A prospective study to evaluate the change in cognitive function in stimulant users

評估興奮劑使用者認知功能變化的前瞻性研究

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1. Background

Stimulants are a broad class of sympathomimetic drugs that increase movement, arousal, vigilance, anorexia, and attention. At high doses, stimulants can produce euphoria, sexual arousal, and addiction. In Hong Kong, the use of methamphetamine (MET) is common, and cocaine (COC) use has steadily increased over the past few years. While the use of ketamine decreased from 49.8% among all psychotropic substances in 2012 to 14.4% in 2022, MET and COC have become the most commonly used psychotropic substances in the latest report by the Narcotics Division (2023). However, these data only represent the tip of the iceberg of stimulant use in Hong Kong because the numbers in these reports are generated from drug abusers who have voluntarily agreed to be reported to the Narcotics Division.

Misuse of MET has long been associated with profound psychological and cognitive disturbance. In reviewing the cognitive data from reasonably well-matched groups of chronic MET users and healthy controls, the majority of studies have found that chronic MET users had lower scores on at least some cognitive tests (Gonzalez et al., 2004; Henry et al., 2009; Hoffman et al., 2006; Kalechstein, Newton & Green, 2003), although some studies are exceptions with entirely nonsignificant differences (Chang et al., 2005; King et al., 2010; Leland et al., 2008; Simon et al., 2010). A meta-analysis of 17 cross-sectional studies found that chronic MET users demonstrated significantly lower cognitive scores than healthy controls. The effects were largest for measures of learning, executive functions, memory, and processing speed, although the majority of cognitive domains significantly differed between the groups (Scott et al., 2007). Reviews on COC abuse also indicated impairments across executive functions and several cognitive domains particularly for attention, impulsivity and executive functions (Inozemtseva et al., 2016; Potvin et al., 2014). Nevertheless, both executive functions and cognitive functions were found to improve after at least

3-month abstinence of COC albeit limited literature investigating the residual effects of long-term COC use.

Converging evidence indicated that changes in frontal areas are associated with cognitive function deficits in chronic MET users (Rogers et al., 1999). Functional imaging studies confirmed that chronic MET users had a pattern of hypo-frontality, with diminished activation in a host of frontal regions during the task (Paulus et al., 2002). Using diffusion tensor imaging, chronic MET users consistently displayed lower fractional anisotrophy, an indicator of white matter integrity, in frontal areas and it correlated with the result of Wisconsin card sorting test which assesses subjects' executive function in terms of attention, working memory and visual processing (Chung et al., 2007). The corpus callosum has also been implicated in cognitive function deficits in chronic MET users. A structural MRI study found a number of differences within regions of the corpus callosum, such as increased curvature of the genu, decreased width of the posterior midbody and isthmus in abstinent MET users compared with controls (Oh et al., 2005). A diffusion tensor imaging study examining the corpus callosum in chronic methamphetamine users showed that index of fractional anisotrophy correlated with performance in the Stroop interference task which assesses subjects' executive function in terms of selective attention, cognitive flexibility and processing speed (Salo et al., 2009a).

Similar reduced engagement of amygdala-striatal, middle-frontal and right-frontoparietal networks were also found in cocaine users, where negative toxicology results and abstinence were associated with increased activity in these networks (Morie et al., 2021). It further confirms the impacts of cocaine use on inhibitory-control-related activations and attentional control. Long-term reductions in engagement of the networks may also occur where limited change in middle-frontal was only found in COC abusers with early abstinence (Morie et al., 2021). Given the inhibitory-

control functions of middle-frontal network, the change in its activation and the actual COC use patterns could affect each other over time.

If stimulant use is associated with cognitive deficits, one may expect that chronic stimulant users with higher exposure might exhibit greater cognitive deficits than those exposed to lower doses. In spite of an imprecise measure of cumulative dose, several studies have obtained self-reported duration of MET use (in years, months or days) as a proxy for cumulative stimulant exposure. One study found that years of MET use was associated with worse performance on the Stroop Task in MET-dependent adults (Salo et al., 2009b). However, the vast majority of studies correlating duration of MET use with cognitive performance in chronic MET users showed insignificant results (Henry, Minassian & Perry, 2010; Hoffman et al., 2006; Iudicello et al., 2011; Monterosso et al, 2005; Simon et al., 2000).

