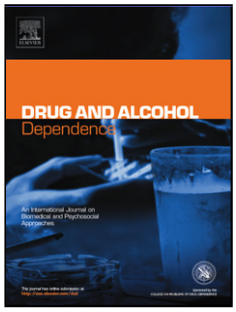

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Compulsivity and Impulsivity in Opioid Dependence

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Highlights

- Heroin, buprenorphine and abstinent groups exhibited impaired performance in pre-extradimensional reversal stages during the Intra-Extra Dimensional Shift task compared to healthy controls.
- Heroin, methadone and buprenorphine groups exhibited impaired behavioral responses to feedback, consisting of increased Cambridge Gambling task deliberation time and poorer risk adjustment.
- Our results suggest that compulsivity and impulsivity are core neurocognitive dimensions for opioid dependence which differ in their presentation according to the *stage* of treatment.
- Participants taking higher morphine equivalent doses performed better in compulsivity measures.
- These findings have implications for the treatment of opioid dependence and longitudinal studies are warranted.

Abstract

Objective: Chronic exposure to illicit opioid drugs can cause serious health and social problems. However, less is known about the differential effect of various opioid treatments, such as methadone and buprenorphine, on neurocognitive domains such as compulsivity and impulsivity, despite their relevance to the treatment of opioid dependence.

Methods: A total of 186 participants were recruited with a cross-sectional design: i) illicit heroin users (n=27), ii) former heroin users stabilized on methadone MMT (n=48), iii) a buprenorphine maintenance treatment (BMT) group (n=18), iv) an abstinent (ABS) group with a history of opioid dependence who were previously stabilized on MMT or BMT (n=29) and v) healthy controls (HC) (n=64). We used the Intra-Extra Dimensional Shift (IED) and Cambridge Gambling Task (CGT) paradigms for measuring compulsivity and impulsivity constructs respectively.

Results: Heightened compulsivity persisted in the heroin, buprenorphine and abstinent groups. Heroin, methadone and buprenorphine groups exhibited impaired behavioral responses to feedback, consisting of increased deliberation time and poorer risk adjustment. Higher compulsivity measures were negatively associated with opioid dose which may reflect sedation effects.

Conclusions: Our results suggest that compulsivity and impulsivity are core neurocognitive dimensions for opioid dependence which differ in their presentation according to the *stage* of treatment. Participants taking higher morphine equivalent doses performed better in compulsivity measures. These findings have implications for the treatment of opioid dependence and longitudinal studies are warranted.

Keywords: buprenorphine, compulsivity, impulsivity, methadone, opioid dependence

1. Introduction

Misuse of illicit heroin and prescribed opioids is a worldwide international problem closely associated with increased morbidities such as blood-borne virus infections (Swart et al., 2012), cardiopulmonary disorders (Elman et al., 2001), fatal overdoses (Larochelle et al., 2018) and criminality (Chetty et al., 2017). Over the past decade, the number of opioid dependent individuals worldwide has increased

significantly to 34 million (https://www.unodc.org/wdr2018/prelaunch/WDR18_Booklet_1_EXSUM.pdf), whilst the number of deaths due to heroin and prescription opioids has increased fivefold (Lipari R, Kroutil LA, 2015). The two main pharmacological interventions in the treatment of opioid dependence are methadone and buprenorphine (Glanz et al., 2019). Evidence suggests that they are both instrumental in facilitating recovery and/or reducing morbidities and moralities (Glanz et al., 2019).

Impulsivity has been linked to the initial stages of addictive behavior and conversely, compulsivity has been associated with the later stages of addiction, notably continuation and maintenance of addictive behavior (Koob and Volkow, 2010). Specifically, impairment in impulsivity and compulsivity have been linked to the onset, maintenance and relapsing nature of drug dependence (Pattij and De Vries, 2013). In addition, maladaptive impulsivity is a common neurocognitive phenomenon which has been proposed as a vulnerability trait for drug abuse and dependence, from various studies on humans and animals (Robbins et al., 2012).

