2.16)	27.02 (2.11)	26.88 (2.39)	26.84 (2.92)	26.72 (2.96)
SDS	4.07 (3.48)	3.60 (3.42)	3.92 (3.80)	3.87 (3.72)	2.96 (3.14)	3.94 (3.60)
THC	35 (38.89%)	32 (38.55%)	26 (40.62%)	21 (35.00%)	20 (35.71%)	21 (38.89%)

Note. Values are presented as counts (%) for categorical variables and mean (SD) for continuous variables. Sample size varies across time points due to attrition. N: number of participants assessed at each time point, ABS: days of abstinence e, DAILY: daily cannabis use status, DSM-5: symptom counts according to Diagnostic and Statistical Manual of Mental Disorders (5th edition), FAB: Frontal Assessment Battery, FREQ: frequency of cannabis use (times in the past 3 months), FREQ-Heavy: heavy cannabis use category (30 – 90 times), FREQ-Irregular: irregular cannabis use category (< 30 times), FREQ-Regular: regular cannabis use category (>90 episodes), MoCA: Montreal Cognitive Assessment, SDS: Severity of Dependence Scale, THC: urine positivity for tetrahydrocannabinol (THC), WMS-GM: Wechsler Memory Scale - General Memory Index, WMS-IM: Immediate Memory Index, WMS-MC: Mental Control subtest score, WMS-WM: Working Memory Index.

Supplementary Table 2A. Results of linear mixed-effects model for longitudinal changes of the 90 participants in all memory subdomains from Wechsler Memory Scale.

	AI			VI			IM		
	B	95%CI	<i>p</i>	B	95%CI	<i>p</i>	B	95%CI	<i>p</i>
(Intercept)	91.88	88.30 – 95.46	<0.001	102.10	97.74 – 106.47	<0.001	96.33	92.51 – 100.15	<0.001
MONTH	1.49	1.17 – 1.81	<0.001	0.94	0.58 – 1.30	<0.001	1.39	1.07 – 1.71	<0.001
SDS	0.15	-0.46 – 0.75	0.636	-0.35	-1.06 – 0.36	0.331	-0.13	-0.75 – 0.49	0.673
THC	2.11	-2.81 – 7.03	0.400	8.23	2.39 – 14.07	0.006	5.60	0.51 – 10.69	0.031
ABS (log)	0.75	-0.84 – 2.33	0.354	1.31	-0.58 – 3.20	0.174	1.09	-0.56 – 2.73	0.195
DAILY	1.47	-4.19 – 7.14	0.609	1.75	-5.04 – 8.53	0.613	1.92	-3.97 – 7.80	0.523
FREQ (regular)	-3.30	-7.62 – 1.02	0.134	-3.17	-8.33 – 1.98	0.227	-3.53	-8.01 – 0.95	0.122
FREQ (heavy)	-8.34	-16.97 – 0.30	0.058	-3.98	-14.07 – 6.11	0.438	-7.04	-15.85 – 1.77	0.117
AGE	0.61	0.02 – 1.19	0.042	0.71	-0.06 – 1.48	0.070	0.77	0.10 – 1.44	0.024
SEX	-3.51	-8.54 – 1.52	0.171	-5.32	-11.97 – 1.33	0.116	-5.05	-10.85 – 0.75	0.088
EDU	4.39	3.30 – 5.47	<0.001	2.90	1.47 – 4.33	<0.001	4.16	2.90 – 5.41	<0.001
LIFETIME	-0.26	-0.81 – 0.29	0.348	-0.32	-1.05 – 0.41	0.393	-0.34	-0.98 – 0.30	0.293
MONTH × SDS	-0.03	-0.08 – 0.03	0.374	-0.00	-0.07 – 0.06	0.969	-0.01	-0.07 – 0.05	0.718
MONTH × THC	-0.58	-1.13 – -0.02	0.041	-0.86	-1.51 – -0.22	0.009	-0.82	-1.38 – -0.25	0.005
MONTH × ABS	-0.16	-0.33 – -0.00	0.047	-0.14	-0.33 – 0.05	0.144	-0.16	-0.32 – 0.01	0.058
MONTH × DAILY	-0.25	-0.90 – 0.39	0.439	-0.29	-1.05 – 0.46	0.447	-0.29	-0.95 – 0.37	0.394
MONTH × FREQ (regular)	0.66	0.10 – 1.21	0.021	0.76	0.10 – 1.41	0.023	0.80	0.23 – 1.37	0.006
MONTH × FREQ (heavy)	0.90	-0.04 – 1.83	0.059	0.64	-0.44 – 1.73	0.242	0.89	-0.05 – 1.84	0.064
Random Effects									
σ^2	74.89			114.30			84.33		
τ_{00}	110.34 _{Code}			180.77 _{Code}			140.02 _{Code}		
τ_{11}	0.22 _{Code.MONTH}			0.14 _{Code.MONTH}			0.14 _{Code.MONTH}		
ρ_{01}	-0.03 _{Code}			0.50 _{Code}			0.36 _{Code}		
ICC	0.63			0.67			0.67		
N	90 _{Code}			90 _{Code}			90 _{Code}		
Observations	394			394			394		
Marginal R ² / Conditional R ²	0.461 / 0.799			0.208 / 0.735			0.383 / 0.799		