Some studies using self-reported frequency of methamphetamine use as an estimate of exposure showed that chronic MET users with more frequently use performed worse than those using less on tests of memory, abstract reasoning and executive function. Another study found that a functional measure of financial abilities was negatively associated with the number of times used per month in chronic methamphetamine users. However, other functional abilities measured were unrelated to the frequency of use.

Although the sheer volume of studies showing cognitive function deficits in stimulant users may seem authoritative, concerns has been emerging regarding the methodology of the aforementioned cross-sectional studies. Much of the published research has fallen victim to using controls with significant baseline differences from the chronic stimulant users, such as years of education. In addition, none of the studies available provided scatter plots of their cognitive data to evaluate the overlap in performance between chronic stimulant users and healthy controls.

Therefore, the use of the term ‘impairment’ or ‘deficit’ in many studies is not fully justified. Another limitation of a cross-sectional study is that it cannot differentiate cognitive weaknesses that may predate stimulant use from those that result from it. Notably, longitudinal studies have shown that childhood deficits in executive function can predict drug abuse in adolescence (Tarter et al., 2004), suggesting that at least some of the cognitive weaknesses pre-exist in chronic stimulant user. These and other limitations provoked a conclusion that the evidence for cognitive deficits in chronic stimulant users is weak.

The vast majority of research has not found a relationship between cognitive function and duration of stimulant use. One of the possible explanations is that duration of stimulant use is not the most accurate measure of stimulant exposure. Theoretically, use of repeated high doses of stimulants within a short period of time can also be associated with significant cognitive deficits. Besides, recall bias remains to be a major concern especially among stimulant users with a longer exposure. Findings from studies utilizing potentially more accurate measures of stimulant administration such as frequency of use or amount of recent use have been mixed, with the majority of studies not finding a relationship between cognitive function and estimates of cumulative exposure. Almost all of the studies evaluated this association in *post-hoc* analyses. The relationship between stimulant exposure and multiple cognitive tests were analysed without consideration of Type I error or confounding variables. As such, the available evidence for a linear relationship between self-reported stimulant usage and cognitive performance is weak.

In order to overcome the methodological issues observed in previous cross-sectional studies (Frazer, Richards & Keith, 2018), we conducted a prospective study to determine the change in cognitive function among stimulant users over time. A repeated-measures design can eliminate the effects of pre-existing conditions and confounders, such as age and education level

of stimulant users. Besides, fewer subjects are required to demonstrate a statistically significant difference in cognitive function.

To date, there has been limited research showing the change in cognitive function among stimulant users and no study comparing the effect of stimulant use on cognitive function among stimulant users with different severities of stimulant use disorder (SUD). We hypothesized that the change in cognitive function is different among stimulant users with different severities of SUD. The cumulative exposure to stimulants will be measured in order to determine the association between frequency of stimulant use and change in cognitive function among stimulant users with different severities of SUD. According to the dose response relationship of a stimulant, the effects of stimulants become apparent at doses higher than the threshold. However, the effects of stimulants may reach plateau if high doses are used repeatedly. Therefore, it is rationale to analyse the effect of stimulant use on cognitive function according to different levels of consumption, especially among stimulant users with mild to moderate SUD.

In this study, we aimed at demonstrating the decline in cognitive function among stimulant users instead of showing the difference in cognitive function between stimulant users and healthy controls. By determining the change in cognitive function among stimulant users in a longitudinal course should warrant a higher scientific merit than previous cross-sectional studies.

2. Methods

2.1. Design

This is a prospective study using repeated-measures design to investigate the change of cognitive functions in stimulant users. Each subject was assessed every three months within the 12-month study period in face-to-face structured interviews. Each interview lasted 30-45 minutes.

After each assessment interview, subjects would receive an honorarium of HK$280. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) (IRB reference number: UW 19-616).

2.2. Participants

All subjects were recruited from the community through referrals from non-governmental organizations and from the substance abuse clinics in the Hong Kong West Cluster. Individuals recruited were between 18-65 years old, repeatedly using stimulants as the primary psychoactive substance of abuse for more than six times in 12 months, and actively using stimulants within the 28 days at the time of enrollment. Subjects would be excluded if they had been diagnosed with moderate or severe other substance use or related disorders, were currently taking regular prescribed medications, or had been diagnosed with neurodevelopmental disorders or other psychiatric disorders. All subjects were required to provide consent for their participation.