Compulsivity and impulsivity have been proposed as neurocognitive *endophenotypes* (Dalley et al., 2011; Fineberg et al., 2010; Robbins et al., 2012); behavioral abnormalities linked to specific brain circuits, such as the prefrontal cortex and basal ganglia, conceptualized *transdiagnostically* as also being relevant to other psychiatric disorders such as Obsessive Compulsive Disorder (OCD) and Attention Deficit Hyperactivity Disorder (ADHD)(Robbins et al., 2012). A recent study highlighted that impulsivity and compulsivity may also be relevant neurocognitive *endophenotypes* of opioid dependence (Tolomeo et al., 2018). However, it is difficult to define, measure, characterize and validate notions of compulsivity across different clinical populations (Yücel et al., 2019b; Yücel and Fontenelle, 2012).

Yücel, Fontenelle and Chamberlain (2019) highlighted in a recent *Special Issue* that specific neurocognitive, pharmacological and technological approaches are essential to better understand, diagnose and treat substance and behavioral addictions (Yücel et al., 2019a). Further study of compulsivity was a priority, as it has been far less studied than impulsivity (Tolomeo et al., 2018; Yücel et al., 2019a).

Previous work has shown that patients with chronic opioid dependence receiving methadone have significant neurocognitive impairments in compulsivity and impulsivity measures (Alex Baldacchino, John Douglas Steele, Fleur Davey, 2019; Baldacchino et al., 2015; Tolomeo et al., 2018, 2016). In addition, we found that increased cognitive impulsivity correlated with grey matter reductions in the orbitomedial prefrontal cortex (Tolomeo et al., 2016) and increased compulsivity with cingulate cortex, dorsolateral prefrontal cortex and ventral tegmental area grey matter reductions (Tolomeo et al., 2018).

However, a recent systematic review of neurocognitive functioning in participants receiving chronic methadone and/or buprenorphine for the treatment of opioid dependence concluded that the literature still lacks robust, methodologically good quality studies, to discriminate cause from effect. The authors concluded that methadone-maintained patients might be associated with fewer neurocognitive impairments when compared with methadone users (Tolomeo et al., 2016).

From a neurocognitive perspective, opioid dependence could represent a long-term consequence of opioid use which may or may not be reversible (Tolomeo et al., 2016). Previous studies have highlighted how crucial the impact of sedation is on neurocognitive functioning (Baldacchino et al., 2015; Bracken et al., 2012; Clark et al., 2006; Tolomeo et al., 2016). Nevertheless, one study reported no significant correlations between methadone dose and cognitive performance, whilst another reported a significant relationship between methadone dosage (*current* and *initial titration*) and structural magnetic resonance imaging measures, particularly striatal grey matter (Tolomeo et al., 2016). These authors also reported that methadone dose has important clinical implications for enhancing treatment and recovery (Tolomeo et al., 2016). For instance, using individual predictions (*within-study replication*), the initial methadone dose provided strong predictive accuracy of achieving successfully (Tolomeo et al., 2016). Building on our previous studies (Tolomeo et al., 2018, 2016), here we tested the hypothesis that i) chronic opioid dependent and abstinent patients are impaired in compulsivity and impulsivity and ii) the extent of cognitive impairments correlates with *morphine* equivalent dosage as a *proxy* measure of sedation in the methadone and buprenorphine groups.

2. Methods

2.1. Participants

Participants were recruited from a National Health Service (NHS) based addiction treatment service in Scotland. Data were obtained from five groups: i) illicit heroin users (n=27), ii) former heroin users stabilized on Methadone Maintenance Treatment (MMT) (n=48), iii) or stabilized on Buprenorphine Maintenance Treatment (BMT) (n=18), iv) abstinent individuals with a history of opioid dependence who were also previously stabilized on MMT or BMT (n=29) and iv) healthy controls (n=64). Participants had a diagnosis of DSM IV Opioid Dependence, and all had histories of poly-substance misuse with illicit heroin use and dependence as the primary 'drug of choice' preceding initiation of MMT or BMT. Healthy controls were subjected to the same stringent exclusion criteria as the experimental cohorts and recruited from the general population where participants were residing. None of the healthy control group had a history of past or current history of substance use.

