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Published in:
Psychological Medicine

DOI:
10.1017/S0033291718003318

Publication date:
2018

Document Version
Peer reviewed version

Profiles of visuospatial memory dysfunction in opioid exposed and dependent populations.

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Abstract

Background: Chronic opioid exposure is common world-wide, but behavioural performance remain under investigated. This study aimed to investigate visuospatial memory performance in opioid exposed and dependent clinical populations and its associations with measures of intelligence and cognitive impulsivity.

Methods: We recruited 109 participants: i) patients with a history of opioid dependence due to chronic heroin use (n=24), ii) heroin users stabilised on methadone maintenance treatment (n=29), iii) participants with a history of chronic pain and prescribed tramadol and codeine (n=28) and iv) healthy controls (n=28). The neuropsychological tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) included the Delayed Matching to Sample (DMS), Pattern Recognition Memory (PRM), Spatial Recognition Memory (SRM), Paired Associate Learning (PAL), Spatial Span Task (SSP), Spatial Working Memory (SWM) and Cambridge Gambling Task (CGT). Pre-morbid general intelligence was assessed using the National Adult Reading Test (NART).

Results: As hypothesised this study identified differential effects of chronic heroin and methadone exposures on neuropsychological measures of visuospatial memory ($p<0.01$) that were independent of injecting behaviour and dependence status. The study also identified an improvement in DMS performance (specifically at longer delays) when the methadone group was compared to the heroin group and also when the heroin group was stabilised onto methadone.

Results identified differential effects of chronic heroin and methadone exposures on various neuropsychological measures of visuospatial memory independently from addiction severity measures, such as injecting behaviour and dependence status.

4479 Words, 79 References, 5 Tables, 1 Supplementary Table, 2 Figures

Introduction

Working memory is a limited capacity cognitive system that functions to hold information in an active manner to facilitate the performance of complex cognitive tasks (**Miyake & Shah, 1999**). Such tasks include, for example, language comprehension, learning, abstract thinking (**Twamley *et al.* 2006**), problem-solving (**Westen, 2006**), understanding the meaning of complex texts and planning verbal communications (**Zihl *et al.* 1979**). Working memory (WM) is limited in both capacity and duration and is often used synonymously, but inaccurately, with the term "short term memory" (**Westen, 2006). Baddeley & Hitch (1974)** expanded upon this WM concept and proposed a tripartite working memory model that includes a central executive and two 'slave systems'; the phonological loop and the visuospatial store. The visuospatial store is further broken down into (1) visual memory information that includes dimensions such as colour and shape and (2) spatial memory information that includes capacity to understand, reason and to remember the spatial relations among objects or space. **(Baddeley & Logie, 1999**; **Mammarella *et al.* 2008)**. There is accruing evidence that the two components of visuospatial memory are selectively engaged and/or processed by distinct brain regions and neuropsychological functions (**Della Sala *et al*. 1999; Passolunghi *et al*. 2010, Bormann *et al.*2015; Erikson *et al.* 2015**)**.**

There are a few brain imaging studies on visuospatial memory impairments among drug users. Kubler and colleagues reported that cocaine dependent individuals were impaired in visuospatial working memory. These were associated with prefrontal, cingulate and striatal regions (**Kubler *et al*. 2005)**. In another study opiate dependent individuals were impaired in working memory-related brain areas (**Bach *et al,* 2012**).

Hyman and colleagues have conceptualised the behavioural phenomena typically described as 'addiction' to a "pathological usurpation of the neural mechanisms of learning and memory that under normal circumstances serve to shape survival behaviours related to the pursuit of rewards and the cues that predict them" (**Hyman., 2005; Hyman *et al.* 2006**).

In support of the potential centrality of learning and memory changes within drug addiction, two recent meta-analyses of observational studies suggested that chronic opioid exposure is associated with deficits across a range of different neuropsychological domains including attentional set-shifting, spatial planning and (**Baldacchino *et al.* 2012**; **2016; Tolomeo *et al*. 2016; 2018**). However, these meta-analyses also suggested that opioid exposed groups with apparent working memory impairments are a highly heterogenous group with mixed ages, educational attainment, gender and socio-economic status (**Baldacchino *et al.* 2012, 2016).** Additionally, visuospatial memory

impairments in opioid exposed groups are confounded by, for example, comorbid personality disorders (**Prosser *et al.* 2008**), anxiety and/or depression (**Henry *et al.* 2012**), past and present medical conditions, neurological disorders and history of head trauma and non -fatal overdose (anoxic) episodes (**Prosser *et al.* 2008**; **Rounsaville *et al.* 1982; Shmygalev *et al.* 2011; Specka *et al.* 2000**). Cognitive function may also be influenced by the global sedative effects of opioid drugs, sub-acute responses to the drugs or the presence of untreated withdrawal states (**Baldacchino *et al.* 2016**) at time of testing. **Table 1 summarises** studies that have recorded significant impairments in visuospatial memory in chronic opioid using populations.