Note: SDS: Severity of Dependence Scale, THC: Tetrahydrocannabinol, ABS: days of abstinence, DAILY: daily use status, FREQ: frequency of cannabis use, EDU: years of education, LIFETIME: lifetime duration of cannabis use.

Supplementary Table 2B. Results of linear mixed-effects model for longitudinal changes of the 90 participants in all memory subdomains from Wechsler Memory Scale.

	AD			VD			ARD		
	B	95%CI	<i>p</i>	B	95%CI	<i>p</i>	B	95%CI	<i>p</i>
(Intercept)	93.84	89.85 – 97.83	<0.001	99.91	95.13 – 104.69	<0.001	92.26	87.88 – 96.64	<0.001
MONTH	1.26	0.94 – 1.58	<0.001	1.05	0.64 – 1.46	<0.001	1.16	0.79 – 1.54	<0.001
SDS	0.07	-0.57 – 0.71	0.828	0.06	-0.73 – 0.84	0.889	0.10	-0.65 – 0.86	0.790
THC	2.17	-2.92 – 7.26	0.402	5.30	-1.11 – 11.71	0.105	2.01	-4.11 – 8.12	0.519
ABS (log)	0.42	-1.19 – 2.03	0.609	0.34	-1.72 – 2.40	0.748	-0.52	-2.48 – 1.44	0.603
DAILY	-2.22	-7.93 – 3.50	0.446	-1.76	-9.12 – 5.59	0.637	-3.85	-10.87 – 3.16	0.281
FREQ (regular)	-4.02	-8.44 – 0.41	0.075	-4.01	-9.63 – 1.61	0.162	-2.59	-7.97 – 2.79	0.344
FREQ (heavy)	-3.22	-12.15 – 5.71	0.479	-0.93	-12.13 – 10.27	0.871	-3.51	-14.27 – 7.25	0.522
AGE	0.23	-0.40 – 0.87	0.470	0.22	-0.58 – 1.03	0.590	0.45	-0.16 – 1.06	0.145
SEX	-2.92	-8.39 – 2.54	0.293	-5.83	-12.78 – 1.12	0.100	-2.23	-7.46 – 3.00	0.403
EDU	4.25	3.05 – 5.44	<0.001	2.81	1.31 – 4.31	<0.001	2.49	1.35 – 3.64	<0.001
LIFETIME	-0.00	-0.61 – 0.60	0.988	0.07	-0.69 – 0.84	0.848	-0.24	-0.82 – 0.34	0.417
MONTH × SDS	-0.02	-0.08 – 0.03	0.422	-0.01	-0.08 – 0.07	0.866	-0.06	-0.13 – 0.01	0.086
MONTH × THC	-0.58	-1.13 – -0.02	0.042	-0.59	-1.30 – 0.13	0.109	-0.42	-1.08 – 0.24	0.211
MONTH × ABS	-0.16	-0.33 – -0.00	0.048	-0.16	-0.37 – 0.05	0.134	-0.04	-0.23 – 0.15	0.669
MONTH × DAILY	0.14	-0.50 – 0.77	0.676	-0.32	-1.15 – 0.51	0.446	-0.03	-0.79 – 0.74	0.943
MONTH × FREQ (regular)	0.65	0.10 – 1.21	0.020	0.72	0.01 – 1.44	0.048	0.95	0.30 – 1.61	0.004
MONTH × FREQ (heavy)	0.48	-0.46 – 1.42	0.316	0.19	-1.01 – 1.39	0.755	0.38	-0.74 – 1.50	0.502
Random Effects									
σ^2	70.81			125.71			114.91		
τ_{00}	170.64 _{Code}			214.96 _{Code}			153.56 _{Code}		
τ_{11}	0.29 _{Code.MONTH}			0.34 _{Code.MONTH}			0.24 _{Code.MONTH}		
ρ_{01}	-0.45 _{Code}			0.01 _{Code}			-0.58 _{Code}		
ICC	0.68			0.66			0.52		
N	90 _{Code}			90 _{Code}			90 _{Code}		
Observations	394			394			394		
Marginal R ² / Conditional R ²	0.398 / 0.808			0.194 / 0.725			0.258 / 0.644		