2.2. Ethical Approval

The study was approved by the East of Scotland Research Ethics Committee (REC). REC reference number is 06/S1401/32. Written informed consent was obtained from all participants.

2.3. Assessment

2.3.1 Clinical

Clinical histories and diagnoses were based on the structured Mini International Neuropsychiatric Interview (MINI Plus v 5.0) (Sheehan et al., 1998) together with a detailed review of the participants' clinical case records. The latter included recording the doses of methadone and buprenorphine that each participant received at the time of this study. Total morphine equivalent doses for each prescription were calculated by multiplying the quantity of each prescription by the strength of the prescription (milligrams

of opioid per unit dispensed). The quantity and strength of the product were then multiplied by conversion factors derived from published sources to estimate the milligrams of morphine, equivalent to what was dispensed in the prescription in accordance with Vieweg and colleagues (Vieweg et al., 2005). Each methadone dose was multiplied by 20 and each buprenorphine dose was multiplied by 12 (Vieweg et al., 2005). This was used as a proxy measure for sedation (Vieweg et al., 2005).

Ongoing abstinence from illicit drug use was confirmed just prior to testing using a urine drug test (Armbruster and Krolak, 1992) with the sample tested using an automated enzyme-mediated immunoassay to identify drugs that could confound the results of the neurocognitive tests and cause additional sedation. Participants receiving Opioid Replacement Treatment (ORT) (either MMT or BMT) were all abstinent from heroin which is prescribed to help keep individuals abstinent from illicit drug use, especially heroin. All participants in the abstinent (ABS) group underwent ORT stabilisation, reduction and subsequent stoppage of ORT under clinically controlled conditions as per clinical guidelines. The ABS group was entirely free from any opioid. When receiving ORT, there was objective evidence for patients not relapsing to heroin use and/or other illicit opioids by regular drug urine screening.

The Clinical Opioid Withdrawal Scale (COWS) quantified the level of any opioid withdrawal that might be present as a result of inadequate dosage of methadone or buprenorphine (Wesson and Ling, 2003). Current and premorbid intelligence was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI) and National Adult Reading Scale (NART) respectively (Nelson and Willison, 1991; Woerner and Overstreet, 1999).

Details of screening, diagnostic criteria used and recruitment details are presented in Supplemental Table 1 and 3. Exclusion criteria included: past or current diagnoses of psychotic disorder, post-traumatic stress disorder, personality disorders, neurological and neurodevelopmental disorders, head injury, confirmed history of non-fatal overdose episodes and co-occurring benzodiazepine, stimulant and/or alcohol dependence. Data were collected from case notes where all of the treatment seeking population had a screening for human immunodefiency (HIV) and hepatitis C virus (HCV) through a blood test. Since the presence of these infections were an exclusion criteria, none of the participants were HIV and HCV

positive. Cohorts exhibiting polysubstance dependence identified using urine screening were also excluded. We previously published three experimental studies reporting neuropsychological investigations of the heroin, methadone and abstinent groups (Baldacchino et al., 2015; Tolomeo et al., 2018, 2016), where we reported neurocognitive impairments in impulsivity and compulsivity and brain structural abnormalities. Here we increased the control group sample size and recruited a new group currently on buprenorphine treatment.

2.3.2. Neurocognitive

The Cambridge Gambling Task (CGT) and the Intra-Extra Dimensional (IED) task have been extensively validated and shown to be sensitive to behavioural abnormalities in opioid dependent populations (Baldacchino et al., 2015; Ornstein et al., 2000; Tolomeo et al., 2018). Performance on these tasks have has been linked to specific brain regions, especially the prefrontal cortex and basal ganglia regions (Rogers et al., 2000, 1999; Tolomeo et al., 2016). These tasks are part of the Cambridge Neuropsychological Automated Test Battery (CANTAB, www.camcog.com).