INSERT TABLE 1 here

The present study aimed to extend our understanding of neurocognitive performance in dependent and non-dependent opioid users, focusing on visuospatial memory function. Employing an ambispective cohort design, we tested representative samples of male participants exposed to illicit and therapeutic opioid drugs and matched, non-substance using, healthy controls. Specifically, the study aimed to determine if performance on tasks measuring visuospatial memory, especially delayed memory performance, which is very sensitive for the varying of 'executive demands', was affected by (1) the *type* of the opioid exposure (methadone vs. heroin) at different stages of treatment seeking, (2) the *context* (opioids prescribed for pain control compared with illicit opioids) and (3) the presence or absence of syndromal *opioid dependence* (opioid dependent compared to non–opioid users) and (4) administration route – *injection status* (opioid dependent and injecting compared with dependent and non-injecting participants). We have previously identified and reported differential effects of heroin, methadone and prescribed analgesic medication on neurocognitive measures of impulsivity (**Baldacchino *et al.* 2014**) from the same study cohort.

Method

Participants

Ethical permission for the conduct of this study was provided by the East of Scotland Research Ethics Service (REC reference number: 06/S1401/32). A full description of the participants can be found in **Baldacchino *et al* (2014**). Male only participants were recruited from UK NHS substance misuse and pain management services. A control group of healthy participants was also recruited. All participants were screened to exclude lifetime or current histories of psychosis, PTSD, neurological

and neurodevelopmental disorders, borderline or psychopathic personality disorders, head injuries; individuals with a lifetime history of non-fatal overdose episodes requiring medical attention (e.g. ambulance call out, CPR), co-occurring benzodiazepine, psychostimulant and alcohol dependence. All participants were screened by an experienced clinician (AB) for acute opioid and opioid withdrawal symptoms prior to the neuropsychological testing.

The Heroin group (H) (N=24) were 'first time' referrals to a structured Methadone Maintenance Treatment (MMT) programme. The Methadone group (M) (N=29) were established and stable participants in a MMT programme with objective confirmation of absence of illicit drug use for more than six months. Eighteen of the twenty-nine MMT group participants who showed objective continuing clinical stability were retested six months after baseline testing. All recruits making up the H and MMT cohorts presented initially with opioid dependence and reported a history of *more* than three years of continuous and daily illicit opioid use.

Heroin participants (H) performed repeated neuropsychological testing during a single blinded procedure that permitted the objective observation of participants (a) 3-5 hours after their last illicit heroin administration to minimise the confounding cognitive effects of acute intoxication; (b) 10-15 hours after the last heroin dose in a state of controlled opioid withdrawal and subsequently (c) following more than two weeks on a stable dose of MMT. Clinically this is known as tolerance testing which is a single-blinded procedure that permitted the objective observation of individuals during stages of acute intoxication, withdrawal and subsequent stabilisation on a fixed dose methadone within a period of 7-14 days **(Baldacchino, 2011**).

The two opioid dependent groups (H and M groups) were matched for lifetime drug use history, morphine equivalent dosages and other drug use (including tobacco smoking) history 30 days prior to baseline testing. The CANTAB neuropsychological tests presented here refer to the standard tests selected from the batteries used at baseline testing. Where available, parallel versions of the tasks were used with the same participant to minimise practice effects.

This approach offered the opportunity to test whether any visuospatial memory measures that differed from those of control participants represented a stable phenomenon, or could be modified by differential opioid exposure and switch to an alternate opioid (MMT). A cohort of non-dependent participants prescribed opioids for chronic pain for more than 3 years (P) (N=28) with no history of 'illicit' opioid use, or methadone treatment, was also recruited. This group were prescribed

tramadol, codeine, or both, for moderate chronic pain. Both P and HC groups were tested only once (**Table 2).**

INSERT TABLE 2 here

Instruments

(A) Clinical: All subjects were screened using the MINI Plus v 5.0 (**Sheehan *et al.* 1998**), Maudsley Addiction Profile (MAP) (**Marsden *et al.* 1998**), and Fagerström Test for Nicotine Dependence (FTND) (**Fagerström & Schneider, 1989**). Urine samples were collected from all participants to confirm their history of recent opioid intake and to confirm the *absence* of any other illicit drugs throughout the study period. The Clinical Opiate Withdrawal Scale (COWS) (**Wesson & Ling, 2003**), quantified the level of opioid withdrawal in the heroin group. A senior research nurse and an experienced clinician conducted the assessments. Both were clinically trained. No participants had HIV or AIDS or other medical comorbidities that could affect cognitive functions.

(B) Cognitive: The neuropsychological tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (**Robbins *et al.* 1994**) were selected on the basis of their known sensitivity to detect impairments in (a) *visual* [Delayed Matching to Sample (DMS), Pattern Recognition Memory (PRM), Spatial Recognition Memory (SRM) and Paired Associate Learning (PAL) and (b) *spatial* [Spatial Span Task (SSP), and Spatial Working Memory (SWM) memory performance. Pre-morbid general intelligence was assessed using the National Adult Reading Test (NART) (**Nelson, 1982**) **(Supplementary Table 1).**

Data Analysis

Data meeting assumptions of normality and homogeneity of variance were analysed using ANOVA (**Winer *et al.* 1991**). All other data were compared using appropriate non-parametric tests (e.g. Kruskal-Wallis and Mann-Whitney tests). Preliminary analysis of all the experimental and control groups separately indicated that the samples did not come from normally distributed populations with the same standard deviation. A planned (*a priori*) contrasts analysis was, therefore, run to test for significant differences between the four independent study groups. Mann Whitney U tests established that NART, age, morphine equivalent dosage and previous alcohol use all needed to be used as covariates for further analyses.

