Malta Medical Journal, 32 (1): Pages (2020)
http://mmsjournals.org/index.php/mmj/article/view/144

MMJ

ORIGINAL ARTICLE

Beyond the stigma of methadone maintenance treatment:

Neurocognitive recovery in individuals with opiate use disorders

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Background

Studies of cognitive functioning in drug addiction have shown consistent impairments among substance dependent populations. Several attempts to highlight the neurocognitive recovery of former opioid dependent individuals who are stabilised on methadone, have resulted in contradictory conclusions. The aim of this study is to compare the cognitive function of recovering opioid dependent individuals on methadone maintenance treatment to those who are not on methadone treatment, relative to healthy controls.

Methods

The Montreal Cognitive Assessment Tool was administered to three groups of participants: 22 former opioid dependents receiving methadone maintenance treatment, 21 former opioid dependents withdrawn from all opiates and 22 healthy controls without a history of illicit substance dependence. The specific cognitive domains tested include executive function, visuospatial skills, naming, attention, language, abstraction, delayed recall and orientation.

Results

Visuospatial skills and executive function were significantly improved with methadone. The language domain appears to be significantly impaired in both opioid dependent groups with a strong negative correlation to the duration of dependency. Participants who had stopped methadone were significantly impaired in all other aspects of cognition tested apart from naming and orientation when compared to healthy controls. Participants on methadone did not significantly differ in the other areas of cognition when compared to controls.

Conclusions

Methadone treatment appears to be associated with an improvement in cognitive function in opioid dependent individuals. Thus, methadone may facilitate public health by ensuring compliance of opioid dependent individuals to their treatment plan with fewer relapse rates and mitigation of risky behaviours.

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Introduction

The pivotal notions conveyed by prominent medical definitions of substance addiction primarily include the persistent engagement in drug-related behaviours mirroring impaired control in the face of devastating repercussions.[1-2] Underlying pathological brain changes, which are put forth as induced by the repeated exposure to psychoactive substances, are manifested most noticeably through tolerance to drug effects and withdrawal symptoms on abrupt cessation. Most importantly, altered intellectual function, disrupting reward processing and executive tasks is driven primarily by the neurotoxic drug effects.[3]

The reported prevalence of cognitive impairment in substance use disorder (SUD) varies widely between 30-80%.[4-7] The overall impact of various drugs on cognition also varies, but research indicates that individuals with SUD have alterations in brain structures including the striatum, prefrontal cortex, amygdala, and hippocampus.[8-10] Exposure to substances including heroin which dates back to the neuro-maturation stages of adolescence is particularly worrisome in this regard.[11]

The brain regions and neural processes that underlie addiction overlap extensively with those that support cognitive functions; including executive functioning, learning, memory, attention, reasoning, decision-making and impulse control.[12] Cognitive shifts that drive continued drug use through maladaptive learning hinder the adoption of alternative behaviours that promote abstinence. This leads to poorer treatment outcomes through decreased treatment adherence, engagement and readiness to change.[13-14]

The evidence surrounding the extent of neurocognitive recovery with methadone maintenance treatment (MMT) for opioid disorders (OD) is often contradictory. Some have reported persistent impairments, while others have described comparable cognitive performance to that of healthy controls (HC) who have never abused any type of illicit substance.[15-16] Others found no significant deterioration in the cognitive performance of patients on long-term and relatively high dose MMT.[17] Nonetheless, MMT is associated with amelioration in specific cognitive domains amongst patients with OD, especially executive function and visuo-construction.[18] After two months of MMT, improvements in verbal learning and memory, visuospatial memory, and psychomotor speed, were recorded in a sample of persons with OD.[19]

When OD individuals engage with MMT, treatment retention is high and a significant proportion manage to reduce or stop opioid use.[20] It has been shown that MMT is many times more cost-effective than no treatment and the extent to which these improved outcomes are underpinned by a mechanism of cognitive enhancement is debatable.[21] MMT was associated with intact cognitive control in OD individuals, mitigation of risky behaviours and enhanced behavioural learning.[22] On the other hand, OD individuals are at an increased risk of relapse of illicit opioid use after methadone detoxification.[23]

A Cochrane review uncovered the superiority of MMT over non-opioid interventions, questioning the one-size-fits-all philosophy of traditional psychosocial interventions to OD.[24] The insistence on methadone cessation is not without risks and can precipitate adverse effects including elevated relapse and death rates.[25-27]

Unfortunately the integration of MMT in therapeutic communities is not mainstream, despite reported effectiveness.[28] The impact of an intervention with documented harm reduction benefits such as MMT on cognitive function is paramount, especially when one takes an overall view of the process of recovery which warrants the mobilisation of cognitive skills to confront the various individual challenges to reestablish a meaningful existence.