2.3. Outcome Measurements

Demographic data including age, gender, ethnicity, education level, type and duration of stimulant use was collected. Severity of SUD, exposure to stimulants and cognitive functions were assessed upon enrollment as baseline and then on every three-monthly follow-up visit.

The degree of severity of SUD for each subject was assessed using the Structured Clinical Interview for DSM-5 (SCID-5) by trained personnel. In the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), the severity of SUD was categorized subjects into mild, moderate, or severe. Regarding the exposure to stimulants, Question set 6 provided by the Narcotics Division, Security Bureau was used to record the frequency of stimulant use in the past

three months for each subject. A multidrug urine test was also performed on every follow-up visit to confirm the status of recent or active stimulant use.

The Montreal Cognitive Assessment (MoCA) was used to assess the subjects' global cognitive functions. MoCA is a brief instrument that screened for mild cognitive impairment and dementia. The sensitivity and specificity for identifying cognitive impairment was 83.3% and 72.9% respectively (Copersino et al., 2009). In the current study, the validated Hong Kong version with the cut-off score ≥ 22 for normal cognitive function was used. In addition, the Frontal Assessment Battery (FAB) was used to assess their executive function (Cunha et al., 2010). FAB consists of six subtests to evaluate their conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control and environmental autonomy. The Chinese version of FAB which provided age- and education- adjusted scores ranging from -10 to 26 was used. Its cut-off score of -3 defined the presence of frontal dysexecutive phenotype (Wang, Hung & Yang, 2015).

2.4. Statistical Analysis

Data analyses were performed using SPSS 29.0, with a significance of alpha = .05. Demographic data of all subjects and their stimulant use history were presented with descriptive statistics. The generalized linear mixed model (GLMM) was performed to determine whether there were differences in cognitive function between stimulant users with different SUD severities over time. The between-subjects factor in this study was the severity of SUD and the within-subjects factor was time. The change in individual-specific cognitive function, measured by MoCA and FAB, was modeled as random effects. Covariates including age, gender, education level and duration of lifetime stimulant use were adjusted in the model.

The differences in frequency of stimulant use between different severities of SUD were analyzed with the Kruskal-Wallis test. Spearman's correlation was performed to determine whether there was an association between the change in cognitive function, measured by MoCA and FAB, and the amount of stimulant used during the study period. The frequency of stimulant used was measured by the average number of days of stimulant use within three months, while the change in cognitive function was determined by the difference in MoCA and FAB scores at baseline and at the 12th month visit. The test was repeated based on the change of the SUD severity: a) from no SUD on enrollment to the presence of any severity of SUD at the 12th month visit, b) from having a SUD at baseline to SUD in remission at the 12th month visit, and c) without any changes over the 12-month study period. Bonferroni correction was performed on the correlation tests with a significance of alpha = .017.

3. Results

A total of 93 stimulant users fulfilling the inclusion criteria consented and participated in this study. However, 17 subjects completed the baseline assessments only and were then lost to follow-up. Thus, 76 subjects (82%) were included in the analysis which were eight cases less than the proposed sample size of 84 subjects. The power of the analysis was maintained at around 0.8 to detect a similar effect size of 0.28 with a type I error of 0.05. The completion rates of each 3-monthly follow-up were as follows: 62 subjects (81.6%) at the 3rd month, 56 subjects (73.7%) at the 6th month, 47 subjects (61.8%) at the 9th month, and 57 subjects (75%) at the 12th month.

3.1. Demographics, Stimulant Use & Cognitive Functions at Baseline

The mean age of the subjects was 37.97 years (SD = 10.78) and the majority were males (68.4%). Their mean years in education were 9.21 (SD = 2.76). Most of them were single (52.6%), with 14 subjects married (18.4%), 21 subjects divorced (27.6%), and one widowed (1.3%). Many of them were active smokers (85.5%) and drinkers (71.1%), and had known forensic records (61.8%). Only six subjects (7.9%) were single stimulant users. (Table 1)

All subjects used MET and/or COC in the current study. 31 of them had lifetime use with either MET (25%) or COC (15.8%) as the sole stimulant; the majority (59.2%) used both. Within the three months period prior to enrollment, there are 60 (78.9%) subjects and 35 (46.1%) reported currently using MET and COC, respectively. The mean age of first use for MET was 21.5 years (SD = 8.89) and the mean duration of lifetime use was 148.69 months (SD = 108.62). While for COC users, the mean age of their first use was 23.64 years (SD = 7.98) and the mean duration of lifetime use was 73.96 months (SD = 89.09). At the time of enrollment, 8 subjects did not have any SUD (10.5%), 14 subjects had mild SUD (18.4%), 18 subjects were in moderate SUD (23.7%), and 36 subjects suffered from severe SUD (47.4%). Six subjects (7.9%) were screened to have mild cognitive impairment (MCI) based on the MoCA assessment and all of them had SUD. No subject exhibited frontal dysexecutive phenotype as assessed by FAB at baseline.

