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Neuropsychological functioning and chronic methadone use: a systematic review and meta-analysis.

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Abstract

Introduction: There is a presumption that neurocognition is commonly impaired in chronic methadone exposed individuals (CM) when compared with healthy controls (HP). Additionally, it remains unclear if short term (< 1 year) abstinence (AP) is associated with an altered cognitive profile when compared with CM. **Method:** A random effect model approach was used on data assembled into the Comprehensive Meta-Analysis programme. Cohen's *d* effect sizes and a significance levels of $p<0.01$ were calculated for each domain. **Results**: Data from a total cohort of 1063 CM, 412 AP and 879 HP participants, from 23 independent studies indicate global impairments in neurocognitive function in CM relative to HP participants. The smaller body of evidence comparing CM to AP participants is inconclusive. **Conclusion:** Methodological issues such as small sample sizes, heterogeneity and poor quality limited the interpretation of the results and does not address whether the observed impairments reflect co-morbid functioning, methadone-related sedation and/or other factors. Only higher quality longitudinal studies will permit confident interpretation of the results observed in this meta-analysis.

Keywords: Opioid Dependence; Cognitive Impairments; Methadone; Abstinence; Meta-analysis

Introduction

Replacement prescribing with methadone represents the primary pharmacotherapeutic strategy for the treatment for opioid dependency in the United Kingdom and many other countries. Its use is supported by a largely observationally derived evidence base which suggests that methadone prescription can be helpful in delivering several positive outcomes in treatment-seeking populations (Fullerton et al., 2013; Connock et al., 2007). For example, carefully prescribed and adequately supported methadone prescribing is associated with notable harm reduction outcomes in opioid dependent patients (Scottish Government., 2007; Department of Health., 2007). It is also associated with reduced mortality and improved quality of life (Connock et al., 2007). The duration and dosage of methadone prescription are also thought to be relevant factors in these positive treatment outcomes (Farrell et al., 1994; Van Beusekom & Iguchi., 2001; Faggiano et al., 2007).

There is, however, a widespread and general presumption that neuropsychological performance is commonly impaired in patients treated with methadone, possibly as a direct pharmacological consequence of this treatment (Darke et al., 2000). This possibility is one key justification cited for striving to limit the duration of methadone treatment of opioid dependence (Castle Craig., 2016). Several neuropsychological studies of populations chronically exposed to methadone – typically formerly illicit opiate using and opioid dependent patients - have identified impairments in aspects of executive functioning and memory. These have included specifically impairments in cognitive flexibility (Darke et al., 2000; Pirastu et al., 2006), strategic planning (Ersche et al., 2006; Ornstein et al., 2000) and decision making (Prosser et al., 2006). Other studies, however, have reported no clear impairments when comparing the performance of healthy controls with that of short term

(less than 1 year) abstinent former opiate users or methadone patients (Lombardo et al., 1976; Rotherham- Fuller et al., 2004). Thus, it remains unclear if short term exposure to methadone or subsequent abstinence from methadone is associated with an improved cognitive profile when compared with patients currently in receipt of methadone.
We have recently reported a systematic review and meta-analysis of observational studies of opioid exposure and neurocognitive function which found that chronic opioid exposure was associated with impaired cognitive impulsivity, cognitive flexibility and working memory. The magnitude of effect size across these cognitive domains was, by convention, medium.

In the present review we sought to determine the strength and consistency of reported evidence for neuropsychological impairments in patients exposed to chronic methadone (CM) as part of a MMT programme when compared with (a) opioid naïve / healthy participants (HP) and also with (b) former MMT patients who met the criteria to be described as previously opioid dependent but now abstinent for a period of at least one month (AP) using a quantitative synthesis of the existing primary literature (Wolf., 1986; Borenstein et al., 2009). We used the same methods and range of neuropsychological domains as reported in our previous review and meta-analysis which explored impairments associated with chronic opioid misuse (Baldacchino et al., 2012).

Two broad questions were formulated to guide our analysis. First, does the existing literature provide reliable evidence for neuropsychological impairment in patients exposed to chronic methadone as part of a MMT programme? Second, if present, which neuropsychological domains are implicated when comparing methadone patients with

either (a) opioid naïve / healthy participants (HP) or with (b) former MMT patients who met criteria to be described as previously opioid dependent but now abstinent for a period of at least one month (range 1-12months)?

Method

Inclusion and Exclusion Criteria

Relevant literature was identified and reviewed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2012) and the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009).

For inclusion, studies had to report on participants aged 18 years or older. All treatment-seeking, methadone-exposed participants had to meet DSM-IV criteria for opioid dependence (APA., 1994) of more than six months duration. All studies reporting any experimental or quasi-experimental study methods were included. Also, included studies had to report evidence that objective biochemical measures (e.g. urine samples) were collected from all study participants to confirm either a history of recent opioid intake or to confirm the *absence* of any other illicit drugs throughout the study period (Spitzer & Robins., 1978; APA., 1952; APA., 1987; WHO., 1977; WHO., 1993). Studies were excluded if they either recruited participants who were tested when taking different types of licit and illicit opioids (polydrug use), or were not prescribed methadone. Studies were also excluded if they were conducted in non-substance misuse treatment settings (e.g. chronic pain and psychiatric settings). Moreover, all studies that compared methadone patients to individuals taking buprenorphine and/or where there was co-occurring benzodiazepine, psycho-

stimulant or alcohol dependence, a history of psychosis, post-traumatic stress disorder (PTSD), neurological and neurodevelopmental disorders, borderline or psychopathic personality disorders and/or head injury were also excluded. Additionally, other studies that reported statistical significance of any effects but did not provide actual values permitting effect size calculations were excluded.

Search Strategy

Electronic and hand search methods were employed. The electronic search was performed using the following databases: PUBMED (1975 to 30th Dec 2014), EMBASE (1980 to 30th Jan 2016), Project CORK, PsychINFO (1980 to 30th Jan 2016) and MEDLINE (1975 to 30th Jan 2016). No language constraints were applied. Subject headings included *'chronic and/or repeated drug use/abuse/misuse/dependence/addiction and/or chronic opiate use/abuse/misuse/dependence/addiction and/or methadone/opioid treatment AND neuropsychological deficits/impairments and/or cognitive deficits/impairments'.* The term neurocognitive/neuropsychological was then replaced with a succession of terms describing cognitive domains. These were: *'verbal working memory tests, episodic memory tests, visuospatial working memory tests, verbal fluency tests, executive function tests, digit symbol substitution tests, intelligence, reaction time, attention measures'.* The term neurocognitive/neuropsychological was also subsequently replaced with a succession of terms describing names of a list of cognitive tests and using wild cards.

Three of the authors (AB, AM and KM) independently reviewed all abstracts identified from the electronic search and selected the studies meeting inclusion criteria. A snowballing technique was employed such that the reference list of identified articles was screened for

suitable studies. A hand search of 21 mental health / addiction / psychiatric journals for the years 2004-2016 was completed. These were: *The American Journal of Psychiatry, Archives of General Psychiatry, British Journal of Psychiatry, Journal of Nervous and Mental Disease, Psychiatry Research, Psychological Medicine, Psychopharmacology, Neuropsychology Review, Neuropsychopharmacology, Archives of Clinical Neuropsychology, Experimental and Clinical Psychopharmacology, Journal of Clinical Psychopharmacology, Journal of Psychopharmacology, Neuropsychologia, Human Psychopharmacology, Brain and Cognition, Drug and Alcohol Dependence, Addictive Behaviours, Addiction, European Addiction Research and The Lancet.*

A heuristic (trial and error) method was derived to systematically analyse data across heterogenous research designs. For the present analysis, if more than one control group was reported in a given paper, the most appropriate comparison (i.e. chronic methadone users compared to either healthy controls and/or abstinent groups) was made. If multiple occasions of testing were reported in a given study, such as to address practice effects or as a follow up study, only the data derived from the first assessment was used.

Data Analysis and Study Detail

Standard meta-analytic techniques were employed for this review (Cooper & Hodges., 1984; Rosenthal., 1995). Magnitude was indexed with the effect size *d* to reflect the degree to which the dependent variable was present in the sample group or the degree to which the null hypothesis was false (Cohen., 1988). In mathematical terms *d* was the difference between two group means standardised via pooled standard deviation units. Effect sizes (i.e. Cohen's *d* statistics) were calculated for each neuropsychological test and then adjusted

for sampling bias (Hunter & Schmidt., 1990). A value above 0.80 was considered as a large effect, with less than 0.50 as a small effect and 0.50-0.79 as intermediate (Cohen., 1992; Hedges & Olkin., 1985). Formulae were appropriately adjusted so that all derived statistics informally represented the same direction; that is the same polarity of performance when comparing groups. Negative scores in this review always represented impaired performance on the part of the chronic opiate user group. A significance level of $p<0.01$ (two tailed) was used.

All relevant test variables were coded into one of seven neuropsychological domains listed under five headings (Ersche & Sahakian., 2007);

1. Impulsivity was divided into 3 domains of Cognitive, Motor and Non-Planning Impulsivity (Ersche & Sahakian., 2007; Baumeister & Scher.,1988; Cooper et al., 2003; Kirby et al., 1999; Owen., 1997)
2. Cognitive Flexibility (Reynolds et al., 2006)
3. Attention and Information Processing
4. Short Term Memory (Grattan & Eslinger., 1989; Baddeley & Logie., 1999)
5. Longer Term Memory

In keeping with recommendations on meta-analytical research in neuropsychology, previous factor-analyses of cognitive measures in addictions informed the placement of each measure into the aforementioned domains (Passolunghi & Mammarella., 2010; Goldstein et al., 2004). This approach provided an objective alternative to the arbitrary grouping of neuropsychological variables on the basis of face validity or other weak and unconfirmed notions (Bates et al., 2002). Unfortunately, the factor-analytical studies to date do not encompass all of the neuropsychological measures that were encountered in this

comprehensive systematic review. As a result we also relied on the classification used by the authors of a given study (Demakis., 2006).

INSERT TABLES 1 & 2: Neuropsychological domains

Tests for the presence and degree of heterogeneity were conducted using the Q statistic (Hedges & Olkin., 1992) and I^2 index (Ersche et al., 2005) respectively. A value of 0% to the I^2 index indicated no observed heterogeneity, whereas as value of 75% or above indicated high heterogeneity**.** However, quantification of heterogeneity was only one component of a wider investigation of variability across studies; the most important of these were diversity in clinical and methodological domains and the observed degree of inconsistency across studies with regards to the direction of effects (Huedo-Medina et al., 2006). As different scales were sometimes used by different studies, Standardised Mean Difference (SMD) effect-size estimates were routinely calculated. Random effects models were applied (Higgins et al., 2003; Hedges & Verea., 1998).