Methodological differences and various study limitations such as a small sample size and a vast array of confounding factors (polysubstance abuse, severity and duration of OD, attained educational level, duration of stability on methadone and abstinence from illicit drugs, methadone dose and the presence of neuropsychiatric conditions) make it difficult to conclusively determine whether methadone offers cognitive stability.[29]

The goal of the current study is to investigate the cognitive performance of individuals who have gained stability on MMT and attained abstinence in comparison to those who were previously on the same treatment, underwent detoxification and are currently abstinent for at least 1 month. A third matched group with no SUD history is included. To our knowledge previous comparisons of cognitive function were not carried out specifically on these groups with the aim of deciphering whether it is methadone detoxification or maintenance that impacts best on cognitive performance, in a way that fosters the ability to cope with further rehabilitation and the challenges of life in general.

The Montreal Cognitive Assessment Tool (MoCA) is a 10-minute 30-point test with known sensitivity to mild cognitive impairment and which has effectively detected cognitive deficits in SUD patients.[17] It is quick, easy to administer and also sheds light on the specific neural circuitry underlying habitual behaviour in addiction. In accordance with previous literature reports, we hypothesised that both groups of former opiate users would perform worse than the control group. We additionally hypothesised that MMT stabilises neurocognitive function in those individuals who abstain from the illicit drugs. OD individuals who stabilise on methadone are expected to have a better neurocognitive function than those who come off methadone to access traditional rehabilitation programmes.

Materials and Methods

Healthy male and female subjects, 18-50 years of age, were selected for inclusion in one of three groups based on their opioid use history: (1) Individuals having a history of OD who are stable on MMT; (2) Individuals having a history of OD who were on methadone but have undergone methadone detoxification (NOMT); and (3) HC individuals without a history of opioid or other illicit substance dependence, matched for gender, district and educational level. For inclusion in the MMT and NOMT groups, participants were required to fulfil a former DSM-5 diagnosis of OD and to have been free of any illicit drug for at least one month, confirmed through negative urine toxicology screening tests (excluding methadone in the MMT group).

The MMT participants were recruited either from (i) Mount Carmel Psychiatric Hospital, whereby, patients had been admitted and stabilised on methadone for at least one month, (ii) Substance Misuse Outpatients

Clinic, whereby patients were on a stable methadone dose or (iii) Substance Misuse Outpatients Clinic, whereby patients had been granted the Take Home Methadone Policy.

The NOMT participants were recruited from a residential drug rehabilitation program (Caritas or Sedqa). The inclusion criteria for this group consisted of prior MMT, followed by gradual methadone detoxification to complete abstinence. All NOMT participants required to be methadone-free for a minimum of one month.

The HC population participants were recruited from Bormla public health centre general practitioner's clinic attendees. A southern harbour health centre was chosen whilst attempting to select a healthy sample resembling the OD sample as much as possible, in accordance with the National Audit Office Report (2012) which stated that the district that registers the highest proportion of individuals with SUD is the southern harbour region.[30] Patients or their relatives who presented with a minor health complaint which was not psychiatric in origin and who had never used any type of illicit substance, underwent cognitive testing.

Exclusionary criteria for all participants were any current Axis I diagnosis (other than OD for the MMT and NOMT groups, and nicotine dependence for all groups), history of head trauma, brain injury, neurological disease, substance-induced psychoses, epileptic seizures, human immunodeficiency virus infection, pregnancy, or any other medical condition which might affect the individual's cognitive function. Individuals who were administered any opioid replacement strategy e.g. Buprenorphine / DHC / Tramadol / Codeine were excluded from this study. Those who refused to give urines were automatically excluded from this study. Routine screening tested the detection of amphetamines, cocaine, cannabinoids, methadone and opiates. Exclusion criteria for control subjects included current or past history of any illicit substance.