3.2. GLMM Results from MoCA (Table 2)

At the end of the study, only two subjects had MCI and both of them had their SUD in remission. Results from GLMM suggested no significant within-subject effect from time ($F[4, 268] = 2.029$, $p = .091$), nor between-subject differences based on the severities of SUD ($F[3, 268] = 1.398$, $p = .244$) were found (Figure 1). Interaction effect between time and SUD severity also

showed no difference on MoCA scores for each SUD severity group at all timepoints (F[12, 268] = .356, p = .977).

Within-subject change in global cognitive functions were associated with the baseline demographic covariates (B = 1.09, SE = .29, p < .001), but not the urine toxicology results with test done at the time of the MoCA assessment. Male stimulant users (M = 26.18) scored higher than female users (M = 24.09) (B = 2.09, SE = .34, p < .001) in MoCA (Figure 2). Stimulant users with higher education level also scored higher than those with lower education level (B = .17, SE = .05, p = .002). On the other hand, older stimulant users (B = -.04, SE = .01, p =.007) and longer lifetime stimulant use (B = -.01, SE = 0, p = .002) were both associated with lower MoCA scores.

3.3. GLMM Results from FAB (Table 3)

No significant within-subject effect from time (F[4, 270] = .151, p = .962), nor between-subject differences based on the severities of SUD (F[3, 270] = 1.445, p = .23) were found over the 12-month period (Figure 3). No interaction effect between time and severity of SUD could be established (F[12, 270] = .622, p = .823). Nevertheless, within-subject change in frontal lobe function was noted in relations to the duration of lifetime stimulant use and the urine toxicology results (B = .97, SE = .41, p = .018). Users with longer lifetime stimulant use scored significantly lower in FAB than those with shorter use (B = -.02, SE = 0, p < .001). Subjects with positive urine results with stimulants scored lowered (M = 15.56) than those with negative results (M = 17.52) (B = -1.97, SE = .53, p < .001) (Figure 4).

3.4. Frequency of Stimulant Use in Different SUD

Significant differences were demonstrated between the frequency of stimulant use and different severities of SUD ($\chi^2[3] = 23.218$, df = 3, $p < .001$). Stimulant users who had no SUD reported an average of 17.48 use-days within any three-month period, followed by 27.55 days for mild SUD group and 30.67 days for moderate SUD group. Users with severe SUD reported the number days of stimulant use peaking at 45.89 days (Figure 5).

3.5. Frequency of Stimulant Use and Cognitive Functions

No significant correlations were found from the changes in MoCA and FAB scores to the frequency of stimulant use at baseline to 12 months, nor to the average frequency of use during the three-monthly follow-ups in any groups of SUD status (adjusted $p > .017$).

4. Discussion

The current 12-month longitudinal study did not demonstrate any significant association between DSM-5 defined SUD severity to global cognitive and executive deficits in a group of chronic MET and COC users. Despite the increase in frequency of stimulant use went alongside the severity of SUD significantly, no significant correlation could be established between the average frequency of stimulant use and the changes in cognitive functions. Our study using chronic stimulant users as their own controls did not show cognitive declines over time within the 12 months study period.

Nevertheless, several covariates identified in this study, including female gender, older age, lower educational level, longer lifetime duration of stimulant use, and recent active stimulant use as reflected by positive urine results, concurred with the existing literature with their significant negative impacts to cognitive functions in stimulant users (Fitzpatrick et al, 2020; Morie et al.,

2021; Salo et al., 2009b; Wang et al., 2017). Lifetime duration of stimulant use and recent active stimulant use were widely acknowledged to impose greater negative effects than the frequency of stimulant use on cognitive performances among stimulant users (Fitzpatrick et al., 2020; Salo et al., 2009b). While recent stimulant abstinence may improve the amygdala-striatal network resulting in better cognitive functions, long-term stimulant use. on the contrary, might limit the flexibility of the network alteration and restrict the beneficial effects in cognitive performance from the reduction in stimulant use frequency (Morie et al., 2021). Thus, the duration of lifetime history of stimulant use and recent active stimulant use might serve as better predictors for cognitive functions than the severity of SUD or frequency of stimulant use in chronic stimulant users.