2.3.2.1. Intra/Extra Dimensional Shift – Compulsivity

Compulsivity is defined as persistent repeated actions without a focus on obtaining a useful goal to the extent it interferes with everyday life, involving behaviours such as checking, counting and repetition of acts. The Intra/Extra Dimensional Shift is a cognitive rule-learning and set-shifting task adapted from the Wisconsin Card Sorting Test (WCST). Participants are required to learn a series of different visual dimensions, such as number, shape and colour and to shift their attention between these dimensions. The task starts with simple discrimination for stimuli varying in one dimension, then introduces a different stimulus set. See Supplemental Table 2 for more details regarding the compulsivity domains and variables used. The specific measures of compulsivity that were used were: Pre-Extra Dimensional (Pre-ED) Errors and Total Errors (Ersche et al., 2006; Lee et al., 2019). Fineberg and colleagues proposed the IED measures compulsivity and ‘cognitive flexibility’. Notably, compulsivity measures include pre-ED errors,

EDS errors and total errors (Banca et al., 2016a; Fineberg et al., 2010; Wildes et al., 2014). We chose these variables because of our previous experimental study (Tolomeo et al., 2018) and our meta-analysis (Baldacchino et al., 2015).

2.3.2.2. Cambridge Gambling Task – Impulsivity

Impulsivity is the tendency to act prematurely, characterised by little or no consideration of the immediate consequences. The Cambridge Gambling Task (CGT) assesses decision making under conditions of risk (Rogers et al., 1999). On each trial a participant is presented with a row of ten boxes across the top of the screen, some of which are red, the others blue, the ratio being the 'box ratio'. At the bottom of the screen are rectangles containing the words 'Red' and 'Blue'. The participant has to guess whether a yellow token is hidden 'under' a Red or Blue box for eight sequences each of nine trials.

Participants start with 100 points displayed on the screen and have to select a proportion of these points to ‘gamble’ based on their confidence in their decision. Trials have a pseudo-randomised ‘box ratio’ and the size of the available bet varies in ascending (from low to high ratio) to descending (high to low ratio) order. A 'stake box' displays the amount of the current bet. Participants are instructed to accumulate as many points as possible and to consider the points as valuable. No money or gift voucher was given at the end of the task. See Supplemental Table 2 for more details regarding the cognitive impulsivity domains. Significantly reliable measures of impulsivity are Deliberation Time, Risk Adjustment (adjustment of behaviour according to the risk of loss), Quality of Decision Making and Delay Aversion (Baldacchino et al., 2015; Rogers et al., 1999; Tolomeo et al., 2016).

Fineberg and colleagues subdivided compulsivity and impulsivity. They clarified that extra-dimensional attentional set-shifting correlates with compulsivity as cognitive inflexibility and Cambridge Gambling task correlates with impulsivity (Fineberg et al., 2010). There are a number of studies that used these specific tasks IED and CGT to measure of compulsivity (Banca et al., 2016b; Kim et al., 2017; Tolomeo et al., 2018) and impulsivity (Baldacchino et al., 2015; Tolomeo et al., 2016). In addition,

Robbins argued that impulsivity and compulsivity constructs should be considered key neurocognitive endophenotypes in psychiatry research(Robbins et al., 2012).