Mann Whitney U tests were also performed to examine: (a) sociodemographic characteristics for participants in the H group, comparing those who experienced the lowest (n=8) and highest (n=8) scores on the COWS. Similarly, the same test was used to determine if there were differences between the H group of participants who were tested at baseline and those who were followed up and tested in withdrawal and, subsequently, on methadone. (b) sociodemographic characteristics for participants in the MMT group, comparing those tested at baseline (n=29) and those followed up after six months (n=18). (c) sociodemographic characteristics for participants in the H and M groups comparing those with a lifetime subjective history of injecting illicit opioids (n=41) and those with no history of injecting (n=11). A high COWS score was defined as a score between 18-25; a low COWS score was defined as a score 8-14.

The data were first analysed using an omnibus test to determine if significant differences existed between the groups. If the test revealed significance, appropriate pair wise comparisons were performed. In order to control for family wise error, post hoc *Bonferroni* corrected pairwise comparisons was used (**Fields, 2009**). *P* values <0.01 were considered significant. This minimised the effects of multiple comparisons, subgroup analyses and/or repeated measures as we were considering a family of statistical inferences simultaneously (**Sainani, 2009**). Those reported as between $p<0.05$ and $p>0.01$ are presented as non-significant trends when they are considered relevant to substantiate the interpretation of other significant results.

ANCOVA was used to test for group differences with respect to visuospatial memory performance measures. The PRM and SWM outcomes did not meet assumptions of normality and were square root transformed prior to performing the ANCOVA. However, PAL outcomes were $\log_{10}$ transformed prior to performing the ANCOVA. For incremental levels of difficulty within the testing sessions, the *within-subject* factor DIFFICULTY was introduced, (e.g. SWM (between/within search errors), SSP (span length between 1-9), DMS (0, 4 and 12 second delays), and PAL (1, 2, 3, 6, or 8 shapes)). Homogeneity of variance was assessed using the *Mauchly Sphericity Test*. Where data sets significantly (*p<0.05*) violated this requirement, the *Greenhouse Geisser Epsilon* ($\hat{}\varepsilon$) correction parameter for degrees of freedom was used to calculate a more conservative p value for each F ratio.

Further *a priori* subgroup analyses were conducted using (1) a two-group factor reflecting DEPENDENCE status (H and M groups vs P and HC groups) and (2) a two-group factor reflecting INJECTING status (H and M injecting vs. H and M never injecting groups) separately as *between subject factors.* Importantly, we had specific a priori hypotheses about the impact of dependence for

the H and M groups, however we could not draw any particular conclusion about the exposure of the opiate use. In addition, we used DEPENDENCE as a proxy clinical measure of severity without any biological basis.

Similarly, repeated measures ANCOVA was used to evaluate all neuropsychological performance measures between the H group at baseline, in controlled opioid withdrawal and subsequently when stabilised on methadone with presumed *opioid receptor occupancy state* as a *within-subjects factor***.** Similarly, repeated measures ANCOVA was performed for the M group at baseline and at six months follow up with *duration* as a *within-subjects factor.*

All analyses were conducted using SPSS for Windows (v.18, SPSS Inc. Chicago, Ill.).

Results

Demographic characteristics

A description of demographics, drug use and smoking variables for the four groups is presented in **Table 3**. The H and M groups differed from the P and HC groups with respect to several clinical characteristics. Opioid dependent participants started to drink alcohol approximately two years earlier than the other groups**.** The mean morphine equivalent daily dose for the P group was significantly lower (59.1 mg) than the H and M groups (165.9mg) (*p<0.001*).

INSERT TABLE 3 here

When comparing high against low scores for COWS in the H group, there were no differences between age (p=0.88), SIMD score (p=0.75), years in education (p=0.38), years when starting using alcohol (p=0.07), alcohol amount used in last month (p=0.87) or current level of nicotine dependence (Fagerström scores) (p=0.96)

Similarly, there were no group differences identified on these measures when comparing H group tested at baseline and those retested either through the tolerance testing protocol six months later when taking methadone. There were no significant differences with demographic and drug use characteristics between injecting participants (n=43) and non-injecting participants (n=10). However, NART scores were significantly higher *(p<0.01)* in the injecting group.

Visual Memory

Performance on DMS

There was a significant effect on the percentage of correct responses [GROUP F (3,100) =10.3, *p<0.001*]. There were no significant performance differences between groups with respect to the simultaneous matching condition. *Post hoc Bonferroni* comparisons, however, showed participants from the H group made significantly more errors than (a) the HC group at the 0 (*p<0.005*), 4 (*p<0.001*) and 12 second (*p<0.001)* delay stages, (b) the P group for the 4 (*p<0.01)* and 12 (*p<0.005*) second delay stages and (c) the M group for 0 (*p<0.005*), 4 (*p<0.005*) and 12 (*p<0.001*) second delay stages (**Figure 1).** In summary the H group exhibited significant delay-dependent memory impairment when compared with the comparison and control groups.