Discrepancies in the outcome measurements used for assessing the cognitive functions in stimulant users and using healthy controls with salient demographic differences, such as educational levels, might explain the non-concordance of our MoCA results to other studies that showed cognitive deficits for stimulant users over time (Inozemtseva et al., 2016; Potvin et al., 2014; Scott et al., 2007; Frazer, Richards & Keith, 2018). In fact, Garavan and colleagues (2008) had demonstrated an acute amelioration of neurocognitive dysfunction in chronic COC users on performing inhibitory-control-related-tasks immediately after intravenous COC injection. They argued such improvement might be related to the transient normalization of the chronic dysregulated activation over prefrontal regions of the brain. With a number of demographic characteristics found to significantly influence cognitive performance, it might be inappropriate to compare stimulant users' scores directly to the normative data in the absence of their baseline cognitive functions before using stimulant (Frazer, Richards & Keith, 2018).

Various neuroimaging studies suggested that stimulant use could diminish activations in various frontal regions of the brain (Morie et al., 2021; Sabrini et al., 2019). These translated to our finding on the association between positive urine result with stimulants, a proxy for recent active stimulant use, and the lowered FAB scores. Recent active stimulant use affects executive functions and inhibitory-control activities regulated by the middle frontal networks more than the other brain regions (Morie et al., 2021). The worsened decision-making and inhibitory-control impairment in stimulant users might further contribute to drug-dependent behavioral patterns due to the compensatory reinforcing effects from stimulants through dopaminergic activity. Nevertheless, these dysexecutive impairments could be improved with sustained abstinence as evidenced by the self-reported decrease in frequency of stimulant use and negative urine test results (Morie et al., 2021; Zhong et la., 2016).

While the current study showed that stimulant users with higher severity of SUD tended to consume stimulants more frequently, both the degree of severity in SUD and the frequency of stimulant use appeared not better indicators than their lifetime history of stimulant use and actual use pattern in correlating cognitive functions for stimulant users. This might be attributed to the constructs in the DSM-5 diagnostic criteria for SUD which focuses mainly on the subjective psychological and physical dependence, and impairments in psychosocial functionings. As such, the actual use pattern, especially recent active use, may better reflect the current cognitive functions among stimulant users in clinical settings.

The major merit of the current study was its repeated-measure longitudinal design that captured a more comprehensive overview on the relationship between the actual stimulant use pattern and the changes in executive and cognitive functions over time. However, the self-reporting exposure and pattern of stimulant use were subject to recall bias. Although urine drug test was

performed on every follow-up assessment for each subject, it only reflected the recent stimulant use but not the actual frequency or dosage of stimulant exposure within the 3-monthly follow-up period. Last but not least, only 7.9% of the study subjects were single drug users, and hence the lack of cognitive deficits in chronic stimulant users should be interpreted with cautions.

5. Conclusion

To conclude, the current longitudinal study could not establish any cognitive decline in a group of chronic stimulant users over a 12-month study period. No significant differences in cognitive functions were found among different SUD severity groups. The use of methamphetamine and/or cocaine appeared to be harmful to cognitive functions in female and older users, and in those with lower educational levels. Both longer duration of lifetime stimulant use and recent stimulant use may forecast frontal dysexecutive syndrome in stimulant users. Cautions should be reminded that stimulant abuses could cause significant cognitive impairments when compared to healthy non-stimulant users (Henry, Minassian & Perry, 2010; Hoffman et al., 2006; Iudicello et al., 2011; Monterosso et al, 2005; Simon et al., 2000). Future research may consider the dose-effect of stimulants on cognitive changes in stimulant users.

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BDF 180058 Full Report Tables

Table 1. Demographics, Stimulants Use and cognitive functions at baseline visit.