Eligible research studies comprising a common dependent variable, as well as test statistics that could be transformed into effect sizes, were systematically sampled and surveyed. Individual study results (typically means and standard deviations from each group) and relevant moderator variables considered as relevant by previous reviews (chronicity of opioid use, dosage of methadone, quality of the study, period of abstinence, Intelligence Quotient (IQ), age and educational status of the populations studied) were employed as moderators during this review.

For continuous moderator variables (dosage of methadone, chronicity of opioid use, period of abstinence less or equal to one year duration, age, IQ, and educational status) we attempted to conduct a meta-regression to test whether there were significant relationships between each of these moderators and the effect size. Meta-regression was only conducted in neuropsychological domains in which more than 10 studies were available.

The risk of publication bias was assessed informally by visual inspection of funnel plots and formally by its statistical analogue, Fail Safe N, according to Orwin (1983).
The data were abstracted, quantified, coded and assembled into a database run by Comprehensive Meta-Analysis Version 2 (CMA., Bio-Englewood, New Jersey, US).

Assessment of Study Quality

All data were extracted by two reviewers (AB and MA) and checked by another two reviewers (KM and GH). Discrepancies were resolved by referral to the original studies. If necessary, arbitration was conducted by a third reviewer (DB). Duplicate publications were actively screened for and, when retrieved, the latest and most complete data set was used. The Effective Public Health Practice Project (EPHPP) quality assessment checklist was also used (Armijo-Olivo et al., 2012).

Results

Studies Selected and Populations Studied

Electronic and hand searching yielded 1348 references. In total, 303 articles were retrieved for further assessment following the exclusion of non-relevant or ineligible studies. There were 176 studies that compared current chronic methadone exposed patients (CM) with

either abstinent individuals (AP) and/or healthy participants (HP). From these studies, a further 152 were excluded because, on detailed inspection, they did not satisfy the inclusion criteria (e.g. included polydrug users, no data presented, did not attend substance misuse services, no healthy or abstinent comparators, etc.) (**Figure 1).**

INSERT FIGURE 1

Of the 28 articles identified, 21 compared chronic methadone (CM) exposed patients with healthy and non-substance using individuals (HP) and 7 studies compared chronic methadone (CM) patients with short term abstinent, but previously opioid-dependent individuals (AP). Overall, there were 23 independent studies (Darke et al., 2000; Pirastu et al., 2006; Ersche et al., 2006., Ornstein et al., 2000; Prosser et al., 2006; Rotherham-Fuller et al., 2004; Ersche et al., 2005; Schindler et al., 2004; Mintzer et al., 2005; Soyka et al., 2008; Yates., 2009; Fadardi & Ziaee., 2010; Yin et al., 2012; Lin et al., 2012; McDonald et al., 2012; Anderson et al., 2013; Liao et al., 2014; Baldacchino et al., 2014; Clark et al., 2006; Gupta et al., 2014; Wang et al., 2014; Gritz et al, 1975; Davis et al., 2002) and from these, 5 studies used both healthy and abstinent groups as comparators to a methadone cohort (Prosser et al., 2006; Schindler et al., 2004; Lin et al., 2012; Anderson et al., 2013; Tolomeo et al, 2016). All studies reported from urban settings. Two studies (Mintzer et al., 2005; McDonald et al., 2012) were longitudinal in design, with the remainder (21 studies) being cross sectional, observational studies. In terms of quality assessment, two recent studies were appraised as strong (Liao et al., 2014; Tolomeo et al, 2016), 19 studies appraised as moderate and two studies appraised as weak (Wang et al., 2014; Gritz et al., 1975).

Chronic Methadone (CM) and Healthy Participant (HP) Comparisons

Twenty one studies described a total number of 884 CM compared with 879 HP participants. The mean age for the CM group was 36.9 years compared to 32.9 years for the HP group. Mean duration of opioid use was 10.3 years with a mean duration of methadone exposure of 3.2 years (n=18) in the CM group. The mean daily methadone dose was 61.1 mg (n=20). One study (Gupta et al., 2014) did not record daily methadone dose **(Table 3a).**

Chronic Methadone (CM) and Abstinent Participant (AP) Comparisons

Seven studies described a total number of 279 CM compared with 412 AP participants. The mean age for the CM group was 35.6 years compared to 35.1 years for the AP group. Mean duration of opioid use for the CM group was 14.1 years compared to 11.2 years for the AP group. The mean daily methadone dose was 61.8 mg, with an overall mean period of abstinence of 0.5 years (6 months) **(Table 3b).**

INSERT TABLES 3a & 3b: Specific characteristics of selected studies.

Pooled Effect Sizes

There were 14 effect size estimations possible from the selected studies. Analysis of homogeneity (Q and I^2) within each neuropsychological domain tested, revealed that the assumption of homogeneity could not be met. Therefore, a random effects model was applied for all analyses

(1) Chronic Methadone (CM) Exposure and Healthy Participant (HP) Comparisons **(Table 4a).** For cognitive impulsivity data derived from a total of 7 studies, including 214 CM and 185 HP participants were pooled to reveal an effect size of 0.89 in favour of the HP participants being less impulsive (Z = 2.8, *p<0.006*) (**Figure 2).** For motor impulsivity a total of 9 studies, including 490 CM and 448 HP participants , were pooled to reveal an effect size of 0.41, again in favour of superior performance (less impulsivity) in the HP (Z = 4.5, *p<0.001*) (**Figure 3).** For non-planning impulsivity a total of 7 studies, including 293 CM and 230 HP participants, were pooled to reveal an effect size of 1.38 in favour of a superior performance (less impulsive) in the HP group (Z = 3.1, *p<0.002*) (**Figure 4).** For cognitive flexibility a total of 12 studies, including 557 CM and 532 HP participants, were pooled to reveal an effect size of 0.464 in favour of a superior performance (greater flexibility) in the HP group (Z = 6.4, *p<0.001*) (**Figure 5).**For measures of attention a total of 8 studies, including 467 CM and 418 HP participants, were pooled to reveal an effect size of 0.71 in favour of a superior performance in the HP group (Z = 3.5, *p<0.001*) (**Figure 6).** For short term memory a total of 12 studies, including 556 CM and 524 HP participants, were pooled to reveal an effect size of 0.67 in favour of a superior performance in the HP group (Z = 5.8, *p<0.001*) (**Figure 7).** For longer term memory a total of 9 studies, including 481 CM and 449 HP participants , were pooled to reveal an effect size of 0.68 in favour of superior performance in the HP group (Z = 3.4, *p<0.001*) (**Figure 8).**

INSERT FIGURES 2-8: **Forest Plots**

INSERT TABLE 4a: Pooled effect sizes for individual neuropsychological domains in chronic methadone exposed (CM) patients compared to opioid naïve healthy participants (HP)

(2) Chronic Methadone (CM) and Short Term Abstinent Participant (AP) Comparisons (**Table 4b**).

For cognitive impulsivity only 2 studies were available for analysis and included 66 CM and 48 AP participants. A non-significant pooled effect size estimate of 0.34 in favour of superior performance in the AP group (Z = 1.7, p=0.08) was found. Supplementary material is available to the reader online **(SFigure1).** For motor impulsivity a total of 3 studies, including 112 CM and 311 AP participants, were pooled to reveal an estimated effect size of 0.14 (non-significant) in favour of a superior performance in the AP group (Z = 1.2, p=0.21). Supplementary material is available to the reader online **(SFigure2).** For non-planning impulsivity 2 studies, including 142 CM and 78 AP participants, were pooled to reveal an effect size of 0.75 (non-significant) in favour of the AP group (Z =1.3, p=0.21)**.** Supplementary material is available to the reader online **(SFigure3**). For cognitive flexibility a total of 5 studies, including 240 CM and 378 AP participants were pooled to reveal an effect size of 1.12 (non-significant) in favour of AP (Z = 2.6, p=0.01) (**Figure 9)**.For measures of attention a total of 4 studies, including 137 CM and 96 AP participants , were pooled to reveal an effect size of 0.70 (non-significant) in favour of AP (Z =2.4, p=0.01) (**Figure 10).** For short term memory a total of 5 studies, including 166 CM and 123 AP participants were pooled to reveal an effect size of 0.38 in favour of AP (Z = 2.8, *p<0.01*) (**Figure 11).** For long term memory a total of 4 studies, including 137 CM and 96 AP participants, were pooled to

reveal an effect size of 0.35 in favour of AP (Z = 2.0, p=0.04) (**Figure 12).** This effect size was deemed non-significant using the criteria outlined in the methods section.

INSERT FIGURES 9-12: **Forest Plots**

TABLE 4b: Pooled effect sizes of individual neuropsychological domains between methadone exposed (CM) patients compared to the former MMT, but abstinent (AP) at time of testing group

Subgroup Analysis: Meta-Regression

There were not enough studies to report significant relationships between continuous moderator variables (dosage of methadone, chronicity of opioid use, period of abstinence less or equal to one year duration, age, IQ, and educational status) and most neuropsychological domains in both CM and AP groups to justify utilising meta-regression methodology. We were limited in reporting the Z value and associated *p* value in cognitive flexibility and short term memory domains for one continuous moderator (age) from the studies comparing CM with HP participants. It identified a non-significant effect in cognitive flexibility (Slope Z= -0.102, *p*=0.92) and short term memory (Slope Z= -0.741, *p*=0.46) (**Tables 5a and 5b**) with older CM participants exhibiting greater cognitive impairment when compared with their younger peers.

INSERT TABLES 5a and 5b: Subgroup Analysis: Meta-Regression of chronic methadone exposed patients by age with respect to (a) Cognitive Flexibility and (b) Short Term Memory.

Discussion

Key Findings

In this quantitative review of the literature of neuropsychological functioning and chronic methadone exposure, our meta-analysis suggests that that a broad range of functional domains appear to be impaired in methadone-exposed populations compared with opioid naïve, healthy controls. There was also some inconclusive evidence that the impairments exhibited by the CM participants were greater than those exhibited by those in the AP group. . This stands in contrast to the differential patterns of impairment observed in an earlier, comparable, meta-analysis which explored the neuropsychological consequences of chronic opioid use (Baldacchino et al., 2012) where the only cognitive domains with evidence of impairment were those of verbal working memory, cognitive impulsivity and cognitive flexibility. There are several potential explanations for this discrepancy that include ascertainment and sampling bias, the heterogenous nature of different opioids in their cellular and molecular effects resulting in subtle pharmacological differences in activity, potency, effectiveness, tolerability, neurotoxicity and neuropsychological impairments (Baldacchino et al., 2014).