Note: SDS: Severity of Dependence Scale, THC: Tetrahydrocannabinol, ABS: days of abstinence, DAILY: daily use status, FREQ: frequency of cannabis use, EDU: years of education, LIFETIME: lifetime duration of cannabis use.

Supplementary Table 2C. Results of linear mixed-effects model for longitudinal changes of the 90 participants in all memory subdomains from Wechsler Memory Scale.

	GM			WM			MC		
	B	95%CI	<i>p</i>	B	95%CI	<i>p</i>	B	95%CI	<i>p</i>
(Intercept)	95.21	91.12 – 99.31	<0.001	93.17	89.66 – 96.68	<0.001	13.34	12.68 – 13.99	<0.001
MONTH	1.43	1.10 – 1.75	<0.001	0.44	0.19 – 0.69	0.001	0.05	-0.00 – 0.10	0.055
SDS	0.12	-0.53 – 0.78	0.708	-0.82	-1.37 – -0.28	0.003	0.01	-0.09 – 0.11	0.834
THC	3.47	-1.84 – 8.78	0.200	-0.68	-5.05 – 3.70	0.761	-0.43	-1.21 – 0.35	0.282
ABS (log)	0.28	-1.43 – 1.98	0.748	-0.43	-1.82 – 0.97	0.546	-0.27	-0.52 – -0.03	0.028
DAILY	-2.86	-8.95 – 3.24	0.357	-0.02	-5.01 – 4.96	0.992	0.02	-0.84 – 0.88	0.964
FREQ (regular)	-4.13	-8.79 – 0.53	0.083	0.26	-3.57 – 4.09	0.895	-0.32	-0.99 – 0.35	0.350
FREQ (heavy)	-2.98	-12.17 – 6.21	0.524	-4.87	-12.39 – 2.66	0.204	-0.17	-1.55 – 1.21	0.809
AGE	0.28	-0.43 – 1.00	0.440	0.22	-0.39 – 0.82	0.483	-0.05	-0.16 – 0.06	0.380
SEX	-5.53	-11.69 – 0.62	0.078	2.18	-3.00 – 7.37	0.408	-0.53	-1.45 – 0.40	0.265
EDU	3.94	2.61 – 5.28	<0.001	2.63	1.50 – 3.76	<0.001	0.55	0.35 – 0.75	<0.001
LIFETIME	-0.01	-0.68 – 0.67	0.983	-0.12	-0.70 – 0.45	0.671	0.03	-0.07 – 0.13	0.594
MONTH × SDS	-0.04	-0.10 – 0.02	0.189	0.05	0.00 – 0.09	0.042	-0.00	-0.01 – 0.01	0.515
MONTH × THC	-0.59	-1.17 – -0.01	0.047	-0.13	-0.60 – 0.33	0.574	0.03	-0.06 – 0.11	0.525
MONTH × ABS	-0.16	-0.32 – 0.01	0.071	-0.04	-0.17 – 0.10	0.578	0.01	-0.02 – 0.03	0.520
MONTH × DAILY	-0.05	-0.72 – 0.63	0.889	-0.02	-0.56 – 0.52	0.937	-0.05	-0.15 – 0.05	0.293
MONTH × FREQ (regular)	0.87	0.29 – 1.45	0.003	0.12	-0.34 – 0.59	0.595	0.10	0.01 – 0.18	0.026
MONTH × FREQ (heavy)	0.40	-0.57 – 1.37	0.422	0.42	-0.35 – 1.20	0.285	0.09	-0.06 – 0.24	0.221
Random Effects									
σ^2	88.20			58.76			1.50		
τ_{00}	173.28 _{Code}			139.14 _{Code}			5.26 _{Code}		
τ_{11}	0.13 _{Code.MONTH}			0.05 _{Code.MONTH}			0.01 _{Code.MONTH}		
ρ_{01}	0.07 _{Code}			-0.33 _{Code}			-0.47 _{Code}		
ICC	0.68			0.69			0.75		
N	90 _{Code}			90 _{Code}			90 _{Code}		
Observations	394			394			394		
Marginal R ² / Conditional R ²	0.355 / 0.794			0.235 / 0.764			0.291 / 0.825		

Note: SDS: Severity of Dependence Scale, THC: Tetrahydrocannabinol, ABS: days of abstinence, DAILY: daily use status, FREQ: frequency of cannabis use, EDU: years of education, LIFETIME: lifetime duration of cannabis use.