Initial screening for the MMT group was done through the Substance Misuse unit database, whereby eligible patients were contacted and informed about this current study. Similarly, potential NOMT participants who were enrolled in Caritas and Sedqa residential drug rehabilitation programs and expressed interest in participating were invited for a face-to-face interview, consisting of the Beck's Depression and Anxiety Inventories. Only those participants who did not suffer from any psychiatric condition which might impair cognitive function were selected and assessed with the MoCA. All interviews were conducted by the same clinician to eliminate any observer or systematic bias. No sampling method was used to recruit participants as all available patients who were benefiting from these addiction services throughout April-September 2017 and who met inclusion and exclusion criteria were recruited. In all, 22 participants satisfied the criteria for inclusion in the MMT group, 21 participants were included in the NOMT group and 22 HC participants were enrolled out of their own free will. This study was reviewed and approved by the Malta Health Ethics Committee Board and the Foundation for Social Welfare Services Ethics Committee.

A naturalistic cross-sectional comparative design was employed for this study. Randomization of the participants was not possible as the overall management of the participants depended on their own personal choice as to whether to engage in

MMT or enrol in a rehabilitation programme and stay NOMT. The dependent variable was overall cognitive functioning which was assessed at one specific time point through administration of the MoCA cognitive tool. The independent variable was treatment with methadone or not, as an opioid replacement. The duration of dependence/abstinence/enrolment in programme, comorbid dependencies, psychiatric treatment, dosage of methadone and the duration of methadone administration were also variables of particular interest.

The MoCA was administered manually using paper and pencil testing. Two versions were available, depending on the participant's preference of daily spoken language; an English and Maltese version (the latter had been already translated and validated in another study).[31] A score of 26 or more is considered normal. The specific cognitive domains tested include executive function, visuospatial skills, naming, attention, language, abstraction, delayed recall and orientation.

Statistical Analysis

SPSS software was used for statistical analysis. Initial analyses compared groups on demographics with analysis of variance (ANOVA) for continuous variables and Chi-square analyses for categorical variables. Any demographic variable that significantly varied across groups, was entered into later analyses as a covariate. The individual cognitive domains tested were compared across groups by conducting a one-way analysis of variance to examine group (MMT, NOMT and HC) effect, followed by post-hoc testing with Bonferroni multiple comparison analysis. Backward stepwise multivariate linear regression was carried out to examine the effects of comorbid cocaine dependence and different classes of psychiatric treatment on cognitive performance and thus, determine the presence and account for any confounders. The effects of duration of dependency/abstinence/methadone administration/enrolment in program and methadone dosage were examined by conducting a correlation analysis.

In reporting the results, a *P* value of 0.05 was considered as showing statistical significance.

Results

Participant Demographics

MMT, NOMT and HC groups did not significantly differ with respect to gender *(x^2 =2.167, P=0.338)* and district locality *(x^2 =7.197, P=0.707)* by Pearson Chi-Square analysis. Neither did the three participant groups differ with regards to years of education *(F=1.284, P=0.284)* by ANOVA. However, they demonstrated significant difference with respect to age *(F=4.059, P=0.022)*. HC participants were the youngest with a mean age of *31.64* ±*8.244*, followed by NOMT participants with a mean age of *34.90* ±6.340 and finally MMT participants being the eldest with a mean age of *37.59* ±*6.005* (Table 1).

Cognitive Domain Performance

One-way ANOVA was applied to test for any significant difference among the participant groups (MMT, NOMT and HC) for each cognitive domain tested. A significant difference was present for visuospatial skills and executive function *(F=13.621, P= 0.000)*, attention *(F=4.777, P=0.012)*, language *(F=9.760, P=0.000)*, abstraction *(F=4.813,*

P=0.011) and delayed recall *(F=5.573, P=0.006)*. No significant difference was noted among the groups for naming *(F=1.049, P=0.356)* and orientation *(F=1.012, P=0.369)*. A highly significant difference was observed among the three groups for the overall total cognitive score *(F=15.782, P=0.000)*. The total cognitive score was previously obtained by adding the score of each individual cognitive domain for each participant in their respective groups. In every cognitive domain tested, the NOMT group obtained the lowest mean score, followed by the MMT group and finally the HC with the highest score (Figure 1).