The available data, although purely cross sectional in nature, also suggest that these impairments may largely be detectable for, at least, the first year of abstinence. The only

neuropsychological domain within which there was no clear and consistent evidence of comparable impairment within the abstinent participants was that of short term memory. It is possible that abstinence may be associated with amelioration of the deficits observed in the CM participants. However, this apparent difference could also be explained by simple sampling and ascertainment bias. The present data cannot attest to whether or not opioid associated impairments recover after longer periods of abstinence (Holst & Schilt., 2011).

Strengths and Limitations

To minimise the potential confounding effects of other influences upon neuropsychological performance in study populations, we applied strict inclusion criteria. Specifically, we wished to minimise the potential impact of co-morbid non-opioid substance use and abuse, particularly alcohol. However, within such a meta-analysis, it is not possible to develop high levels of confidence that any selection criteria will remove the potential cumulative neuropsychological effects of a lifelong career of using different types of drugs and/or neuropsychological or neuropsychiatric precursors that might have predisposed the studied populations to substance misuse. Only high quality longitudinal studies can address this question.

Methodological problems within the primary studies limit the interpretation of the results from this meta-analysis. For example, Tables 3a and 3b clearly describe very heterogenous study populations. Inevitably, study recruitment processes create a selection bias towards the 'treatment seeking' and more highly motivated individuals within substance misuse treatment populations (Ersche et al., 2006) and those with the greatest cognitive

impairments may be less likely to be included in any studies. As such, the magnitude of any effects associated with MMT may be an underestimate. With uncontrolled, opportunistic sampling in populations generating small individual study sample sizes, this will inevitably limit the representativeness and sensitivity of the data generated. Uniformity of group selection becomes relevant if one needs to analyse further significant correlations between residual neuropsychological effects and lifelong and current conditions (Baldacchino et al., 2012). Studies included in this meta-analysis provided relevant information on past medical, neurological and psychiatric history, including history of head trauma, but did not provide other potentially critical information such as neurodevelopmental history and information on prior episodes of non-fatal overdose.

There is uncertainty whether any pattern of impairments associated with concurrent methadone treatment might be caused by the drug itself, or whether these may have been pre-existing impairments that may also contribute to vulnerability to opioid abuse. Dissociating pre-existing impairments from pharmacologically induced changes requires a particular experimental design and such studies were not identified in this systematic review. Similarly, although a comparison of concurrent methadone treated patients with former patients who were abstinent at time of testing has the potential to differentiate direct pharmacologically-associated effects with non-pharmacological ones, this remains a weak method for addressing these questions. A meta-regression could, in theory, have established the extent to which moderators (such as methadone dosage, years of schooling, length of opioid dependence) could have influenced the results. Unfortunately, there were insufficient numbers of studies to reliably perform such comprehensive analyses. This would

only be possible if more studies record detailed information of these continuous moderator variables.

Interpretation of the cognitive impairments in the methadone treated population need to take into consideration the any acute sedative effects of the drug which may exaggerate the global impairments observed when this group are compared with healthy controls (Battistella et al., 2012; Franken et al., 2003). Curran et al (2001)**,** for example, found that a single dose of methadone could induce episodic memory impairments on a task of delayed prose recall, although attention and comprehension were not affected. Methadone can also magnify the effects of sedatives and tranquilizers (Ghoneim., 2004). Since the abstinent group exhibited similar impairments in cognitive impulsivity and flexibility to those seen in the methadone group it would seem reasonable to suggest that the sedative effects of the drug do not play a significant part in the cognitive profile of methadone users. However this meta-analysis did not compare abstinent groups with healthy controls due to the absence of relevant data. This limits our understanding of any effects that sedation especially methadone dosages has on cognitive impairment. Future neurocognitive studies on should also preferably test participants during the first two hours after ingestion of methadone before serum methadone levels peak (Dyer et al., 1999; Mitchell et al., 2003; Ekblom et al., 1993).

In summary, the data presented in this analysis are based on a few cross sectional studies of mixed methodological quality. Therefore, among the features that must be considered in future studies in order to improve the methodological rigour and to maximise interpretation of the research in this field include:

1. Conducting well controlled high quality longitudinal studies of adequate sample size
2. Conducting serial analyses of drug metabolites or utilising newer technology such as a hair analysis which have been shown to provide more definitive information about patterns of use
3. Using ecologically validated neuropsychological tests
4. Recording detailed information on continuous moderator variables such as dosage of methadone, chronicity of opioid use, period of abstinence less or equal to one year duration, age, IQ, and educational status
5. Using latent variable analytic techniques that are designed to examine average effects and individual differences in tandem

Clinical Relevance

Bezeau & Graves, (2001) considered that, to assume the clinical usefulness of the study, it would be necessary for both populations (in this case, methadone users and controls) to be separated by at least 0.80 typical deviations in the variable measured (Bezeau & Graves., 2001). The only effect sizes that exceeded 0.8 were cognitive and non-planning impulsivity when compared between chronic methadone users and healthy controls. The authors, however, feel justified in proposing that the neuropsychological impairments observed in this meta-analysis, although statistically significant, are still inconclusive for clinicians to justify changing current practice with regard to methadone treatment for opioid dependence.

Conclusion

Available data support the contention that there is broad neuropsychological impairment, across many domains, in patients receiving MMT when compared with opioid naïve, healthy controls. It is unclear, however, if this is related to opioid dependence, methadone exposure or a global sedative effect on performance. Additionally, there is indicative evidence of comparable impairment in short term abstinent, former methadone treated patients. However, the number of studies available for analysis was small, limiting the capacity for sensitive analyses and diminishing confidence in the representativeness and robustness of the results generated. It remains unclear if the impairments noted in MMT populations persist into periods of abstinence and further studies will be required to determine this. Prospective evaluation of neuropsychological functioning in well-designed longitudinal studies will be required to determine whether neuropsychological impairments are attributable to biological vulnerability, physical and mental co-morbidities, non-specific aspects of drug misuse, exposure to opioid drugs or to non-specific sedative effects.

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Declaration of Interests

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Figures.

Figure 1: Neuropsychological Consequences of Chronic Methadone Use: Quality of reporting of meta-analysis (QUOROM): 1975-2016