INSERT FIGURE 1 here

Performance on PRM, SRM and PAL

There were no significant GROUP effects on the number of correct trials [F<1] and mean response latencies [F<1] on the PAL and PRM tests. There was a non-significant GROUP trend on the total number of correct trials [F (3,102) = 3.6, p=0.02] on the SRM only.

Spatial memory

Performance on SSP

There was a significant GROUP [F (3,102) =16.8, *p<0.001*] effect for total errors. *Post hoc Bonferroni* comparisons showed that the participants from the H group significantly made more errors compared to the M (*p<0.001, d=1.25*) and HC (*p<0.005, d=1.14*) groups (**Figure 2).** The total error score for the P group lay between those of the H, M and HC groups and did not differ significantly from any of the other three groups (p=1.0).

There was also a significant GROUP [F (3,101)=3.7, *p<0.01*] effect for span length with *post hoc Bonferroni* comparisons showing the M group was significantly less able to recall successfully the longest sequence compared to HC group (*p<0.01, d-1.17*). The span length for the H (p=.41) and the P (p=.21) groups lay between those of the M and HC groups and did not differ significantly from any of the other groups (**Figure 2)**.

INSERT FIGURE 2 here

Performance on SWM

There was a non-significant GROUP trend for: total mean errors [F(3,102)=3.2, p=0.03] and strategy score [F(3,102)=2.9,p=0.04]

INSERT TABLE 4 here

Chronic opioid dependence or injecting status and visuospatial memory performance

There were no significant effects for either of the factors DEPENDENCE or INJECTING STATUS on any of the DMS, PRM, SRM, and PAL outcome measures.

However, there were significant DEPENDENCE effects for total errors [F (3,104)=6.5, *p<0.01*] on the SWM, but with no significant DEPENDENCE effects on the strategy score [F(1,104)=4.8,p=0.03]. There was a significant DEPENDENCE status and task *difficulty* interaction on the SWM test for total errors [F (3,133.75)=6.2, *p<0.01*]. Analysis using INJECTING status failed to reveal any significant effects or interactions on any SWM outcomes.

There was a significant effect of DEPENDENCE status [F (1,103) = 7.1, *p<0.01*] for span length on the SSP test, but not for total errors [F (1,104)=1.1, p=0.29]. There was no significant effect on INJECTING status on SSP outcomes.

Type of the opioid exposure at different stages of treatment and visuospatial memory performance.

When the H group was tested during different state*s* of opioid exposure (tolerance testing) there was a significant effect of on the DMS mean correct latency [F (2, 34.22)=10.5, *p<0.001*]. *Post hoc Bonferroni* comparisons showed a significant *improvement* at the 12 second delay stage (*p<0.001*) but not the 0 second and 4 second delay conditions. These improvements were noted in comparison with the stable MMT, the 'withdrawal' stage (*p<0.005*) and the illicit heroin stage (*p<0.001*). There was no effect on PRM, SRM, PAL , SSP and SWM outcomes.

There was a trend (p<0.05) for the M group to improve on DMS and SWM outcomes in selecting the right stimulus following prolonged exposure to a stable dose of methadone. There were no significant additional effects on all PRM, SRM, PAL, and SSP outcomes in the M group following prolonged exposure to a stable dose of methadone.

Discussion

This study identified differential effects of chronic heroin and methadone exposures on neuropsychological measures of visuospatial memory that were independent of estimates of addiction severity (injecting behaviour, dependence status). The study also identified an improvement in DMS performance (specifically at longer delays) when the M group were compared to the H group and also when the H group was tolerance tested and then stabilised on methadone.

INSERT TABLE 5 here

Interpretation

Although there are likely commonalities in the ways in which all opioids can affect cognitive performance, much can be learned from considering the distinctive features of each type of opioid and its effect on visuospatial memory. In this study, we have described significant differences in performance between the heroin, methadone and chronic pain groups. The H but not the M group differentially showed impairment in visual memory whereas both the H and M groups showed impairment in spatial memory. Importantly, the performance of the licit opioid exposed group was broadly similar to that of the HC group. However due to the significantly lower dose equivalence in the licit opioid group one needs to cautiously suggest that the impairments in visuospatial memory reported are evoked by chronic exposure to illicit opioids. Participants with potential confounders, such as impaired mood state (**Jollant *et al.* 2007**), non-fatal overdoses, co-morbid personality disorders (**Vassileva *et al.* 2007**) or a co-occurrence of polydrug dependence were excluded from the study. Thus, the impairments in visuospatial memory measures, seen in the participants who are opioid dependent, cannot be caused by these potential confounders.

Heroin users presented with significant delayed memory impairments when compared to either M or P groups using a cross sectional comparison. These impairments diminished with a longer duration of stable methadone. Additionally, within-subject comparisons of participants who had used illicit heroin but had been transferred to a stable dose of methadone for only a few weeks also described a significant improvement in visuospatial impairments when stabilised on methadone. The poor performance of the H group compared to the M group supports previous findings of deficits in learning and memory that may be a function of damage from neurotoxicity to the hippocampal formation in the temporal lobe (**Day *et al.* 2003**) which is structurally altered by drug addictions (**Robbins & Everitt, 2002**) and possibly reversed through administration of opioid replacement therapy such as methadone.