Variables	N (%) / M (SD)
Demographics	
Gender	
Male	52 (68.4%)
Age	37.97 (10.78)
Educational levels (in years)	9.21 (2.76)
Marital status	
Single	40 (52.6%)
Married	14 (18.4%)
Divorced	21 (27.6%)
Widowed	1 (1.3%)
Active smokers	65 (85.5%)
Active drinkers	54 (71.1%)
Forensic records	47 (61.8%)
Single drug users	6 (7.9%)
Stimulant Use Status	
MET users	
Lifetime ever-use	64 (84.2%)
Current use within three months	60 (78.9%)
Age of first use	21.5 (8.89)
Duration of lifetime use (in months)	148.69 (108.62)
COC users	
Lifetime ever-use	57 (75%)
Current use within three months	35 (46.1%)
Age of first use	23.64 (7.98)
Duration of lifetime use	73.96 (89.09)
Severity of SUD	
None	8 (10.5%)
Mild	14 (18.4%)
Moderate	18 (23.7%)
Severe	36 (47.4%)
Cognitive functions	
MoCA score	24.99 (2.74)
Mild Cognitive Impairment (MCI)	6 (7.9%)
FAB score	15.79 (4.4)
Frontal Dysexecutive Phenotype	0

Table 2. Results of generalized linear mixed model of MoCA for all subjects (N = 76).

	B	SE	*p*	95% CI
Fixed Effects				
Intercept	24.31	1.21	<.001	21.93, 26.7
Time				
Baseline (ref)	-	-	-	-
3rd month	0.23	0.98	.812	-1.7, 2.17
6th month	0.29	0.96	.767	-1.6, 2.17
9th month	0.03	1	.973	-1.93, 2
12th month	-0.35	1	.727	-2.32, 1.62
Severity of SUD				
None (ref)	-	-	-	-
Mild	-0.48	1.09	.66	-2.63, 1.67
Moderate	-0.51	1.06	.634	-2.6, 1.59
Severe	0.31	0.97	.751	-1.6, 2.21
Time*Severity of SUD^	-	-	> .05	-
Gender				
Female (ref)	-	-	-	-
Male	2.09	0.34	<.001	1.43, 2.75
Age	-0.04	0.01	.007	-0.07, -0.01
Educational year	0.17	0.05	.002	0.06, 0.27
Stimulant lifetime use	-0.01	0	.002	-0.01, 0
Urine Toxicology				
Negative (ref)	-	-	-	-
Positive	0.01	0.32	.978	-0.62, 0.64
Random Effects				
Variance of individual change of scores	1.09	0.29	<.001	0.65, 1.84

^: All interaction for Time*Severity of SUD shows no significant association.

MoCA: Montreal Cognitive Assessment; ref: reference group; SUD: Stimulant Use Disorder.

Table 3. Results of generalized linear mixed model of FAB for all subjects (N = 76).

	B	SE	*p*	95% CI
Fixed Effects				
Intercept	21.11	1.45	<.001	18.23, 23.97
Time				
Baseline (ref)	-	-	-	-
3rd month	-0.48	1.7	.78	-3.83, 2.88
6th month	-1.71	1.58	.279	-4.81, 1.39
9th month	-1.36	1.62	.403	-4.55, 1.83
12th month	-1.76	1.56	.262	-4.83, 1.32
Severity of SUD				
None (ref)	-	-	-	-
Mild	-2.49	1.72	.148	-5.87, 0.89
Moderate	-1.59	1.66	.339	-4.85, 1.68
Severe	-0.53	1.52	.726	-3.53, 2.46
Time*Severity of SUD^	-	-	> .05	-
Gender				
Female (ref)	-	-	-	-
Male	-0.51	0.51	.323	-1.52, 0.5
Stimulant lifetime use	-0.02	0	<.001	-0.02, -0.1
Urine Toxicology				
Negative (ref)	-	-	-	-
Positive	-1.97	0.53	<.001	-3.02, -0.92
Random Effects				
Variance of individual change of scores	0.97	0.41	.018	0.42, 2.22

^: All interaction for Time*Severity of SUD shows no significant association.

FAB: Frontal Assessment Battery; ref: reference group; SUD: Stimulant Use Disorder.