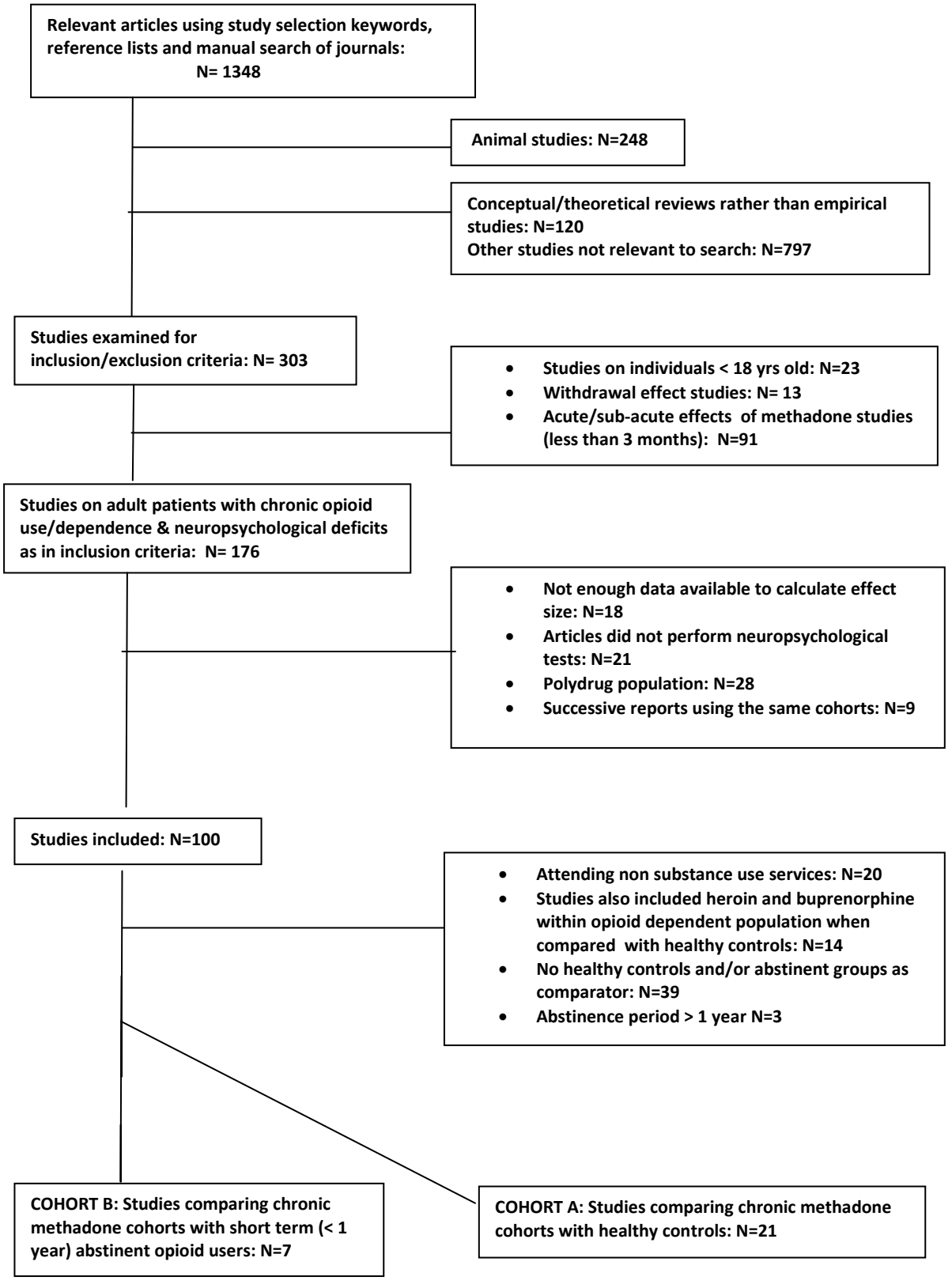


Figure 2

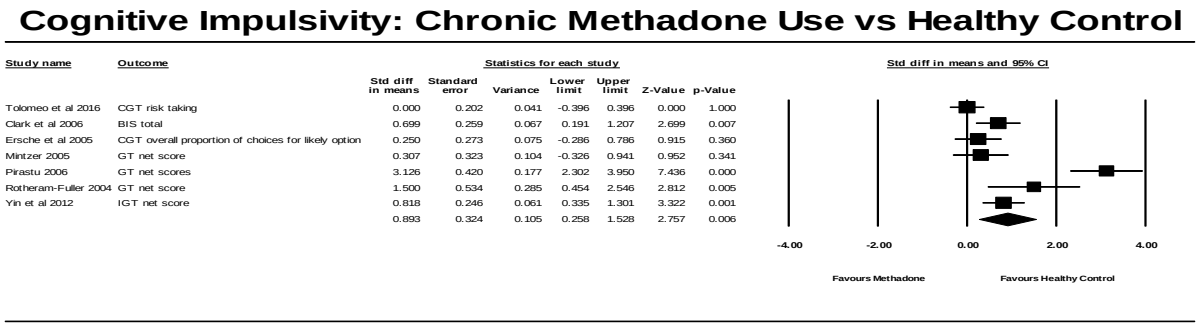

Cognitive Impulsivity: Chronic Methadone Use vs Healthy Control
Study name
Outcome
Statistics for each study
Std diff in means
Standard error
Variance
Lower limit
Upper limit
Z-Value
p-Value
Tolomeo et al 2016 CGT risk taking 0.000 0.202 0.041 -0.396 0.396 0.000 1.000
Clark et al 2006 BIS total 0.699 0.259 0.067 0.191 1.207 2.699 0.007
Ersche et al 2005 CGT overall proportion of choices for likely option 0.250 0.273 0.075 -0.286 0.786 0.915 0.360
Mintzer 2005 GT net score 0.307 0.323 0.104 -0.326 0.941 0.952 0.341
Pirastu 2006 GT net scores 3.126 0.420 0.177 2.302 3.950 7.436 0.000
Rotheram-Fuller 2004 GT net score 1.500 0.534 0.285 0.454 2.546 2.812 0.005
Yin et al 2012 IGT net score 0.818 0.246 0.061 0.335 1.301 3.322 0.001
0.893 0.324 0.105 0.258 1.528 2.757 0.006
Std diff in means and 95% CI
-4.00
-2.00
0.00
2.00
4.00
Favours Methadone
Favours Healthy Control

Figure 3

Motor Impulsivity: Chronic Methadone Use vs Healthy Controls

Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baldacchino et al 201	AGN total commission errors	0.720	0.273	0.075	0.185	1.256	2.635	0.008
Clark et al 2006	BIS motor	0.243	0.253	0.064	-0.252	0.739	0.962	0.336
Fadardi et al 2010	ST interference score	0.701	0.187	0.035	0.335	1.067	3.750	0.000
Gupta et al 2014	ST interference score	0.403	0.102	0.010	0.203	0.602	3.951	0.000
Liao et al 2014	SSRT post errors slowing	0.034	0.138	0.019	-0.237	0.306	0.246	0.805
Mintzer et al 2005	ST correct responses	0.235	0.322	0.104	-0.396	0.867	0.730	0.465
Prosser et al 2006	ST interference score	0.655	0.270	0.073	0.127	1.183	2.430	0.015
Wang et al 2014	ST interference colour %	0.727	0.275	0.076	0.187	1.266	2.638	0.008
Yates et al 2009	ST interference score	0.265	0.237	0.056	-0.200	0.729	1.116	0.264
		0.412	0.091	0.008	0.232	0.591	4.501	0.000

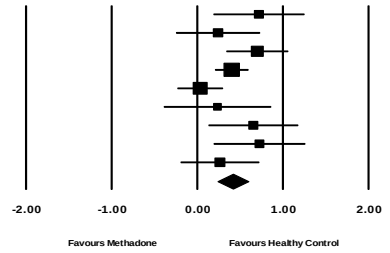


Figure 4

Non Planning Impulsivity: Chronic Methadone Use vs Healthy Control

Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Tolomeo et al 2016	SOC (5 move)	4.667	0.390	0.152	3.903	5.431	11.972	0.000
Clark et al 2006	BIS non planning	1.132	0.270	0.073	0.602	1.662	4.184	0.000
Darke et al 2000	ROCFT copy	0.666	0.265	0.070	0.147	1.186	2.512	0.012
Ersche et al 2006	TOL (4-6 moves)	0.641	0.279	0.078	0.094	1.187	2.295	0.022
McDonald et al 2012	ROCFT copy	0.476	0.177	0.031	0.129	0.824	2.687	0.007
Ornstein et al 2000	TOL % correct	1.179	0.327	0.107	0.538	1.819	3.608	0.000
Wang et al 2014	AM trial completed	0.624	0.273	0.075	0.088	1.159	2.283	0.022
		1.308	0.421	0.177	0.483	2.134	3.106	0.002

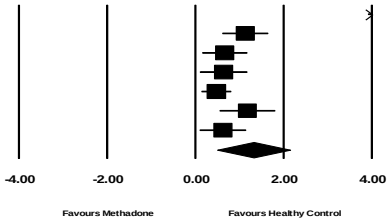


Figure 5

Cognitive Flexibility: Chronic Methadone Use vs Healthy Control

Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Tolomeo et al 2016	IED EDS errors	0.769	0.209	0.044	0.359	1.180	3.673	0.000
Darke et al 2000	COWAT total	0.571	0.263	0.069	0.055	1.087	2.168	0.030
Ersche et al 2006	IED EDS mean errors	0.228	0.273	0.075	-0.307	0.764	0.836	0.403
Gupta et al 2014	CLFT total correct	0.229	0.101	0.010	0.031	0.427	2.263	0.024
McDonald et al 2012	COWAT total	0.404	0.177	0.031	0.058	0.751	2.289	0.022
Mintzer et al 2005	TMT - B total time	0.833	0.335	0.112	0.176	1.489	2.487	0.013
Ornstein et al 2000	IED perseveration	0.430	0.305	0.093	-0.168	1.027	1.408	0.159
Prosser et al 2006	COWAT total	0.750	0.272	0.074	0.218	1.283	2.762	0.006
Rotterham-Fuller et al 2006	WCST perseveration errors	0.104	0.472	0.223	-0.820	1.029	0.221	0.825
Soyka et al 2008	TMT-B	0.740	0.298	0.089	0.155	1.325	2.479	0.013
Wang et al 2014	COWAT word generation	0.336	0.269	0.072	-0.191	0.863	1.251	0.211
Yates et al 2009	WCST perseverative errors	0.651	0.242	0.059	0.177	1.125	2.691	0.007
		0.458	0.071	0.005	0.318	0.599	6.412	0.000

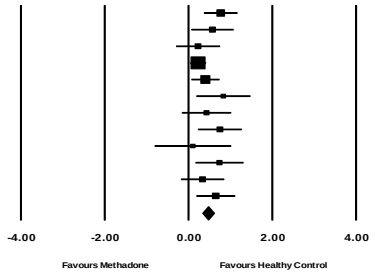


Figure 6

Attention: Chronic Methadone Use vs Healthy Controls

Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Mntzer et al 2005	WAIS Digit Symbol	0.985	0.340	0.116	0.318	1.651	2.896	0.004
Wang et al 2014	TOVA	0.194	0.268	0.072	-0.331	0.718	0.723	0.469
Lin et al 2012	WAIS Digit Symbol	1.108	0.305	0.093	0.511	1.705	3.638	0.000
Darke et al 2000	WAIS Digit Symbol	1.425	0.289	0.084	0.858	1.991	4.928	0.000
Gupta et al 2014	WAIS Digit Symbol	0.044	0.101	0.010	-0.154	0.241	0.432	0.665
Yates et al 2009	TMT-A	0.360	0.238	0.057	-0.106	0.826	1.513	0.130
Soyka et al 2008	TMT-A	0.757	0.299	0.089	0.171	1.342	2.532	0.011
McDonald et al 2012	WAIS Digit Symbol	1.034	0.185	0.034	0.671	1.397	5.579	0.000
		0.713	0.206	0.043	0.308	1.118	3.454	0.001

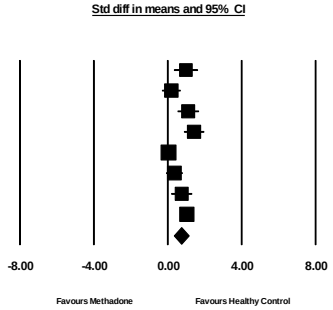


Figure 7

Short Term Memory: Chronic Methadone Use vs Healthy Control

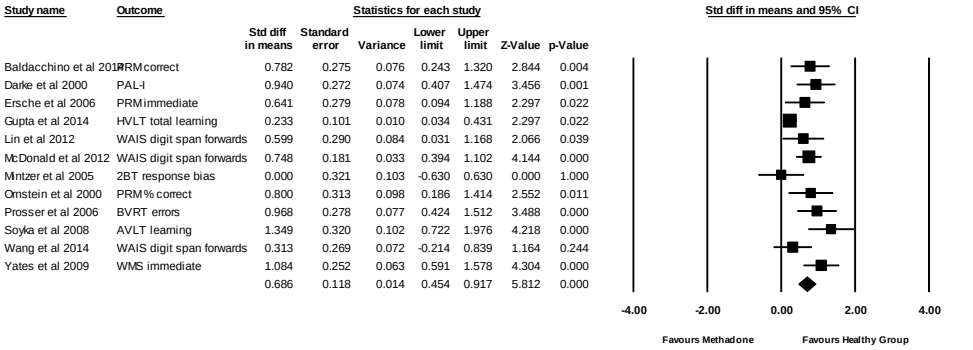


Figure 8

LongTerm Memory: Chronic Methadone Use vs Healthy Controls

Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baldacchino et al 2014	DMS total number of correct responses	1.869	0.318	0.101	1.247	2.492	5.886	0.000
Darke et al 2000	PAL-II	1.546	0.294	0.087	0.969	2.123	5.254	0.000
Ersche et al 2006	PRM delayed	0.076	0.272	0.074	-0.457	0.610	0.280	0.780
Gupta et al 2014	HVLT delayed	0.146	0.101	0.010	-0.052	0.344	1.448	0.148
Lin et al 2012	Remote Life Events	0.442	0.287	0.082	-0.121	1.005	1.539	0.124
McDonald et al 2012	PAL-II	0.678	0.180	0.032	0.326	1.030	3.775	0.000
Mintzer et al 2005	Word Memory Recognition response bias	0.195	0.322	0.104	-0.436	0.826	0.607	0.544
Wang et al 2014	RAVLT long delay	0.158	0.267	0.071	-0.366	0.681	0.589	0.556
Yates et al 2009	WMS delayed	1.140	0.254	0.064	0.643	1.637	4.495	0.000
		0.676	0.201	0.040	0.282	1.069	3.368	0.001