However, since DMS outcome impairment did increase significantly as a function of delay in the heroin group, the results are also suggesting that the impairment might also lie in higher order cognitive executive processes rather than solely as impairment in the memory storage process. Additionally, tasks such as Paired Associates Learning (PAL) are associated with hippocampal function and may be highly sensitive to identify those with memory impairments.

Even though this study did not investigate the cognitive impairments observed in response to different opioids using molecular pharmacological techniques one still needs to be aware that heroin, methadone, codeine and tramadol interact with different μ opioid receptor subtypes exhibiting different activation profiles. This results in subtle pharmacological differences in potency, effectiveness, tolerability and neurotoxicity of the drugs (**Pasternak, 2012**). These opioids also have variable agonist activity at both δ and κ opioid receptors (**Pathan & Williams, 2012**). Furthermore, the active metabolites of heroin and methadone display multimodal subunit-dependent antagonism of 5-HT3 receptors (**Deeb *et al.* 2009**) and methadone, but not heroin, displays N-methyl- D-aspartate (NMDA) receptor antagonist properties (**Davis & Inturrisi, 1999**). The licit opioid users were prescribed either tramadol, codeine or both in much lower morphine equivalent doses. Tramadol, like methadone, is an opioid receptor agonist that, in addition to its MOP effects, also have activity at other non-opioid sites through the modulation of serotonin and norepinephrine reuptake (**Pathan & Williams, 2012**). These cellular and molecular variations might determine different neuropsychological impairments (**Baldacchino *et al.* 2014).**

The different neuropsychological impairments observed in the heroin and methadone cohorts might be linked to other factors that could selectively influence visuospatial processing. Human studies found impaired vigilance and slower reaction times in patients receiving high doses of methadone (**Hepner *et al.* 2002).** This suggests that there might be a trade-off between the intended effects of opioid agonists and the promotion of cognitive abilities. Current results suggest that spatial working memory capacity is intact in opiate-dependent patients when treated with a moderate opioid dose. However, there may be individual patients (e.g., those treated with high opioid doses, using illicit heroin or using non-opioid drugs frequently) that show deficits in spatial working memory. The strict methodology of our study attempted to minimise such effects.

Limitations

This study recruited treatment-seeking males and, thus, results may not generalise to non-treatment seeking, or female, populations (**Ardila *et al.* 2011; McGivern *et al.* 2012**). It is important to appreciate the potential impact social deprivation and ageing may have on the neuropsychological performance in opioid dependence **(Hackman *et al.* 2010).** Studies indicate that negative and stressful events during the early life period can persistently affect brain development and cognitive function such as learning and memory **(Krugers *et al.* 2017; Hanson *et al.* 2015).** Drug use and risk factor histories of participants were, by necessity, based upon self-report, and no blood, hair or saliva samples taken to validate accuracy of the information. Neuropsychological research has shown that consumption of alcohol, benzodiazepines and psychostimulants are potentially important confounding variables (**Koob & Volkow, 2010**). The present study used stringent criteria to exclude regular and dependent users of most psychoactive substances. The exception to this was lack of nicotine use in the healthy controls. We could not control for the effects of this psychostimulant and this may have influenced our results due to its known effects on visuospatial memory **(Richards *et al.* 2003).**This study also conducted urine drug screen analysis to confirm absence of recent amphetamine, opioids, benzodiazepine and cocaine use prior to every session.

Opioid-dependent participants had a mean daily dose of 165 mg morphine equivalent. The P group, however, had a significant lower mean daily dose of 59.1 mg morphine equivalent. Opioids can cause measurable cognitive impairment even at low doses and equi-analgesic doses of different opioids may have nonlinear and non-equivalent adverse cognitive effects (**Gagnon *et al.* 1999**). Opioid drug dose is often the only drug treatment variable that is included in the analyses of correlates of performance in visuospatial memory. **Grevert *et al.* (1977)** reported a statistically significant correlation (0.37) between methadone dose and trials needed for correct visual recognition. However, when more rigorous statistical methods have been used (such as covariance or regression analyses), the relationships between methadone (**Yin *et al.* 2012**; **Prosser *et al.* 2008; Soyka *et al.* 2008; Specka *et al.* 2000)** or buprenorphine **(Lintzeris *et al.* 2006; Loeber *et al.* 2008; Shmygalev *et al.* 2011)** doses and cognitive performance have turned out to be very low and statistically non-significant. In this study we could not repeat cognitive testing in the healthy control and we could not recruit groups with similar socioeconomic status. It would be warranted for future studies as this will give a further confirmation of the cognitive improvement found in this study Finally we want to highlight that there is no literature to compare, if any, dose related cognitive effects between prescribed methadone, tramadol, codeine and/or combinations.