Post-hoc Bonferroni analysis of multiple comparisons (Table 2) was carried out for each cognitive domain. The NOMT group scored significantly lower than the HC *(P=0.000)* and MMT *(P=0.010)* group for visuospatial / executive function. The difference between MMT and HC was not significant *(P=0.105)*.

There was a significant difference between the NOMT and HC for attention *(P=0.010)*, delayed recall *(P=0.006)*, and abstraction *(P=0.013)* with the NOMT group obtaining the least mean score out of all groups. No difference was observed between the MMT group and HC for attention *(P=0.213)*, delayed recall *(P=0.077)* and abstraction *(P=1.000)* or between MMT and NOMT for attention *(P=0.644)*, delayed recall *(P=0.987)* and abstraction *(P=0.069)*.

HC scored significantly higher than MMT *(P=0.014)* and NOMT group *(P=0.000)* for language. There was no significant difference between the MMT and NOMT group *(P=0.479)*.

The HC overall total score was significantly higher than both MMT *(P=0.007)* and NOMT group *(P=0.000)*. No statistically significant difference existed between MMT and NOMT groups *(P=0.052)*.

Multiple Linear Regression Analysis and Backward Stepwise Multivariate Linear Regression Modelling

The participants' age was entered as a covariate in a secondary analysis comparing each neurocognitive domain performance across groups. Multiple linear regression analysis was carried out to adjust for age since the latter was statistically significantly different among the three groups. Nonetheless, age was not significant in any of the models for each different cognitive domain score.

Backward stepwise multivariate linear regression modelling was used to examine and account for any possible confounders to the MoCA score among the participant groups. Comorbid cocaine dependence and different classes of psychiatric treatment were studied for any effect on cognitive performance. No confounder was found to be statistically different for the neurocognitive score across the three groups.

Correlation Analysis

The relationships between the individual cognitive domain score and duration of dependency/abstinence from heroin were examined by conducting a correlation analysis specific to the MMT and NOMT group participants only. The dose and duration of methadone administration were also correlated exclusively to the MMT group, while the duration of enrolment in the drug rehab program was correlated with each cognitive domain score exclusively to the NOMT group.

Table 1 Demographic data of Methadone Maintenance Treatment, Not on Methadone Treatment and Healthy Control Groups

Group	Control HC (*n*=22)	Opioid Dependent MMT (*n*=22)	Opioid Dependent NOMT (*n*=21)	Statistic	Significance *P*
Gender					
Male	15(68.2%)	18 (18.8%)	13(61.9%)		
Female	7 (31.8%)	4 (18.2%)	8 (38.1%)	x^2 2.167, df=2	0.338
District					
Southern Harbour District	14(63.6%)	10 (45.5%)	10(47.6%)		
Northern Harbour District	4 (18.2%)	6 (27.3%)	4 (0.19%)		
South Eastern District	0 (0.0%)	2 (9.1%)	3 (14.3%)		
Western District	2 (9.1%)	2 (9.1%)	1 (4.8%)		
Northern District	2 (9.1%)	1 (4.5%)	1 (4.8%)	$x^2$7.197,df=10	0.707
N/A (Outside Malta)	0 (0.0%)	1 (4.5%)	2 (9.5%)		
Education (years: mean ± S.D.)	11.23 ± 2.202	11.91 ± 1.925	10.81 ± 2.657	F=1.284	0.284
Age (years: mean ± S.D.)	31.64 ± 8.244	37.59 ± 6.005	34.90 ± 6.340	F=4.059	0.022

S.D.Standard Deviation, df Degrees of freedom, x^2 Chi-Square,F-statistic

Figure 1 A comparison of the percentage mean score for each cognitive domain across the groups