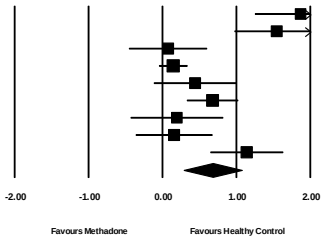


Figure 9

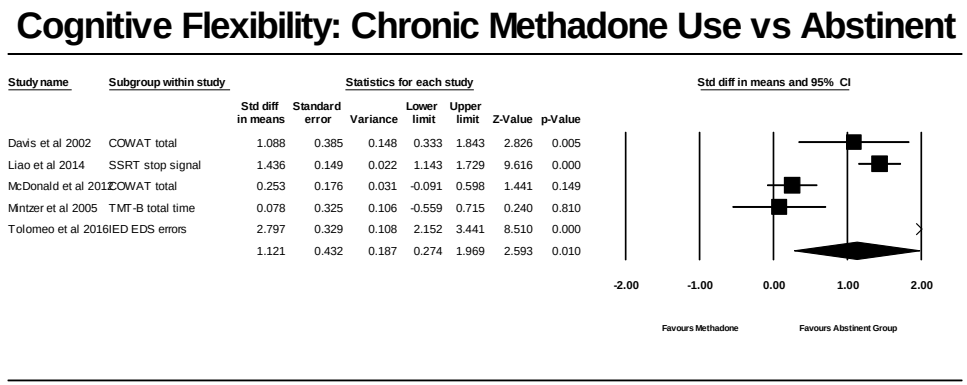

Cognitive Flexibility: Chronic Methadone Use vs Abstinent
Study name
Subgroup within study
Statistics for each study
Std diff in means
Standard error
Variance
Lower limit
Upper limit
Z-Value
p-Value
Std diff in means and 95% CI
Davis et al 2002 COWAT total 1.088 0.385 0.148 0.333 1.843 2.826 0.005
Liao et al 2014 SSRT stop signal 1.436 0.149 0.022 1.143 1.729 9.616 0.000
McDonald et al 2012 COWAT total 0.253 0.176 0.031 -0.091 0.598 1.441 0.149
Mintzer et al 2005 TMT-B total time 0.078 0.325 0.106 -0.559 0.715 0.240 0.810
Tolomeo et al 2016 IED EDS errors 2.797 0.329 0.108 2.152 3.441 8.510 0.000
1.121 0.432 0.187 0.274 1.969 2.593 0.010
-2.00
-1.00
0.00
1.00
2.00
Favours Methadone
Favours Abstinent Group

Figure 10

Attention: Chronic Methadone Use vs Abstinent

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Davis et al 2002	TEA accuracy	0.346	0.362	0.131	-0.363	1.056	0.956	0.339
Gritz et al 1975	SRRT	2.208	0.567	0.322	1.096	3.320	3.892	0.000
McDonald et al 2012	WAIS digit symbol	0.414	0.177	0.031	0.067	0.760	2.341	0.019
Mintzer et al 2005	WIAS digit symbol	0.495	0.330	0.109	-0.152	1.141	1.501	0.133
		0.701	0.292	0.085	0.128	1.274	2.399	0.016

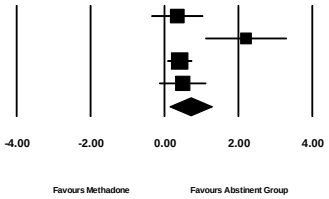


Figure 11

Short Term Memory Chronic Methadone Use vs Abstinent

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Davis et al 2002	AMPB immediate story recall	0.248	0.361	0.130	-0.459	0.955	0.688	0.492
Gritz et al 1975	VLT	1.163	0.484	0.234	0.215	2.110	2.405	0.016
McDonald et al 2012	PAL-I	0.322	0.176	0.031	-0.023	0.667	1.829	0.067
Mintzer et al 2005	2BT response bias	0.024	0.325	0.106	-0.613	0.661	0.073	0.942
Prosser et al 2006	BVRT errors	0.570	0.273	0.074	0.035	1.104	2.088	0.037
		0.381	0.135	0.018	0.116	0.646	2.818	0.005

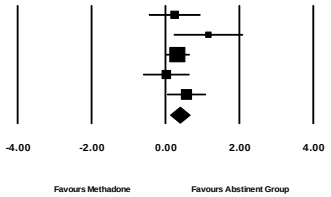
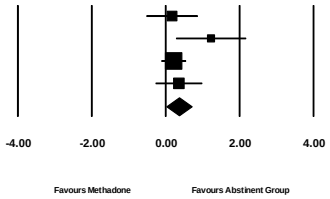


Figure 12

LongTerm Memory: Chronic Methadone Use vs Abstinent

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Davis et al 2002	AMIPB delayed story recall	0.173	0.360	0.130	-0.533	0.878	0.480	0.631
Gritz et al 1975	WPAT total	1.228	0.488	0.238	0.272	2.183	2.519	0.012
McDonald et al 2012	PAL-II	0.216	0.175	0.031	-0.128	0.560	1.229	0.219
Mintzer et al 2005	Word Memory response bias	0.357	0.327	0.107	-0.285	0.999	1.091	0.275
		0.352	0.174	0.030	0.011	0.694	2.022	0.043



Tables

Table 1: Executive Functions

Domain	Subtypes	Other names	Definition	Tests
IMPULSIVITY	**Cognitive Impulsivity**	Delay discounting or urgency	Ability to opt for larger delayed rewards over smaller more immediate rewards	
	Reflection Impulsivity		Decision-making under ambiguity	IGT, MFFT, BIS, DDT, IST
	Risk taking		Decision-making under risk	CGT, IGT, RDMT, GDT
	Non-planning Impulsivity	Reasoning, Strategic Planning and Problem Solving, Lack of pre-meditation	Ability to think ahead and actively search for an appropriate solution.	TOL, SOC, ROCFT, PMT, TOH WAIS –R/III (Block Design, Matrix Reasoning), SSP, AM, BADS
	Motor Impulsivity	Inhibitory Control	Ability to suppress emotional, cognitive and behavioural responses	
	Behavioural Inhibition	Motor Response Inhibition	Process requires to stop a planned movement	AGN, SS, Go/NoGo
	Cognitive Inhibition	Focused Attention	Process required to suppress a salient but conflicting stimulus while identifying less salient ones	ST
COGNITIVE FLEXIBILITY		Cognitive Rigidity	Ability to shift avenues of thought and action in order to perceive process and respond to situations in different ways	
	Reactive Flexibility	Perseveration or shifting of perceptual set	Ability to realign a behavioural predisposition to altered contingencies	WCST, IED**,** FAT TMT-B, SCT, MCST, BADS (Rule Shift Card, Modified Six Elements), CBT
	Spontaneous Flexibility	Verbal and non verbal fluency	Requires the intrinsic generation of responses or alternatives	COWAT, FAS, VFT, RFFT, WAIS-R/III (Similarities), CLFT, HSCT, RWFT
ATTENTION	Deployment	Arousal/Alertness		DSST
		Focused and Selected Attention/Vigilance	Ability to reject irrelevant information while attending to relevant input	TMT-A, TEA, ST, AVT, RT, SSRT, DR2,Q1
		Sustained Attention	Readiness to detect rarely and unpredictable occurring signals over prolonged periods of time	PASAT, TOVA, TEA, CPT,FTT, ACT, SRT
	Capacity/Encoding or Data Processing		Ability for individuals to hold information in mind and process OR need to process tasks simultaneously	CVLT, RAVLT, DSST,WAIS-R/III (Digit Symbol), FTT

ACT= *Attentional Capture Task*, AGN= *Affective Go-NoGo (CANTAB)* , AM= *Austine Maze*, BADS= *Behavioural Assessment of Dysexecutive Syndrome* , BIS= *Barratt Impulsiveness Scale* , BLC= *Big Little Circle (CANTAB)*, CBT= *Corsi Block Test*, CGT= *Cambridge Gambling Task* (*CANTAB*), CLFT= Category and Letter Fluency Test, CPT= *Continuous Performance Test*, COWAT= *Controlled Oral Word Association Test***,** CTT= *Colour Trail Test*, CVLT =*California Verbal Learning Test*, DDT= *Delay Discounting Test*, DSST= *Digit Symbol Substitution Test*, FAS= *Phonological Fluency Test***,** FTT= *Finger Tapping* Test**,** GDT= *Game and Dice Test***,** HSCT= *Hayling Sentence Completion Test*, IED= *Intra/Extra-Dimensional Set Shifting Task (CANTAB*), IST= Information Sampling Test, IGT= *Iowa Gambling Task*, MFFT= Matching Familiar Figures, MCST= *Maudsley Card Sorting Test*, PASAT= *Paced Auditory Serial Addition Task* , PMT= *Proteus Maze Test*, RAVLT= *Rey Auditory Verbal Learning Test* ,RDMT= *Rogers Decision Making Task*, ROCFT= Rey-*Osterreith Complex Figure Test*, RT= *Reaction Time*, RWFT= *Regensburger Word Fluency Test*, SCT= *Logan Stop Change Task***,** SOC= *Stockings of Cambridge (CANTAB)*, SSP= Spatial Span *(CANTAB*), SS= *Stop Signal*, SRT= *Serial Reaction Time*, SWM= Spatial Working Memory *(CANTAB*), ST= *Stroop Test*, TEA= *Test of Everyday Attention,* TMT= *Trail Making Test*, TOH= *Tower of Hanoi*, TOL=*Tower of London (CANTAB*), *TOVA= Test of Variables of Attention,* VFT= *Benton Verbal Fluency Test***,** WCST= *Wisconsin Card Sorting Test*, WAIS-R/III= *Wechsler Adult Intelligence Scale -Revised/Third Edition.* *Act React Test Systems (ART 90/2020)*: FAT= *Test of Attentional Flexibility*, DR2= *Simple Choice Reaction*, Q1= *Attention under Monotonous Circumstances*, MAT=*Matrices for Intelligence Test*, RST3= *Multiple Choice under Stress*, LL5= *Labyrinth of Lines to Measure Visual Structuring Performance.*