Clinical Interpretation

This study identified opioid specific visuospatial memory impairments that need to be considered within the recovery-oriented treatment programmes for opioid dependent populations (**Ekthiari *et al.* 2017**). The visuospatial memory impairments will have implications for the successful outcomes of current non-pharmacological approaches, such as relapse prevention techniques and motivational enhancement therapies since all these interventions demand intact sophisticated encoding and retrieval strategies, visual processing and inhibition of irrelevant information. These approaches are reported to improve outcomes in individuals with opioid dependence when they are used to complement traditional therapeutic interventions (**Ruiz-Sánchez de León *et al.* 2011; Rezapour *et al.* 2015)**. The aims of these novel clinical interventions are to improve the general cognitive functioning, in particular executive and memory functioning, which the results of this study suggest may be compromised in opioid dependent treatment seeking populations.

Acknowledgements

The authors thank NHS Fife Research and Development Department for assistance with the purchase of the CANTAB system. The authors also acknowledge the following services that helped to identify eligible participants. Fife NHS Addiction Services, Tayside Pain Services, Tayside Arrest Referral Team (NCH), Fife Drug Treatment and Testing Order Team, Frontline Fife, Fife Intensive Rehabilitation Support Team, Fife NHS Clinical Psychology Service and a multitude of General Practitioner Practices and NHS Primary Care Health Centres in the Fife and Tayside areas. Finally, to all individuals who gave up so much of their valuable time to participate in this study with the sole aim of helping in the better understanding of the 'brain' in addiction.

Declaration of Interest

A.B. has received unrestricted educational grants from Schering Plough, Merck Serono, Lundbeck and Indivior. D.J.B. has received research support from Vifor Pharma and a BBSRC Case award in collaboration with MSD and an honorarium from the Society for Research on Nicotine & Tobacco as Editor-in-Chief the Society's research journal, Nicotine & Tobacco Research. K.M. has chaired advisory boards for studies of deep brain stimulation for obsessive compulsive disorder sponsored by Medtronic. He has received educational grants from Cyberonics Inc. and Schering Plough, and he has received research project funding from Merck Serono, Lundbeck and Indivior and also from St Jude Medical for a multicentre clinical trial of deep brain stimulation for depression. He has received travel and accommodation support to attend meetings from Medtronic, St Jude Medical, the Focused Ultrasound Foundation and The Leksell Gamma Knife Society.

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Tables

Table 1: Summary of previous research exploring visuospatial memory profiles in opioid-dependent individuals

Visuospatial memory (sketchpad)	Illicit heroin use and exhibiting opioid dependence	Chronic methadone users in opioid dependent individuals	Chronic buprenorphine users in opioid dependent individuals	Abstinent but previously opioid dependent users	Polydrug misuse but predominantly opioid dependent
Visual memory (visual cache) e.g. colour and shapes	Stevens *et al* (2007)↓ d=0.39 (DMS)	Prosser *et al* (2006)↓ d=0.97 (BVRT) Pirastu *et al* (2006)↓ d=8.26 (BVRT) Lin *et al* (2012) ↓ d=0.60 (WAIS-III) and d= 3.29 (BVRT) McDonald *et al* (2013) ↓d=0.87 (RCFT) Wang *et al* (2014) ↓ d=0.31 (WAIS-III) and d=0.64 (span of visual memory) Yates *et a*l (2009) ↓ d=1.08 (WAIS-III)	Pirastu *et al* (2006)↓ d=1.16 (BVRT)	[1]Prosser *et al* (2006) ↑ d=0.57 (BVRT) [1]McDonald *et al* (2012) ↑ d=0.32 (PAL) Yan *et al* (2013) ↓ d=0.92 (SOPT)	Ersche *et al* (2006 ; 2005) ↓d=0.62 (PRM) ; ↓d=0.8 (PAL) Ornstein *et al* (2000) ↓ d=0.80 (PRM) ; ↓ d=0.89 (PAL) Bach *et al* (2012) ↔ d=0.27 (SWMT)
Spatial memory (inner scribe) e.g. movement sequences		Darke *et al* (2000)↓ d=0.85 (Digit Symbol inWAIS III) McDonald *et al* (2013) ↓ d=0.75 (WAIS-III)			Ornstein *et al* (2000) ↓ d=0.87 (SRM) ↓ d=0.53 (SWM)

*= *Opioid group compared with healthy controls unless otherwise stated*; [1]= *Abstinent group compared with methadone and/or buprenorphine group and NOT healthy controls*

p<0.05; ↔= *no difference in neuropsychological performance*; ↓= *neuropsychological impairment present*; ↑= *improvement in neuropsychological performance when compared to healthy controls*, *d= Cohen's effect size defined as the difference between two means divided by a standard deviation for the data. Standardised effect sizes are reported regardless of the statistical significance (p-value) of the results reported in the original studies*

BVRT= *Benton Visual Retention Test*; RCFT= *Rey Complex Figure Test*; SOPT= *Self-Ordered Pointing Test*; WAIS-III= *Weschler Adult Intelligence Scale- 3rd Edition;* WMSR= *Weschler Memory Scale Revised*; **CANTAB**:DMS= *Delayed Matching to Sample*; PAL= *Paired Associate Learning Task*, PRM= *Pattern Recognition Memory;* SSP=*Spatial Span*