BDF 180058 Full Report Figures

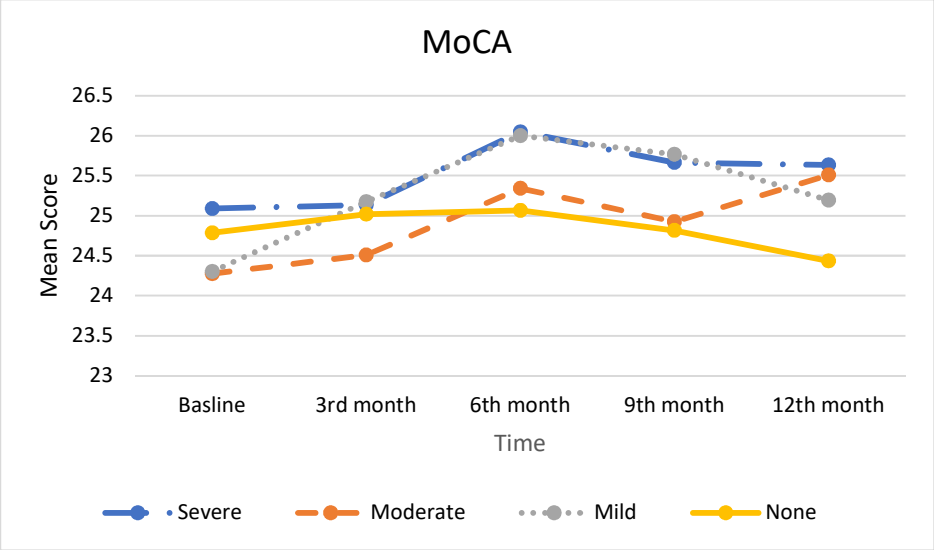

Figure 1. Mean score of MoCA in different severity groups of SUD across the 12-month study period.

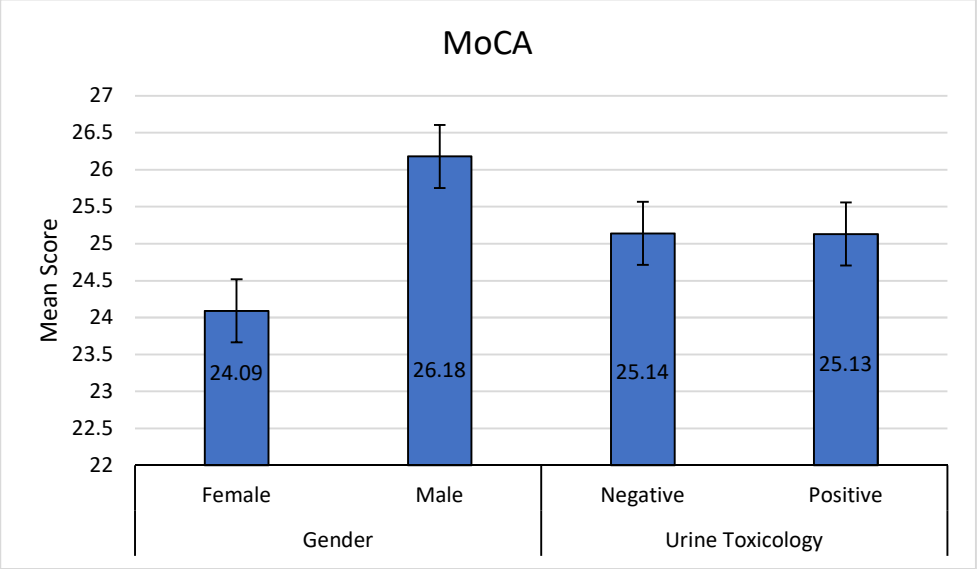

Figure 2. Mean score of MoCA of the 12-month study period under gender and urine toxicology results.