Table 2: Memory and Learning

Domain	Subtypes	Other names	Definition	Test
Short Term Memory	Immediate Memory	Verbal Working Memory	Reproduction, recognition or recall of information directly or sometime after presentation	LMT, RAVLT, CVLT,WAIS-III/R (Digit Span, Letter Numbering), VRM, WMS-R/III (Prose Passage, Associate Learning), WRM, GNT, DFDBT, 2BT, HVLT-R, WCST (Working Memory Index), VLT, WPAT
		Non Verbal (Visuospatial) Working Memory	Allow information to be evaluated and perhaps stored longer through rehearsal and coding	SWM, SSP. DMS, PRM, PAL, BVRT, PAL, SRM,.WMS-R/III, ROCFT, PASAT, WAIS-III/R (Matrix Reasoning),BVMT-R, CCDT, 3D-BCM, CBT, WMS-R/III (Spatial Span)
Long Term Memory	Explicit (Declarative) Memory	Autobiographical, Episodic or Event Memory	Records details salient to individual's life. Needs conscious thinking 'Knowing that'	SOMT, WSLT, BVRT, CVLT, RAVLT, RCFT, WMS-R, WAIS-III/R (Vocabulary)
		Semantic Memory	Meaning of words and concepts or propositional knowledge (facts)	RCFT, RRLET, SAVF,GNT , WMS-R, RBMT
	Implicit (Non Declarative) or Procedural Memory	Motor skill training and Priming or classical conditioning	Does not need conscious thinking 'Knowing how'	

BVMT-R= *Brief Visuospatial Memory Test-Revised*, BVRT=*Benton Visual Retention Test*, CBT= *Corsi Block Test*, CCDT= *Colour Change Detection Tas* , COWAT= *Controlled Oral Word Association Test*, CVLT= *California Verbal Learning Test*, DFDBT= *Digit Forward and Digit Backwards Test*, DMS=*Delayed Matching to Sample (CANTAB)*, GNT=*Graded Name Test (CANTAB*), HVLT-R= *Hopkins Verbal Learning Test-Revised*, LMT= *Logical Memory Test*, SRM=*Spatial Recognition Memory (CANTAB*), PAL= *Paired Associate Learning (CANTAB),* PASAT= *Paced Auditory Serial Addition Task*, PRM= *Pattern Recognition Memory (CANTAB)*, RAVLT= *Rey Auditory Verbal Learning Test*, RBMT= Rivermead Behavioural Memory Test, ROCFT= *Rey Osterreith Complex Figure Test*, RRLET= *Remote and Recent Life Event Test*, SAVF= *Semantic Association of Verbal Fluency* , SOMT= *Six Object Memory Test*, SWM=*Spatial Working Memory (CANTAB)*, SSP=*Spatial Span (CANTAB),* 2BT= *Two Back Test*, 3D-BCM= *Three Dimensional Block Consitution Model*, VLT= *Verbal Learning Task*, VRM= *Verbal Recognition Memory (CANTAB*), WAIS-R/III= *Wechsler Adult Intelligence Scale-Revised/ 3rd Edition*, WMS-R/III= *Wechsler Memory Scale-Revised/3rd Edition, WPAT= Wechsler Paired Associate Test,* WRM= *Word Recognition Memory,* WSLT= *Word Sequence Learning Test.*

Table 3a: Specific Characteristics of Selected Studies Comparing Chronic Methadone Users with Healthy Participants (n=21).

			Methadone Group								Healthy Participants				
Study	**Country**	**Qual**	**N**	**Age (yrs)**	**Gender M:F**	**Education (yrs)**	**Mean IQ (sd)**	**Mean /Min*[1] opioid use in yrs**	**Mean methadone use in yrs**	**Mean daily methadone dose (mg)**	**N**	**Age (yrs)**	**Education (yrs)**	**Mean IQ (sd)**	**Neuropsychological measures**
Ornstein *et al* (2000)	UK England	Mod	22	33.3	1:0	11.9	108.9 (9.4)	11.6	1.4	43.0	22	32.1	15	112.8 (8.5)	NART(IQ), SRM, SWM, PRM,TOL, VFT, IED
Darke *et al* (2000)	Australia	Mod	30	35.8	3:2	11.2	91.5 (10.4)	5.0*[1]	5.0	78.6	30	35.2	11.7	92.6 (11.1)	WAIS-II (IQ), WMS-R (PAL I & II and VR I& II)), CVLT,ROCFT, COWAT, WCST, WAIS-II (Digit Span & Symbol)
Rotherham-Fuller *et a*l (2004)	US California	Mod	18	41.7	n/a	11.8	83.8 (9.7)	0.5*[1]	0.5	61.6	19	37.0	13.6	90.1 (13.2)	SILS (IQ), WCST, GT
Schindler *et al (*2004)	Austria	Mod	15	25.8	3:2	11.5	n/a	4.3	1.6	45.7	56	26.0	n/a	n/a	LL5, FAT, DR2,Q1,RST3
Mintzer *et al* (2005)	US Baltimore	Mod	18	37.6	2:1	11.2	87.4 (2.7)	15.3	3.8	67.2	21	34.9	12.1	94 (2.8)	SILS (IQ), 2BT, TMT (A&B), DSST, IGT
Clark *et al* (2006)	UK England	Mod	40	34.0	4:1	n/a	112.8 (5.9)	11.0	n/a	42.8	26	34.4	n/a	114.1 (7.2)	NART(IQ), IST, BIS
Ersche *et al* (2005/2006)	UK England	Mod	27	33.8	4:1	n/a	113 .4 (6.5)	10.8	n/a	45.2	27	35.1	n/a	114.4 (6.5)	NART(IQ), PAL, PRM, TOL, IED, CGT
Pirastu *et al* (2006)	Italy	Mod	30	34.0	2 females	8.3	85 (1.8)	15.5	8.3	66.0	21	34.0	10.9	104 (3.4)	WAIS-III (IQ),BVRT, WCST, IGT
Prosser *et al* (2006)	US New York	Mod	29	37.9	4:1	13.0	8.05 (2.2)	15.1	6.4	73.8	29	34.0	15.5	12.2 (3.4)	WAIS-III (IQ), BVRT, COWAT, ST,
Soyka *et al* (2008)*	Germany	Mod	24	32.0	2:1.	10.0	n/a	11.0	0.4	56.0	24	32.0	11.0	n/a	AVLT, RWT,TMT (A&B), DR2
Yates (2009)	New Zealand	Mod	29	36.5	2.2:1.5	11.9	111 (5.3)	12.9	6.9	86.7	47	24.5	13.7	113.5 (5.7)	NART(IQ), WMS (Story Recall), TMT (A&B), ST, WCST
Fadardi *et al* (2010)	Iran	Mod	53	36.6	1:0	10.3	n/a	4.0*[1]	4.0	75.0	71	26.6	14.2	n/a	ST
Yin *et al* (2012)	China Huainan	Mod	42	33.9	1:0	8.9	n/a	8.7	1.6	45.3	31	33.5	9.8	n/a	IGT
Lin *et al* (2012)	Taiwan	Mod	27	37.0	1 female	10.3	n/a	13.9	1.7	36.0	23	34.0	15.4	n/a	SOMT, WSLT, BVRT, SAVF, RRLET, WAIS-R (Digit Span & Symbol), Halstead Reitan Test (Proverbs), 3D-BCM
McDonald *et al* (2012)	Australia	Mod	94	38.0	1.8:1	9.8	98.3 (10.2)	18.8	6.1	83.0	50	35.8	11.2	105.9 (6.9)	WTAR(IQ) , WMS-III (Story Recall), WAIS-III (Digit Span & Symbol), COWAT, HSCT, ROCFT, BADS, RAVLT

Anderson *et al* (2013)*	US Baltimore	Mod	17	44.4	9:8	11.5	n/a	1.7*[1]	1.7	77.9	17	42.9	14.7	n/a	BIS, CCDT,ACT
Gupta *et al (*2014)	China Yunnan	Mod	195	35.8	1.8:1	9.8	n/a	14.0	0.7	n/a	198	34.6	9.9	n/a	WMS-III (Spatial Span), CLFT, WAIS-III (Digit Symbol & Span), TMT (A), CTT, HVLT-R, BVMT-R, PASAT, Halstead Reitan Test (Category), ST
Liao *et al* (2014)	Taiwan	Mod	65	40.2	1:0	8.6	n/a	14.3	0.5	45.0	64	36.8	9.3	n/a	SSRT, SRT
Baldacchino *et al* (2014)	UK Scotland	S	29	27.3	1:0	10.6	108.9 (7.6)	8.8	1.3	55.8	28	24.1	15.4	118.3 (5.1)	NART(IQ), CGT, AGN,SOC ,IED, PAL, SRM, PRM, SWM, SSP, DMS
Wang *et al* (2014)	New Zealand	Mod	32	39.4	1.6:1.3	12.1	45.6 (6.7)	10.0	7.3	70.9	25	36.1	13.9	44.3(7)	SpTW/SCOLP (IQ), RAVLT, WAIS-III (Digit Span), CBT, CRT, FTT, TOVA, ST,TMT (A&B), COWAT, AM
Tolomeo *et al* 2016	UK	S	48	30.2	1:0	10.6	103 (9.4)	9.2	1.4	66.6	50	28.0	15.4	117.9 (6.0)	NART, SOC, CGT, IED

MMP= *Methadone Maintained Programme*, n/a = *not available*, R/L Hand= *Right or Left Handed*, M= *Male*; F=*Female*, yrs= *years; Qual= Quality of Study, Mod=Moderate, S= Strong, W=Weak*
*= Longitudinal Studies, Min *[1] = Minimum years of opioid use (when mean opioid use is not provided in the manuscript)