Table 2: Study procedures

Testing Sessions	Illicit or licit opioid use	Opioid withdrawal	2-4 weeks on methadone	6 months on methadone
HEROIN [H]	†	†	†	—
CHRONIC PAIN [P]	†	—	—	—
METHADONE [M]	†	—	—	†
HEALTHY CONTROL [HC]	†	—	—	—

†= *tested;* —= *not tested*

Table 3: Comparative demographic, clinical and substance use data for experimental and control groups

Demographic and clinical data	HEROIN (H)	METHADONE (M)	PAIN (P)	HEALTHY CONTROLS (HC)	Sig.[1]
N	24	29	28	28	n/a
Age (yrs)*	26.30 (3.45)	27.30 (2.34)	33.97 (4.35)	24.12 (3.56)	H >P= *p<0.001* M>P and M>HC = *p<0.01*
SIMD*	3.60(1.9)	3.41 (1.4)	4.60(2.0)	5.90 (2.5)	H >HC and M>HC =*p<0.001* M >P =*p<0.01*
Unemployed (%)	87.50	86.2	50	0	*p<0.001*
Stable accommodation (%)[2]	87	93	100	92.80	M >P =*p<0.005*
Education (yrs) *	10.80(1.5)	10.60 (2.3)	11.18 (1.22)	15.40 (2.1)	H >HC, P>HC and M>HC = *p<0.001*
NART *	106.10 (12.2)	108.90 (7.6)	115.90 (4.9)	118.30 (5.1)	P>H and HC>H= *p<0.001* HC>M = *p<0.001;* P>M= *p<0.01*
Drug, nicotine and alcohol histories (self-report)	HEROIN	METHADONE	PAIN	HEALTHY CONTROLS	Sig.[1] H/M vs P/C
Percentage nicotine smokers	91.67	89.65	39.29	3.57	H>P,H>HC, M>P, M>HC =*p<0.001*
Days of alcohol use (last 30 days) *	2.20(6.1)(n=10)	4.0(4.9) (n=15)	5.10(8.3) (n=17)	4.00(6.3) (n=17)	ns
Type of opioids and number of participants	Heroin n=24	Methadone n=29	Tramadol n= 18 Codeine n=13*[2]	n/a	n/a
Daily intake expressed as morphine equivalence (mg)[o] *	184.50(82.1) (n=24)	147.40 (59.3) (n=29)	59.10(46.8) (n=28)	n/a	H>P and M>P =*p<0.001*
Age first used heroin (yrs) *	19.40 (4.1) (n=24)	17.90(2.6) (n=29)	n/a	n/a	ns
Age opioid dependent (yrs) *	20.90 (3.9) (n=24)	19.90(2.8) (n=29)	n/a	n/a	ns
Age injecting opioids (yrs) *	20.50 (4.0) (n=17)	19.10(6.0) (n=29)	n/a	n/a	ns
Years of opioid use*	6.10 (2.9) (n=24)	8.80(2.8) (n=29)	5.00(2.3) (n=28)	n/a	M>H and M>P= *p<0.001*
Stable methadone use (yrs) *	n/a	1.30(0.5) (n=29)	n/a	n/a	n/a
Days of heroin use (last 30 days) *	29.50(2.7)(n=24)	n/a	n/a	n/a	ns

Sig [1]= significance at p<0.01 two tailed, [2]Stable accommodation = *own house + rented accommodation + living with parents (excluded hostel, student and homeless*),

**=mean total scores (+/- standard deviation),* *[1=] *mean,* *[2]= Some participants prescribed Tramadol were also prescribed Codeine hence total number (31) higher than number recruited (n=28),

n/a =*no data is relevant as the Pain and HC groups did not present with illicit heroin use and/or dependence history*, yrs=*years*, SIMD= *Scottish Index of Multiple Deprivation*, NART= *National Adult Reading Test*, %= *percentage*, ns=*not significant*, N=*Total number in group*, yrs=*years*, n= *number of individuals analysed*, mg=*milligrammes*, *[o]Opioid equivalence: [Viewing et al (2005)].*

Table 4: Summary of baseline neuropsychological findings for memory and learning (not adjusted for covariates).