2.3.3. Statistical Analysis

Data meeting assumptions of normality were analysed using ANOVA. Data not normally distributed were analysed by using a non-parametric Mann-Whitney U Test. A post-hoc Bonferroni correction was used to control for family-wise error for unplanned tests. NART, age and smoking history were controlled as they were identified as covariates ($p>0.05$). As expected, these variables did not have significant effect on the results. A General Linear Model was performed with 'Groups' as a *factor* and 'Impulsivity' and 'Compulsivity' measures as *dependent variables* using analysis of covariance (ANCOVA). To explore the potential contribution of the impact of morphine equivalent doses (methadone or buprenorphine) on compulsivity, impulsivity, and compulsivity/impulsivity ratio, linear regression models were tested. Morphine equivalent dosage was considered as proxy measure of sedation. Finally, to explore a replication of previous findings (Tolomeo et al., 2018), a correlational analysis was used to test the null hypothesis of no relation between impulsivity and compulsivity. Data were analysed using the Statistical Package for the Social Science (SPSS) version 24 (SPSS Inc.) on Windows 10. The significance level was achieved with $p<0.05$. All methods were carried out in accordance with relevant guidelines and regulations.

3. Results

3.1. Characteristics of participants

Demographic and clinical details are presented in Table 1. The flow chart of our recruitment is shown in Figure 1 with the total number of participants 187. Figure 1 shows the total number of participants in each group and the reasons for exclusion. Data were obtained from five groups as described above: i) patients with a history of opioid dependence due to chronic illicit heroin use (n=27), ii) former heroin users who had been stabilised on methadone maintenance treatment (n=48), iii) former heroin users who have been stabilised on buprenorphine maintenance treatment (n=18), iv) abstinent patients with a history of opioid dependence who were also previously stabilised on methadone maintenance treatment (n=29) and iv) healthy controls (n=64). Patients had a diagnosis of DSM IV Opioid Dependence and had histories of poly-substance misuse with heroin as the primary "drug of choice" preceding initiation of MMT. Participants were matched on the basis of gender (all males). We chose a male-only sample because there are far fewer women seeking treatment for opioid dependency in our service. It is unclear how much this disparity reflects fewer women becoming opioid dependent vs fewer women seeking treatment.

The BMT and ABS groups were older than the Heroin (H) group ($p<0.001$). The BMT and H groups had lower estimated pre-morbid IQ ($p<0.001$) according to the National Adult Reading Test (NART) compared to the healthy controls (HC). As expected, the mean morphine equivalent daily dose for the MMT group was significantly higher than the BMT group ($p<0.001$). Most of the clinical substance history measures were well matched with the exception of age when first used benzodiazepine as BMT was older than ABS, see Table 1 for additional information.

3.2. Compulsivity

There were significant group differences in performance on the IED task especially Pre-ED errors in the H and BMT groups compared to the HC group ($F_{(1, 89)} = 12.4$, $p=0.01$) and ($F_{(1, 81)} = 14.8$, $p=0.009$) respectively (See Figure 2-A). There was a significant difference among the groups in passing each stage, overall the control group performed significantly better than the patient groups ($p<0.05$). Total errors

were significantly different in the H and BMT groups ($F_{(1, 74)} = 6.9$, $p<0.001$) and ($F_{(1, 66)} = 3$, $p<0.001$) compared to the HC group, respectively. The MMT group did not exhibit significant impairment in compulsivity measures when compared to the HC group ($p>0.05$), see Table 2 for further details.

3.3. Impulsivity

Mean percentage correct scores for CGT are reported in Table 3 There was a significant difference in the clinical groups: H ($F_{(1, 88)} = 4$, $p=0.006$), MMT ($F_{(1, 110)} = 7.6$, $p<0.001$), BMT ($F_{(1, 80)} = 1.1$, $p=0.009$) and ABS ($F_{(1, 90)} = 15$, $p=0.003$) in *deliberation time* when compared to the HC group (See Figure 3-A). There was a significant difference in the H ($F_{(1, 88)} = 4$, $p<0.001$), MMT ($F_{(1, 110)} = 2.7$, $p<0.001$), BMT ($F_{(1, 80)} = 0.2$, $p=0.02$) and ABS ($F_{(1, 88)} = 15$, $p=0.003$) in *risk adjustment* when compared to the HC group (See Figure 3-B). There was a significant difference in the H ($F_{(1, 88)} = 15$, $p<0.001$) and ABS ($F_{(1,90)} = 18.8$, $p<0.001$) groups in *quality of decision making* when compared to the HC group and not in the MMT ($F_{(1, 110)} = 4$, $p=0.1$) and BMT ($F_{(1, 81)} = 5$, $p=0.2$). There was a significant difference in *delay aversion* in the H ($F_{(1, 88)} = 9.5$, $p<0.001$) and ABS ($F_{(1, 90)} = 0.6$, $p=0.003$), but this was not observed in the MMT ($F_{(1, 110)} = 1.5$, $p=0.1$) and BMT ($F_{(1, 80)} = 0.5$, $p=0.1$) (Figure 3-C, Table 3).