ACT= *Attentional Capture Task*, AVLT= *Auditory Verbal Learning Test*, AM= *Austine Maze*, BADS= *Behavioural Assessment of Dysexecutive Syndrome*, BIS= *Barratt Impulsiveness Scale* , BVMT-R= *Brief Visuospatial Memory Test-Revised*, BVRT= *Benton Visual Retention Test*, CBT= *Corsi Block Test,* CCDT= *Colour Change Detection Task*, CLFT= *Category and Letter Fluency Test*, COWAT= *Controlled Oral Word Association Test*, CRT= *Choice Reaction Time*, CTT= *Colour Trail Test* , CVLT= *California Verbal Learning Test*, FTT= *Finger Tapping Test*, GT=*Gambling Task*, HSCT= *Hayling Sentence Completion Test*, HVLT-R= *Hopkins Verbal Learning Test-Revised*, IGT= *Iowa Gambling Task*, IST=*Information Sampling Task*, NART= *National Adult Reading Test* , PASAT= *Paced Auditory Serial Addition Test*, RAVLT= *Rey Auditory Verbal Learning Test*, ROCFT= *Rey Osterreith Complex Figure Test*, RRLET= *Remote and Recent Life Event Test*, RWT= *Regensburger Word Fluency Test*,), SAVF= *Semantic Association of Verbal Fluency,* SCOLP (SpTW)= *Speed and Capacity of Language Processing (Spot the Word- %* accuracy*)*, SILS= *Shipley Institute of Living Skills*, SOMT= *Six Object Memory Test***,** ST= *Stroop Test*, SSRT= *Stop Signal Reaction Time*, TOVA= *Test of Variables of Attention*, 3D-BCM= *Three Dimensional Block Consititution Model*, 2BT= *Two Back Task*, VFT= *Verbal Fluency Test*, WAIS- III/II**=** *Wechsler Adult Intelligence Scale- 3rd/2nd Edition***,** WCST= *Wisconsin Card Sorting Test* ,WMS-R/III= *Wechsler Memory Scale- Revised/3rd Edition,* WSLT= *Word Sequence Learning Test,* WTAR= *Wechsler Test of Adult Reading Skills,* <u>*CANTAB*</u>: PAL= *Paired Associate Learning*, PRM= *Pattern Recognition Memory*, SRM= Spatial *Recognition Memory,* SWM= *Spatial Working Memory*, SOC = *Stockings of Cambridge*, TOL= *Tower of London*, IED= *Intra/Extra-Dimensional Set Shifting*, CGT= Cambridge *Gambling Task,* SSP= *Spatial Span,*DMS= *Delayed Matching to Sample;* <u>*Halstead Reitan Neuropsychological Test Battery*</u>: TMT= *Trail Making Test, Proverbs, Category Test,* <u>*Act React Test Systems (ART 90/2020)*</u>: FAT= *Test of Attentional Flexibility*, DR2= *Simple Choice Reaction*, Q1= *Attention under Monotonous Circumstances*, RST3= *Multiple Choice under Stress*, LL5= *Labyrinth of Lines to Measure Visual Structuring Performance.*

Table 3b: Specific Characteristics of Selected Studies Comparing Chronic Methadone Users with Short Term Abstinent Individuals (n=7).

			Methadone Group								Abstinent Group						
Study	**Country**	**Qual**	**N**	**Age (yrs)**	**Gender M:F**	**Education (yrs)**	**Mean IQ (sd)**	**Mean opioid use (yrs)**	**Mean methadone use (yrs)**	**Mean daily methadone dose (mg)**	**N**	**Age (yrs)**	**Education (yrs)**	**Mean IQ (sd)**	**Mean opioid use (yrs)**	**Period of abstinence (yrs)**	**Neuropsychological measures**
Gritz *et al* (1975)[61]	US California	W	10	31.0	1:0	11.4	n/a	11.5	0.4	65.0	10	25.0	15.0	n/a	5	0.3	DSST, DFDBT, SRTT, VLT, WPAT
Davis *et al* (2002)	UK England	W	15	34.0	n/a	11.4	101 (9.5)	14.6	0.6	32.5	16	31.0	10.9	99 (9.9)	11.5	0.5	WAIS-II (IQ), AMIPB, TEA, WAIS-II (Block Design, Object Assembly), COWAT
Mintzer *et al* (2005)	US Baltimore	Mod	18	37.6	2:1	11.2	87.4 (2.7)	15.3	3.8	67.2	20	40.2	11.2	89.8 (2.1)	16.9	0.8	SILS (IQ), 2BT, TMT (A&B), DSST, IGT, ST
Prosser *et al* (2006)	US New York	Mod	29	37.9	4:1	13.0	8.1 (2.2)	15.1	6.4	73.0	27	42.6	11.8	8.6 (3.1)	13.7	0.9	WAIS-III (IQ), BVRT, COWAT, ST
McDonald *et al* (2012)	Australia	Mod	94	38.0	1.8:1	9.8	98.3 (10.2)	18.8	6.1	83.0	50	34.1	10.3	100.7 (9.2)	20.6	0.2	WTAR(IQ), WMS-III (Story Telling), WAIS-III (Digit span & Symbol), COWAT, HSCT, ROCFT, RAVLT
Liao *et al* (2014)	Taiwan	Mod	65	40.2	1:0	8.6	n/a	14.3	0.5	45.0	264	36.4	9.2	n/a	7.2	0.3	SSRT, SRT
Tolomeo *et al* (2016)	UK Scotland	S	48	30.2	1:0	10.6	103 (9.4)	9.2	1.4	66.6	25	36.6	10.6	111.3 (2.1)	3.8	0.5	NART(IQ), CGT, SOC, IED

MMP= Methadone Maintained Programme, n/a = not available, R/L Hand= Right or Left Handed, M= Male, F=Female, yrs= years, Qual= Quality of the Study; S=Strong, Mod=Moderate, W=Weak

AMIPB = *Adult Memory and Information Processing Battery*, BADS= *Behavioural Assessment of Dysexecutive Syndrome* , BIS= *Barratt Impulsiveness Scale*, CDT= Clock Drawing Test, COWAT= *Controlled Oral Word Association Test,* DSST=*Digit Symbol Substitution Test*, DFDBT= *Digits Forward and Digits Backward Test*, HSCT= *Hayling Sentence Completion Test*, IGT= *Iowa Gambling Task*, NART= *National Adult Reading Test* , RAVLT= *Rey Auditory Verbal Learning Test* , ROCFT= *Rey Osterreith Complex Figure Test***,** ST= *Stroop Test* , SSRT= *Stop Signal Reaction Time*, SpTW= *Spot the Word - % accuracy,* SRTT= *Serial Reaction Time Task*, SRT= *Simple Reaction Time*, TEA= *Test of Everyday Attention*, VLT= *Verbal Learning Test,* WAIS- III/II**=** *Wechsler Adult Intelligence Scale- 3rd/2nd Edition***,** WMS-R/III= *Wechsler Memory Scale-Revised/ 3rd Edition* , WPAT= *Wechsler Paired Associate Test*, WTAR= *Wechsler Test of Adult Reading Skills,* CANTAB: PAL= *Paired Associate Learning*, PRM= *Pattern Recognition Memory*, SOC = *Stockings of Cambridge*, IED= *Intra/Extra-Dimensional Set Shifting*, CGT= Cambridge *Gambling Task,* Halstead Reitan Neuropsychological Test Battery: TMT= *Trail Making Test*.

Table 4a: Pooled Effect Sizes for Individual Neuropsychological Domains in Chronic Methadone Users Compared to Healthy Participants.

			Effect Size and 95% Confidence Interval				Test of null (2 tail)		Heterogeneity			Publication Bias
Neuropsychological Domains*	N [1]	Studies [2]	Effect Size [3]	SE [4]	Lower Limit [5]	Upper Limit [6]	Z [7]	*P* for Z [8]	Q [9]	*p* for Q [10]	I^2 [11]	Fail safe N [12]
Cognitive Impulsivity	214	7	0.89	0.32	0.26	1.53	2.8	***0.006***	51.16	*0.00*	88.27	79
Motor Impulsivity	490	9	0.41	0.09	0.23	0.59	4.5	***0.001***	14.14	*0.08*	43.42	80
Non Planning Impulsivity	293	7	1.38	0.42	0.48	2.13	3.1	***0.002***	102.76	*0.00*	94.16	221
Cognitive Flexibility	557	12	0.46	0.07	0.32	0.60	6.4	***0.001***	12.76	0.31	13.82	145
Attention	467	8	0.71	0.21	0.31	1.12	3.5	***0.001***	48.77	*0.00*	85.03	120
Short Term Memory	556	12	0.67	0.12	0.45	0.92	5.8	***0.001***	31.30	*0.001*	64.85	269
Long Term Memory	481	9	0.68	0.20	0.28	1.07	3.4	***0.001***	55.55	*0.00*	85.60	140

[1]*=Total number of methadone subjects* [2]*= Number of studies used to calculate effect size*, [3]*= Cohen's d effect size*, [4]*= Standard Error* , [5]*= Lower limit of the 95% confidence interval for the effect size,* [6]*= Upper limit of the 95% confidence interval for the effect size*, [7]*= One sample Z Statistic*, [8]*= Probability that Z Statistics is significantly different than 0* [9]*= Q statistic*, [10]*= Probability that Q statistics significantly different than 0,* [11]*= I^2 statistics,* [12]*= Classic Fail safe N,* [*] All neuropsychological domains with random effects model employed.

Table 4b: Pooled Effect Sizes for Individual Neuropsychological Domains in Chronic Methadone Users Compared to the Abstinent Group.

			Effect Size and 95% Confidence Interval				Test of null (2 tail)		Heterogeneity			Publication Bias
Neuropsychological Domains*	N [1]	Studies [2]	Effect Size[3]	SE[4]	Lower Limit [5]	Upper Limit [6]	Z [7]	*p* for Z [8]	Q [9]	*p* for Q [10]	I^2 [11]	Fail safe N [12]
Cognitive Impulsivity	66	2	0.34	0.19	-0.04	0.72	1.7	0.08	0.54	*0.46*	0.00	N/P
Motor Impulsivity	112	3	0.14	0.12	-0.08	0.37	1.2	0.21	0.46	*0.79*	0.00	0
Non Planning Impulsivity	142	2	0.75	0.59	-0.41	1.91	1.3	0.21	14.03	*0.00*	92.87	N/P
Cognitive Flexibility	240	5	1.12	0.43	0.27	1.70	2.6	0.01	64.44	*0.00*	93.79	129
Attention	137	4	0.70	0.29	0.13	1.27	2.4	0.01	9.45	*0.02*	68.25	16
Short Term Memory	166	5	0.38	0.14	0.12	0.65	2.8	***0.005***	4.55	*0.34*	12.01	9
Long Term Memory	137	4	0.35	0.17	0.01	0.69	2.0	0.04	3.99	*0.26*	24.98	4

[1]=*Total number of methadone subjects* [2]= *Number of studies used to calculate effect size,* [3]= *Cohen's d effect size,* [4]= *Standard Error,*[5]= *Lower limit of the 95% confidence interval for the effect size,* [6]= *Upper limit of the 95% confidence interval for the effect size,* [7]= *One sample Z Statistic,* [8]= *Probability that Z Statistics is significantly different than 0* [9]= *Q statistic,* [10]= *Probability that Q statistics significantly different than 0,* [11]= *I^2 statistics,* [12]= *Classic Fail safe N,* * All neuropsychological domains with random effects model employed.

N/P= one needs at least 3 studies to determine publication bias

Tables 5a and 5b: Subgroup Analysis: Meta-Regression of Chronic Methadone Group for Age in Years and (a) Cognitive Flexibility and (b) Short Term Memory.