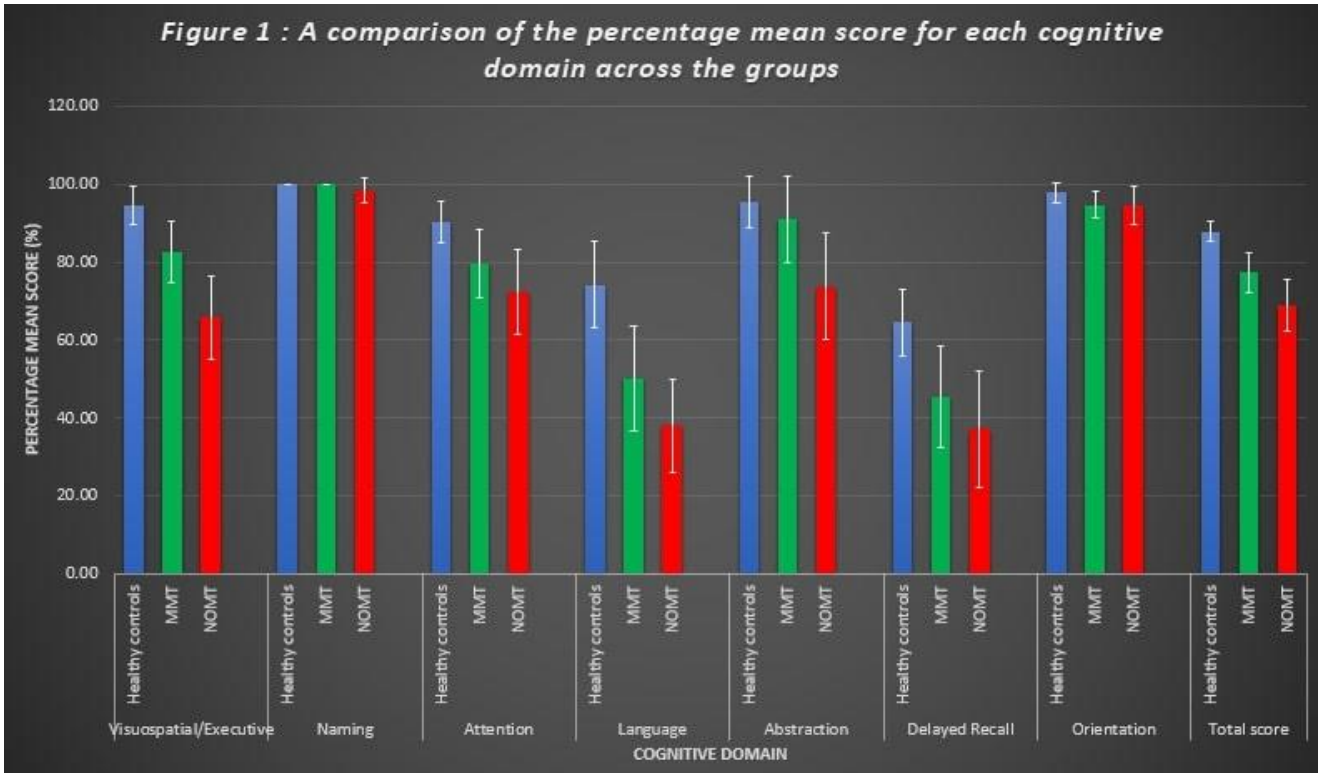


Table 2 Neurocognitive domain performance of MMT, NOMT and HC participant groups

Group	Control	Opioid Dependent		Statistic	Significance *P*	Paired Comparison
	HC	MMT	NOMT			
		Mean ± S.D.				
ANOVA						
Visuospatial/Executive	4.73 ± 0.550	4.14 ± 0.889	3.29 ± 1.189	F=13,621	0.000	B,C
Naming	3.00 ± 0.000	3.00 ± 0.000	2.95 ± 0.218	F=1.049	0.356	_
Attention	5.41 ± 0.734	4.77 ± 1.193	4.33 ± 1.426	F=4.777	0.012	B
Language	2.23 ± 0.752	1.50 ± 0.913	1.14 ± 0.793	F=9.760	0.000	A,B
Abstraction	1.91 ± 0.294	1.82 ± 0.501	1.48 ± 0.602	F=4.813	0.011	B
Delayed Recall	3.23 ± 0.973	2.27 ± 1.486	1.86 ± 1.6221	F=5.573	0.006	B
Orientation	5.86 ± 0.351	5.68 ± 0.477	5.67 ± 0.658	F=1.012	0.369	_
Total Score	26.36 ± 1.677	23.18 ± 3.375	20.71 ± 4.361	F=15.782	0.000	A,B

Figure 2 Scatterplot showing the variability of Language score with Duration of Dependency