	HEROIN N=24	METHADONE N=29	CHRONIC PAIN N=28	HEALTHY CONTROL N=28		
Memory and Learning	Mean (s.d)	Mean (s.d)	Mean (s.d)	Mean (s.d)	*Sig*.	*d*
Delayed Matching to Sample (DMS)						
Total Number of Correct Responses (all delays)	22.04 (3.59)	25.76 (2.87)	25.39 (3.04)	27.43 (1.89)	P>H*** C>H***	1.00 1.87
Mean Correct Latency (all delays)	3630.61(922.64)	4372.35 (1579.98)	3310.22(1049.63)	3536.67(745.99)	M>P**	0.79
Paired Associate Learning (PAL) (log10)						
Total Errors (Adjusted)	0.22 (0.45)	0.46 (0.64)	0.01 (0.06)	0.00 (0.00)	NS	
Mean Errors to Success	0.51 (0.26)	0.42 (0.19)	0.45 (0.27)	0.29 (0.19)	C<H*	0.97
Mean Trials to Success	0.45 (0.09)	0.41 (0.06)	0.43 (0.09)	0.37 (0.05)	C<H*	1.10
Memory Score	1.23 (0.11)	1.30 (0.06)	1.27 (0.08)	1.33 (0.06)	C>H***	1.13
Stages Completed	0.94 (0.03)	0.95 (0.02)	0.95 (0.02)	0.95 (0.00)	NS	
Stages complete 1st trial	0.79 (0.08)	0.84 (0.05)	0.82 (0.07)	0.87 (0.04)	C>H***	1.26
Pattern Recognition Memory (PRM) (SQRT)						
Percentage Trials						
Correct	9.18 (0.69)	9.27 (0.51)	9.26 (0.49)	9.64 (0.46)	C>H*	0.78
Incorrect	3.37 (1.97)	3.46 (1.46)	3.43 (1.52)	1.97 (1.74)	C<H* C<M*	0.75 0.92
Correct Response Latency						
Correct	45.82 (5.36)	47.88 (5.98)	46.37 (6.74)	46.60 (5.56)	NS	
Incorrect	49.80 (11.99)	54.48 (11.74)	50.22 (10.76)	50.15 (8.96)	NS	
Spatial Recognition Memory (SRM)						
Number of Trials						
Correct	15.58 (2.21)	16.48 (1.94)	15.89 (1.77)	17.75 (1.51)	C>H***	1.15
Incorrect	4.42 (2.21)	3.52 (1.94)	4.11 (1.77)	2.25 (1.51)	C<M***	1.15
Mean Latency						
Correct	1979.04 (432.81)	2358.89 (810.68)	2035.71 (505.51)	2040.19 (469.3)	NS	
Incorrect	2172 (878.02)	2520.36 (966.13)	2199.65 (737.71)	2456.38 (122.41)	NS	

d= effect size, SQRT= square root transformation; log10 = *logarithmic 10 transformation*, *Sig= significance*,
*= *p<0.01*, **= *p< 0.005*, ***=*p<0.001*, NS= *no significant impairment in neuropsychological outcomes with p<0.01*, H=*HEROIN Group*, P=*CHRONIC PAIN Group*, M= *METHADONE Group*, C=*HEALTHY CONTROL Group*.

Table 5: Summary of results from analysis of visuospatial test outcomes*.Unless specified comparison is with HEALTHY CONTROL and/or PAIN participants[1]

	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE (Non- OD)	INJECTING (INJ) vs non-injecting
(a) Visual Memory			
Delayed Matching to Sample (DMS)			
Total Correct Responses (0,4,12 second delay stages)	↓HEROIN	↔	↔
Pattern Recognition Memory (PRM)			
Total Number of Correct Trials*	↔	↔	↔
Spatial Recognition Memory (SRM)			
Total Number of Correct Trials*	↓HEROIN	↔	↔
Paired Associate Learning (PAL)			
Mean Total Number of Errors*	↔	↔	↔
Memory Score*	↓HEROIN	↔	↔
(b)Spatial Memory			
Spatial Span (SSP)			
Span Length*	↓METHADONE	↓OD > Non- OD	↔
Total Errors*	↓HEROIN	↔	↔
Spatial Working Memory (SWM)			
Total Search Errors*	↓HEROIN,↓METHADONE	↓OD > Non- OD	↔
Between Search Errors*	↓HEROIN,↓ METHADONE	↓OD > Non- OD	↔
Within Search Errors*	↔	↔	↔
Double Search Errors*	↔	↔	↔

*** = ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately; [1]= significant effects with *p<0.01*, ↓=significant neuropsychological impairments present, ↔= no significant neuropsychological impairments present**

Figures

Legend

Figure 1: DMS-Percentage of correct responses at different delay conditions (Means and Standard Deviation). *Post hoc* Bonferroni comparisons identified participants from the HEROIN group significantly making more errors than did: the HEALTHY CONTROL group in the 0 (**$p<0.005$), 4 (***$p<0.001$) and 12 second (***$p<0.001$) delay stages, the CHRONIC PAIN group for the 4 (*$p<0.01$) and 12 (**$p<0.005$) second delay stages and the METHADONE group for 0(**$p< 0.005$), 4 (**$p<0.005$) and 12 (***$p<0.001$) second delay stages.

Sim= *Simultaneous condition*, SD= *Standard Deviation*.

Figure 2:

A- Total errors in Spatial Span (SSP) task (Means and Standard Deviation). Overall participants significantly made more errors [F (3,102) =16.8, $p<0.001$]. *Post hoc* Bonferroni comparisons identified the HEROIN group participants significantly making more errors compared to the METHADONE ($p<0.001$) and HEALTHY CONTROL ($p<0.005$) groups. The total errors for the CHRONIC PAIN participants lay between those of the HEROIN, METHADONE and HEALTHY CONTROL participants and did not differ significantly from these three groups (p=1.0).

B- Span length in the SSP task (Means and Standard Deviation). Overall participants were significantly unable to recall successfully the longest sequence [F(3,101)=3.7,$p<0.01$] with *Post hoc* Bonferroni comparisons identifying the METHADONE group as the group that significantly was less able to recall successfully the longest sequence compared to the HEALTHY CONTROL group ($p<0.01$).