3.4. Relationship between Morphine Equivalent Dose and Compulsivity/Impulsivity

There was a significant negative correlation between morphine equivalent doses and EDS errors (compulsivity) ($t = -2.9$, $p=0.006$) (Figure 2-B) and between morphine equivalent doses and IED Total errors (compulsivity) ($t = -2.8$, $p=0.007$) (Figure 2-C). A significant negative correlation between morphine equivalent dose and compulsivity/impulsivity ratio was found ($t =-2.4$, $p=0.02$) (Figure 2-D). There was no significant relationship between morphine equivalent dose and each impulsivity measure ($p>0.05$).

3.5. Relationship between Compulsivity and Impulsivity

There was a significant negative correlation between IED total errors (compulsivity) and CGT risk adjustment (impulsivity) (t =-2.6, *p*=0.01) (Figure 3-D), as well as Pre-ED errors (compulsivity) and CGT quality of decision making (impulsivity) (t =-2.4, *p*=0.02). The latter is a replication of our previous study (Tolomeo et al., 2018).

4. Discussion

This study investigated the differential effects of heroin, methadone, buprenorphine and abstinence on cognitive measures of compulsivity and impulsivity. The magnitude of the impairments in compulsivity measures correlated negatively with morphine equivalent dosage in the methadone and buprenorphine groups.

Whilst compulsivity has major implications for addiction it is still an under-studied area (Yücel et al., 2019b; Yücel and Fontenelle, 2012). To our knowledge, no previous studies have tested for impairment in compulsivity during buprenorphine treatment and only one study attempted to test compulsivity during abstinence from opioid dependence (Tolomeo et al., 2018). These findings, therefore, provide new evidence that heroin users, buprenorphine-maintained participants and abstinent, are impaired in some aspects of compulsivity. As Luigjes and colleagues noted, compulsive behaviours are remarkably common in several addictive and psychiatric disorders, although yet no clinical implications are still present (Luijten et al., 2017). In addition, consistent with a previous study by Ornstein and colleagues (Ornstein et al., 2000), we found patient groups were significantly impaired at passing each stage. Importantly, our observations regarding compulsivity and morphine equivalent doses suggest that opioid exposure reduces compulsivity, possibly by altering brain dopamine (e.g., ventral tegmental area, striatum, substantia nigra) and serotonin (e.g., raphe nucleus, hippocampus) which might alleviate compulsive behaviour. Notably, whilst an interesting relationship with morphine equivalent dosage and the compulsivity / impulsivity ratio was found, no relationship was found with impulsivity alone. This finding suggests a dissociation between impulsivity and compulsivity, with compulsivity more linked to the effects of opioid medication dose. This dissociation has not been reported previously so needs

independent replication, and the issue of whether methadone and buprenorphine differentially affect compulsivity and impulsivity requires further study.