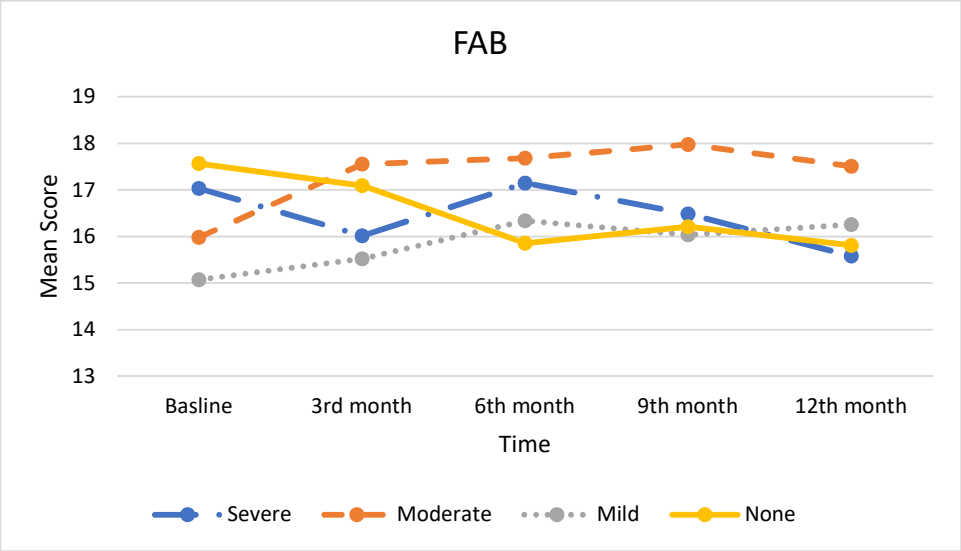

Figure 3. Mean score of FAB in different severity groups of SUD across the 12-month study period.

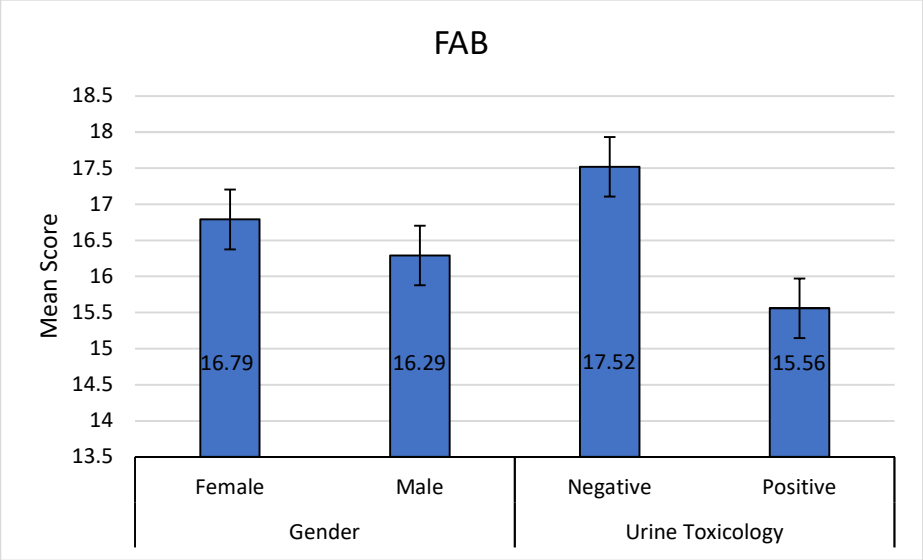

Figure 4. Mean score of FAB of the 12-month study period under gender and urine toxicology results.

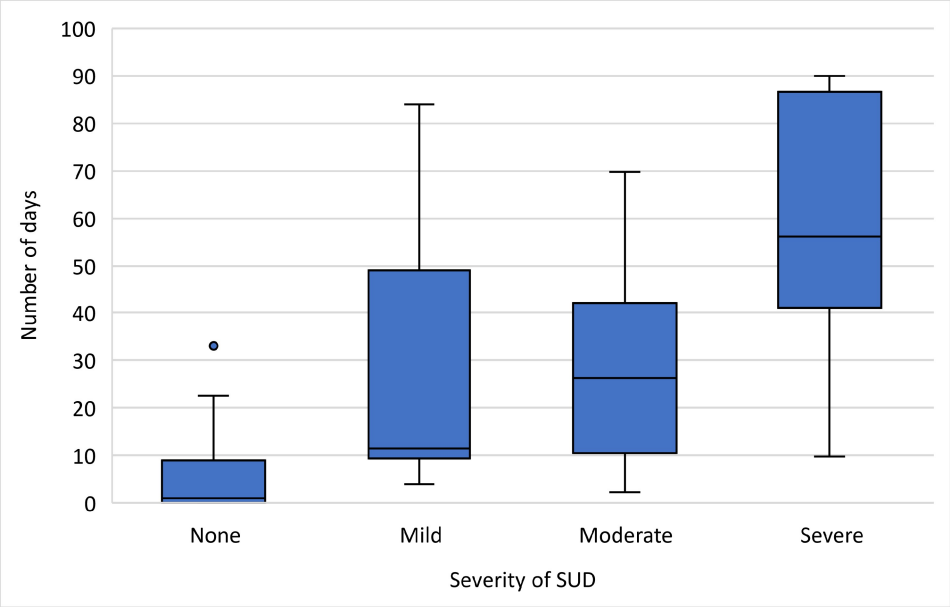

Figure 5. Average frequency of stimulant use within the every 3-monthly follow-up period.