Supplementary Table 3. Comparisons of baseline demographics and scorings of MoCA, FAB and WMS-III indices between low attendance rate group (N = 33) and high attendance rate group (N = 55).

	<i>Low attendance rate group</i>		<i>High attendance rate group</i>				
	Count/ Mean	SD	Count/ Mean	SD	Statistical Test		p-value
SEX	Male: 23; Female: 10	N/A	Male: 33, Female: 22	N/A	chi ²	0.47	0.49
AGE	27.545455	9.20	29.145455	10.31	t-test	-0.73	0.47
EDU	11.893939	2.72	12.145455	2.55	t-test	-0.44	0.66
LIFETIME	10.151515	9.59	11.672727	11.19	t-test	-0.65	0.52
Urine THC	Negative: 21; Positive: 12	N/A	Negative: 29; Positive: 25	N/A	chi ²	0.47	0.49
FREQ	42.28125	59.53	53.436364	78.21	t-test	-0.70	0.49
ABS	13.787879	18.71	23.363636	37.49	t-test	-1.37	0.18
DSM	3.939394	3.09	3.963636	3.04	t-test	-0.04	0.97
SDS	3.666667	4.07	4.796296	3.72	t-test	-1.33	0.19
MoCA	26.0625	2.56	26.054545	2.16	t-test	0.02	0.99
FAB	16.272727	1.66	16.218182	1.62	t-test	0.15	0.88
AI	88.0625	15.70	90.418182	14.90	t-test	-0.70	0.49
VI	93.0	16.07	95.781818	18.57	t-test	-0.71	0.48
IM	89.1875	15.59	91.981818	16.13	t-test	-0.79	0.43
AD	91.375	19.31	93.436364	16.57	t-test	-0.53	0.60
VD	91.46875	18.87	91.981818	16.46	t-test	-0.13	0.89
ARD	89.6875	15.60	92.090909	16.63	t-test	-0.66	0.51
GM	89.40625	17.57	91.145455	15.22	t-test	-0.49	0.63
WM	96.0625	13.60	92.345455	15.80	t-test	1.11	0.27
MC	12.78125	3.70	13.490909	3.15	t-test	-0.95	0.35

Note: Over the 18-month study period, 19 participants attended only baseline assessments, 14 participants attended one subsequent follow-up assessment at any timepoint, 8 participants attended two subsequent follow-up assessments at any timepoint, 13 participants attended three subsequent follow-up assessments at any timepoint, 27 participants attended four subsequent follow-up assessments at any timepoint, and 28 participants attended all 5 follow-up assessments.

SDS: Severity of Dependence Scale, THC: Tetrahydrocannabinol, ABS: days of abstinence, DAILY: daily use status, FREQ: frequency of cannabis use, EDU: years of education, LIFETIME: lifetime duration of cannabis use, N: number of participants, N/A: not applicable.

Supplementary Table 4. Comparisons of baseline demographics and scorings of MoCA, FAB and WMS-III indices between cannabis users who had negative trajectory on cognitive changes (N = 9) and those who did not (N = 81) on LLMs.