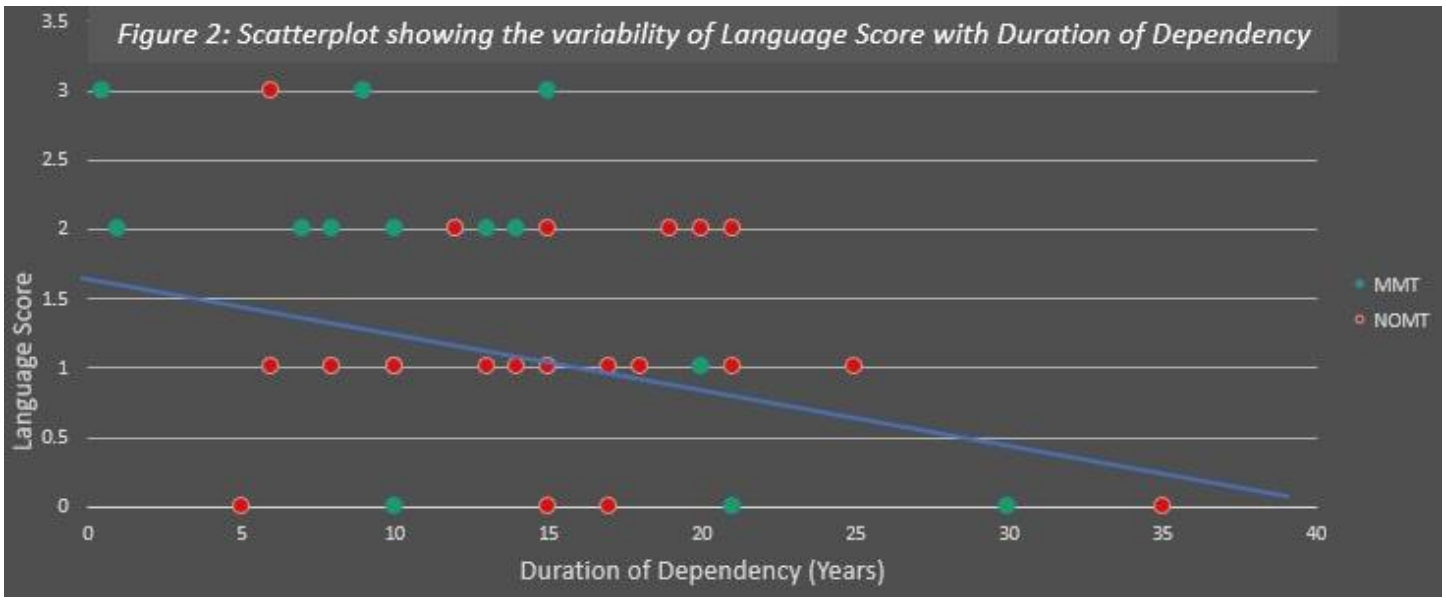
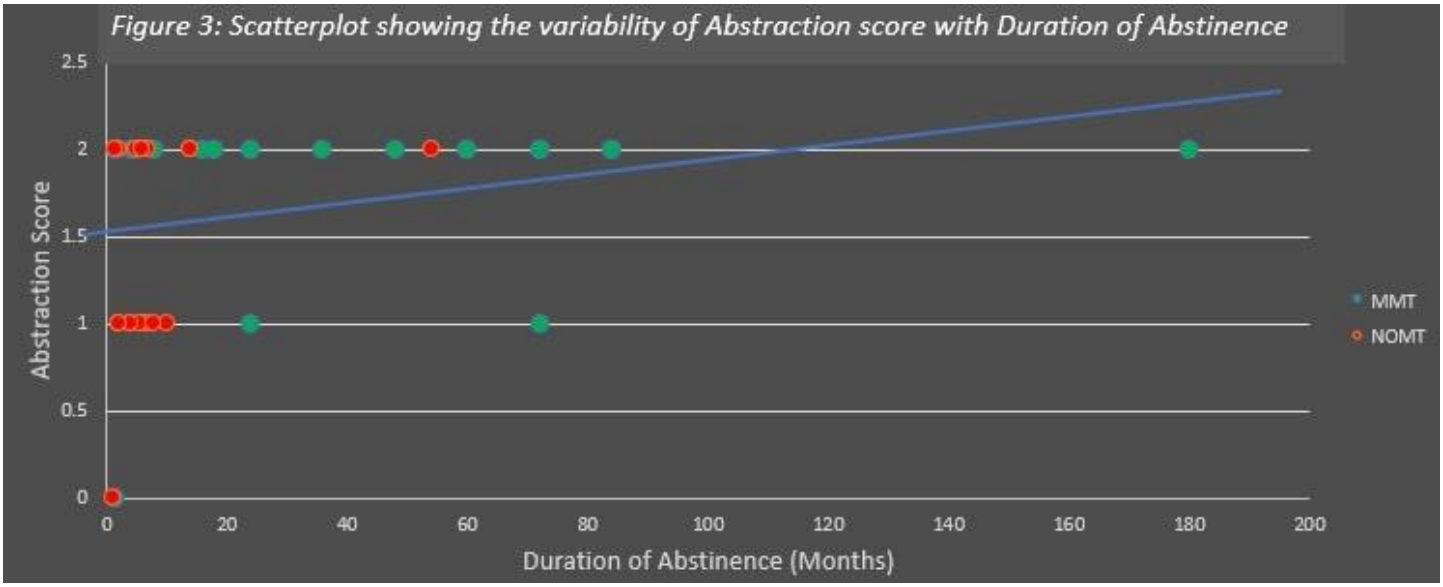