Table 5a:

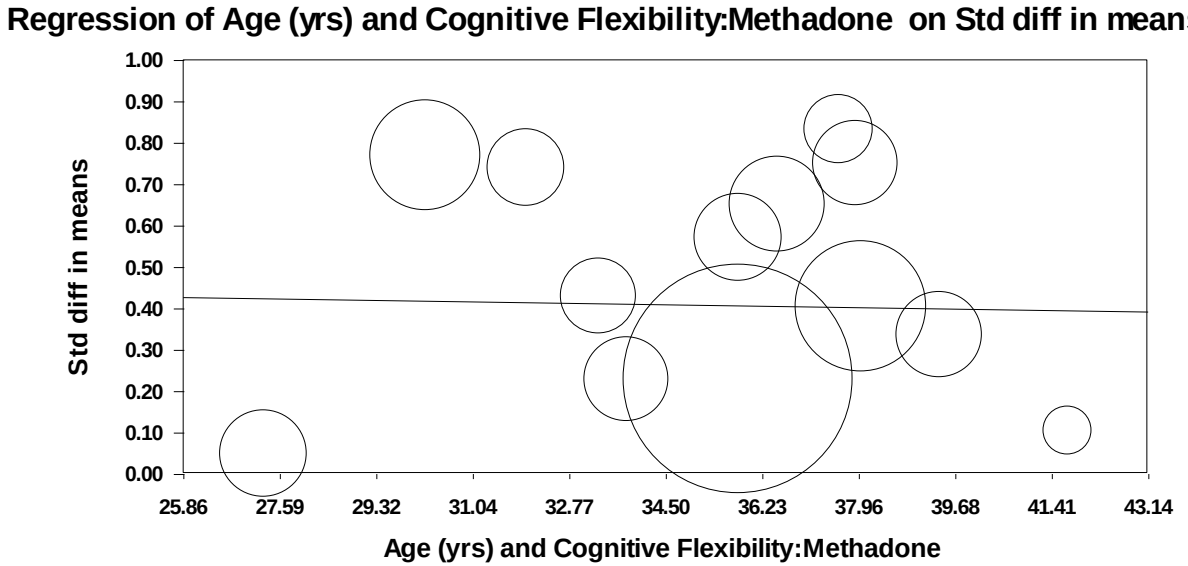
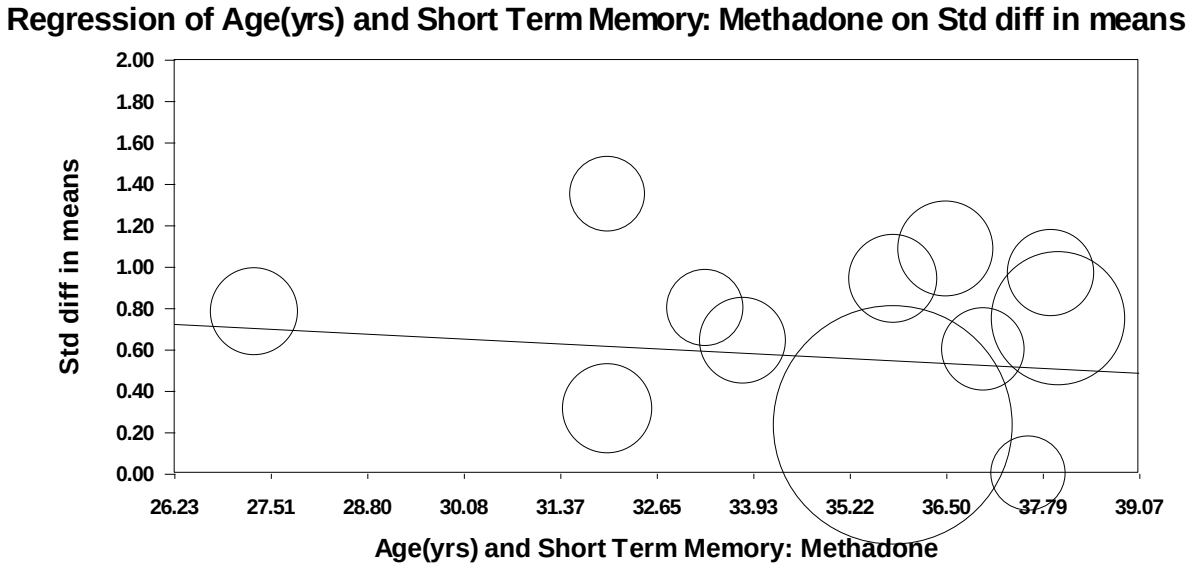
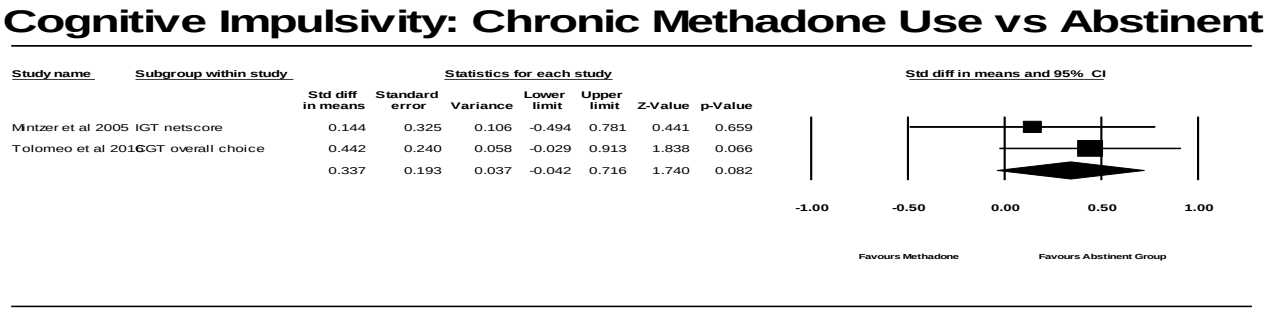


Table 5b:

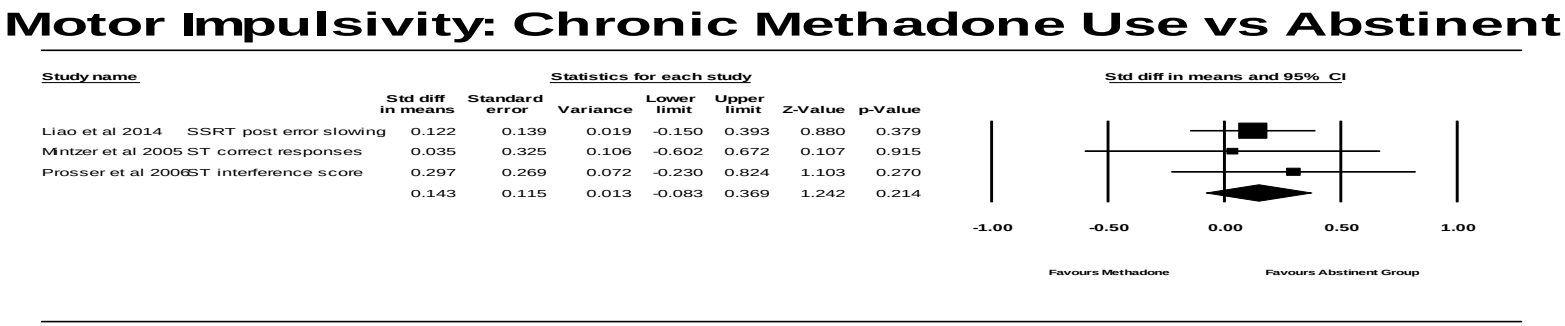

Regression of Age(yrs) and Short Term Memory: Methadone on Std diff in means
Std diff in means
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
26.23
27.51
28.80
30.08
31.37
32.65
33.93
35.22
36.50
37.79
39.07
Age(yrs) and Short Term Memory: Methadone

Online supplementary information

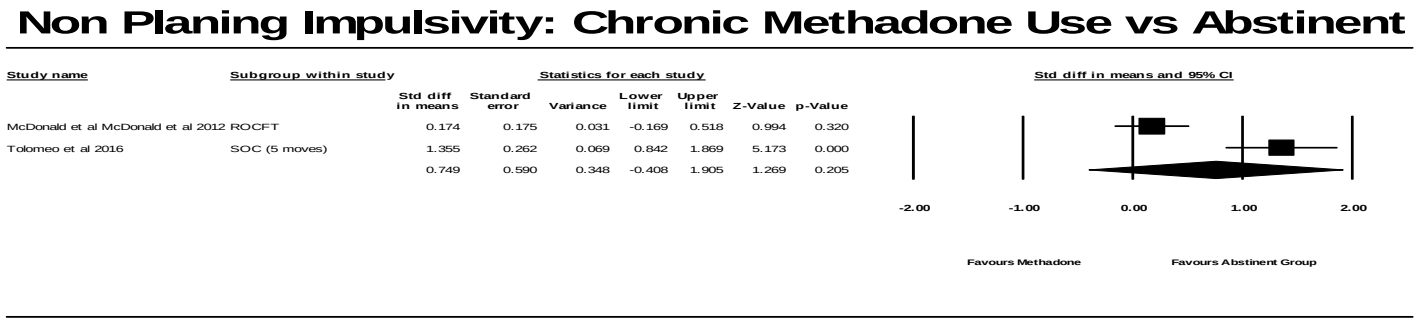
SFigure 1



SFigure 2


Motor Impulsivity: Chronic Methadone Use vs Abstinent
Study name
Statistics for each study
Std diff in means
Standard error
Variance
Lower limit
Upper limit
Z-Value
p-Value
Liao et al 2014 SSRT post error slowing 0.122 0.139 0.019 -0.150 0.393 0.880 0.379
Mintzer et al 2005 ST correct responses 0.035 0.325 0.106 -0.602 0.672 0.107 0.915
Prosser et al 2006 ST interference score 0.297 0.269 0.072 -0.230 0.824 1.103 0.270
0.143 0.115 0.013 -0.083 0.369 1.242 0.214
Std diff in means and 95% CI
-1.00
-0.50
0.00
0.50
1.00
Favours Methadone
Favours Abstinent Group

SFigure 3


Non Planing Impulsivity: Chronic Methadone Use vs Abstinent
Study name
Subgroup within study
Statistics for each study
Std diff in means
Standard error
Variance
Lower limit
Upper limit
Z-Value
p-Value
McDonald et al McDonald et al 2012 ROCFT 0.174 0.175 0.031 -0.169 0.518 0.994 0.320
Tolomeo et al 2016 SOC (5 moves) 1.355 0.262 0.069 0.842 1.869 5.173 0.000
0.749 0.590 0.348 -0.408 1.905 1.269 0.205
Std diff in means and 95% CI
-2.00
-1.00
0.00
1.00
2.00
Favours Methadone
Favours Abstinent Group