	<i>Negative trajectory group</i>		<i>Non-negative trajectory group</i>				
	Count/ Mean	SD	Count/ Mean	SD	Statistical Test		p-value
SEX	Male: 5; Female: 4	N/A	Male: 48; Female: 33	N/A	chi ²	0.00	1.00
AGE	30.0	9.35	28.728395	9.73	t-test	0.37	0.71
EDU	10.722222	1.94	12.419753	2.65	t-test	-1.86	0.07
LIFETIME	12.666667	9.21	10.45679	10.98	t-test	0.58	0.56
Urine THC	Negative: 2; Positive: 7	N/A	Negative: 52; Positive: 28	N/A	chi ²	4.54	0.03
FREQ	97.333333	120.04	40.753086	53.84	t-test	2.56	0.01
ABS	43.277778	120.77	23.080247	33.65	t-test	1.18	0.24
DSM	4.888889	4.04	3.691358	2.69	t-test	1.20	0.23
SDS	6.666667	5.27	3.775	3.13	t-test	2.43	0.02
MoCA	23.888889	2.47	26.345679	2.15	t-test	-3.21	0.00
FAB	15.555556	2.46	16.271605	1.76	t-test	-1.11	0.27
AI	75.444444	16.13	91.419753	14.49	t-test	-3.10	0.00
VI	90.666667	21.37	97.246914	18.11	t-test	-1.02	0.31
IM	80.444444	19.79	93.358025	15.98	t-test	-2.25	0.03
AD	75.333333	22.09	93.851852	16.38	t-test	-3.10	0.00
VD	88.222222	17.97	95.111111	18.80	t-test	-1.05	0.30
ARD	83.333333	20.62	91.54321	16.41	t-test	-1.39	0.17
GM	79.0	20.48	92.592593	15.84	t-test	-2.37	0.02
WM	83.555556	14.77	95.037037	15.20	t-test	-2.15	0.03
MC	11.0	4.87	13.654321	2.72	t-test	-2.53	0.01

Note: SDS: Severity of Dependence Scale, THC: Tetrahydrocannabinol, ABS: days of abstinence, DAILY: daily use status, FREQ: frequency of cannabis use, EDU: years of education, LIFETIME: lifetime duration of cannabis use, N: number of participants, N/A: not applicable.

Supplementary Table 5. Genotyped participant (N = 101) demographics and history of drug use at baseline. *Note.* BDF-Q6: Beat Drugs Fund Evaluation Question Set No. 6, CUD: cannabis use disorder, LSD: Lysergic Acid Diethylamide, MDMA: 3, 4-methylenedioxymethamphetamine, THC: Tetrahydrocannabinol, SD: standard deviation, SCID-5: Structured Clinical Interview for DSM-5 Disorders–Clinician Version, SDS: Severity of Dependence Scale, MoCA: Montreal Cognitive Assessment, FAB: Frontal Assessment Battery, WMS: Wechsler Memory Scale. *: lifetime history.

	Total (N = 101)
Male, Count (%)	60 (59.41%)
Chinese, Count (%)	73 (72.28%)
Age, Mean (SD)	28.71 (9.61)
Education (years), Mean (SD)	12.10 (2.61)
Single, Count (%)	86 (85.15%)
Forensic history, Count (%)	26 (25.74%)
Tobacco smoker, Count (%)	78 (77.23%)
Alcohol drinker, Count (%)	82 (81.19%)
Drinking years, Mean (SD)	11.38 (9.28)
In-patient psychiatric admission*, Count (%)	29 (28.71%)
Out-patient psychiatric care*, Count (%)	50 (49.50%)
Detox center admission*, Count (%)	18 (17.82%)
Cannabis use	
Age of first use, Mean (SD)	17.82 (4.55)
Abstinence (days since last use), Mean (SD)	23.64 (46.40)
Lifetime duration of use (in years), Mean (SD)	10.89 (10.51)
Daily Use, Count (%)	33 (32.67%)
BDF-Q6 Frequency of Use, Mean (SD)	49.12 (68.03)
▪ Irregular Use, Count (%)	48 (47.52%)
▪ Regular Use, Count (%)	45 (44.55%)
▪ Heavy Use, Count (%)	7 (6.93%)
Lifetime use of other substance (Counts [%])	
Cocaine	48 (47.52%)
Ketamine	45 (44.55%)
LSD	33 (32.67%)
Heroin	15 (14.85%)
Magic Mushroom	14 (13.86%)
MDMA	45 (44.55%)
Methamphetamine	39 (38.61%)
Baseline measures	
Positive urine test for THC, Count (%)	43 (42.57%)
DSM-5, Mean (SD)	3.91 (2.93)
SDS, Mean (SD)	3.97 (3.68)
MoCA, Mean (SD)	26.06 (2.39)
FAB, Mean (SD)	16.21 (1.82)
WMS	
▪ Immediate Memory, Mean (SD)	91.36 (16.68)
▪ General Memory, Mean (SD)	90.70 (16.83)
▪ Working Memory, Mean (SD)	93.48 (15.49)
▪ Mental Control, Mean (SD)	13.07 (3.39)

End of the Report