Figure 3 Scatterplot showing the variability of Abstraction score with Duration of Abstinence



The duration of dependency was noted to be negatively correlated with the language domain for both MMT and NOMT groups *(P=0.012)* (Figure 2). An analysis of the language domain as the dependent variable with group, as the between-subject factor (MMT and NOMT) and duration of dependency as covariate, did not reveal a statistically significant effect of group *(P=0.437)*. The covariate of duration of dependency remained

statistically significant *(P=0.017)*. Thus, the difference in language between MMT and NOMT groups is not significant in the presence of the duration of dependency. The duration of dependency was not significantly correlated to any other cognitive domain, nor was it correlated to the overall total score *(P=0.140)*.

The duration of abstinence was noted to be positively correlated with the abstraction domain for both MMT and NOMT groups *(P=0.50)* (Figure 3). An analysis of the abstraction domain as the dependent variable with group, as the between-subject factor (MMT and NOMT) and duration of abstinence as covariate, did not reveal a statistically significant effect of group *(P=0.251)*. The covariate of duration of abstinence from heroin did not remain statistically significant *(P=0.258)*. The duration of abstinence was not significantly correlated to any other cognitive domain, nor was it correlated to the overall total score *(P=0.082)*.

No significant correlation was observed for dose and duration of methadone administration with each cognitive domain tested and with the overall total score for the MMT group *(P=0.585* and *P=0.897* respectively). Similarly, no significant correlation was noted for the duration of enrolment in the drug rehab program with each cognitive domain tested and with the overall total score for the NOMT group *(P=0.529)*.

Discussion

Individuals with no history of SUD tend to exhibit superior cognitive functioning compared to those who abuse opioids and other psychoactive substances, as highlighted in this study and elsewhere. The present research sheds further light on factors that can affect cognitive function in an already impaired group.

Individuals who are stable on methadone appear to have significant problems primarily in the language domain compared to controls whilst those who are weaned off methadone exhibit impairments in multiple cognitive domains, in particular visuospatial and executive function, attention, language, abstraction and delayed recall. Visuospatial impairment was previously reported in an NOMT group in a similar comparison.[16] Another study highlighted enhanced attention in the MMT group, consistent with this study.[18] Executive functions such as impulse control, verbal learning and memory, visuospatial memory, and psychomotor speed, were also previously shown to be superior in the MMT group.[19]

Though the significant language domain impairment of the MMT group in this study influenced the total MoCA score leading to a minimal overall difference compared to the NOMT group, methadone stabilisation appears to offer some sort of stabilisation, if not recovery, especially with regards to visuospatial abilities and executive function. Our findings did not show significant differences between the majority of the cognitive domains tested in the MMT and the HC groups. This was not the case when the HC and NOMT groups were compared, with contrasting levels of cognitive function in multiple domains.

Figure 1 clearly illustrates a typical crescendo pattern, with the mean score for each cognitive domain of the NOMT group being the lowest, reflecting poorest cognitive function, while the HC scoring the highest. The MMT group mean scores appear to lie in between the other two groups, highlighting

the fact that methadone may promote neurocognitive recovery in individuals who had previously been dependent on heroin. This contrasts markedly with the findings of a study where the abstinent group reportedly had an overall better cognitive performance than the MMT group.[15] However, the researchers admittedly included subjects with current illicit drug use and performed retrospective comparisons, increasing the effect of confounders.

The present study and others have sustained the view that individuals with OD who are retained on MMT seem to exhibit better cognitive function compared to those who underwent detoxification, at least partially explaining the superiority of MMT over interventions with a drug-free ideology. The enhanced cognitive stability offered by MMT can come in handy when such patients are subjected to the challenges of psychosocial interventions such as cognitive behavioural therapy. Individuals with OD have an increased risk of emotional dysregulation primarily as a result of impaired cognitive reappraisal.[13-14] In a study comparing the effects of MMT and CBT on cognitive emotional regulation, both were shown to be significantly effective and the authors suspect this may be one of the underlying mechanisms of MMT which instigates improved cognitive function.[32]

This study also revealed a strong correlation between the duration of the OD career with the degree of impairment in the language domain; methadone did not seem to stabilise cognition in subjects who accumulated more brain changes over a longer exposure to opioids. This justifies the Bonferroni analysis for the language domain where both MMT and NOMT groups scored significantly lower than the HC. One possible interpretation of this finding is that a ceiling effect exists in our drug-using participants due to the severity of OD that may have masked any differential effect of chronic opiate use on cognitive function.

The results of this study have important implications in management. Individuals who are on methadone are frequently stigmatised and encouraged to come off methadone at a stage when risk of relapse is still significant. In particular, there is a blanket approach to those planning to join a residential drug rehabilitation programme. For some, methadone detoxification prior to rehab not only lowers their ability to cope with the challenges of the programme due to a possible deterioration in executive function, but exposes them to associated risks. Cognitive function plays a key role in treatment efficacy. Prohibiting proven medical treatments at all costs in rehab programmes may be limiting the effectiveness of the same programmes apart from depriving individuals with complex needs from making progress through their full cognitive potential. In addition, specific interventions targeting neurocognitive dysfunction should become an essential component of all interventions in the addiction field.

Limitations of this current study include a small population size, a demographic difference of age among the group participants and illicit substance use history measures have been collected based on the participants' self-reports. Routine urine testing does not identify all abused illicit drugs, such as the widely consumed synthetic cannabis receptor agonists. A cross-sectional study was performed as opposed to a longitudinal design with MMT patients pre and post methadone detoxification. It is also fairly well recognised that opiate addicts have abused a variety of illicit substances which are

usually under-reported. It is therefore, possible that any type of illicit substance might lead to cognitive deficits due to a direct toxic insult to the brain. In addition, the unhealthy lifestyle associated with severe OD might include malnutrition, exposure to violence or infections which could indirectly contribute to a decreased cognitive performance. We have specifically asked all our participants recruited in this study for any history of head trauma or probed for medical conditions which could affect cognition.

This study is unique in rigorous exclusion of comorbid Axis I and Axis II disorders which could affect cognitive function. In addition, abstinence was ensured by repeated screening for any illicit substance and automatic exclusion of individuals who failed to submit a urine sample or who have abused any illicit substance in the last month. All interviews were conducted by the same clinician to minimise the chances of observer or systematic bias.

Conclusion

Despite its limitations, our study addresses the issue of cognitive impairment in rigorously screened abstinent heroin addicts. Our results indicate that methadone offers a better level of cognitive function compared to premature opioid substitute cessation. Given the extent of opioid addiction in the community, MMT provides public health benefits by augmenting cognitive performance and social function in former OD individuals. It can ensure compliance with treatment plans, reduce relapse rates and risky behaviours in heroin addicts, thus fostering productivity and resumption of important responsibilities. It highlights the importance of performing neuropsychological assessments as an aspect of patient evaluation in drug rehab programmes and other venues of care, thus, identifying and acknowledging significant cognitive impairment, and providing appropriate care packages.

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