Heroin, methadone, buprenorphine users and abstinent individuals deliberated longer and placed bets earlier on the CGT impulsivity measures when compared to healthy controls. Previous studies have reported impaired ability in performing impulsivity tasks in opioid dependent individuals (Baldacchino et al., 2019; Baldacchino et al., 2015; Ersche et al., 2006; Tolomeo et al., 2016) with one study reporting less impairment in impulsivity for the buprenorphine group (Pirastu et al., 2006). We found a negative correlation between compulsivity and impulsivity (Tolomeo et al., 2018). The relevant variables in the linear regression were IED Total Errors and Pre-ED errors for compulsivity and CGT risk adjustment and quality of decision making for impulsivity. This suggests there are different cognitive abnormalities, such as impulsivity and compulsivity, in different stages of the addiction cycle (Koob and Volkow, 2010). Specifically, an initial stage of impulsive drug seeking (positive reinforcement following a period of abstinence), is followed by a later stage of compulsive avoidance of abstinence (negative reinforcement) (Kwako and Koob, 2017). This suggests that impulsivity and compulsivity conceptualised in this way are at opposite ends of a single dimension rather than being independent dimensions.

The present study has some limitations: first, the clinical groups were different from the control group with respect to measures of IQ, age and smoking. However, the results were unchanged when using these measures as covariates. Second, the current study recruited treatment-seeking males and therefore cannot be generalised to either treatment-seeking females or general opioid using populations. Third, the study was not designed to discriminate vulnerability factors for developing opioid dependence from the effects of pre-MMT/BMT polydrug use and the effects of current MMT/BMT use as the study was cross-sectional. Fourth, the morphine equivalent dose was significantly higher in the methadone group in comparison to the buprenorphine group. Fifth, the IED task is sensitive to the identification of impairment in flexibility. Future studies might consider validating the constructs used and adding subjective measures of compulsivity drug use, such as the Obsessive Compulsive Drug Use Scale (OCDUS) (Franken et al., 2002), which can be used to detect craving and the impact of it on life activities.

Longitudinal studies involving individuals at high risk of developing opioid dependence, followed up over many years and long-term abstinence would be required to address the above issues. It is important to note that the present study used stringent criteria to exclude illicit heroin users and co-morbid alcohol, benzodiazepines and stimulants dependence, as these can confound the neurocognitive functions tested. None of the participants had a past or current diagnosis of mood or psychotic disorder, or antisocial or borderline personality disorder. In addition, we managed to control for concomitant confounding variables, such as different previous clinical history with the exception of BMT treatment as being older than ABS when started using benzodiazepines. To our knowledge, this is one of the largest studies providing important evidence for the differential effects of heroin, methadone, buprenorphine and abstinence on compulsivity and impulsivity.

A recent meta-review discussed how impulsivity and compulsivity can be used to inform clinical practice and highlighted more work was required (Lee et al., 2019). This study provides further neurocognitive understanding of the different roles of opioid dependent treatment modalities and abstinence. It also highlights a potential for improving opioid dependence treatments and recovery. Heightened impulsivity is revealed during heroin, methadone and buprenorphine use and abstinence. However, impulsivity may be a risk factor that precedes opioid dependence. Heightened compulsivity persists during heroin and buprenorphine use but not methadone treatment. Additional therapies to enhance cognitive function, such as those that aim to reduce compulsivity might help prevent relapse (Rezapour et al., 2016). A recent systematic review by Verdejo-Garcia and colleagues concluded that Goal Management Training, Contingency Management, plus Cognitive Behavioural Therapy and Reality Therapy had positive effects on decision-making in substance use disorders (Verdejo-García et al., 2019). The authors suggested there is a need for rigorous trials to establish whether these neurocognitive measures have generalised effects on clinical outcomes (Verdejo-García et al., 2019). To focus these efforts, recently Verdejo-Garcia and colleagues proposed that cognitive assessments and neuroimaging methods can help to elucidate biomarkers in substance use disorders for neuroscience-informed interventions (Verdejo-Garcia et al., 2019).

Finally, whilst there is a clinical assumption that a higher dosage of morphine equivalent is more likely to reduce the risk of treatment relapse, this study provides evidence that there is a relationship between higher morphine equivalent dosage and compulsivity but not necessarily impulsivity. Recognition of this relationship could lead to more beneficial treatment trajectories and ultimately better strategies for enhancing treatment and recovery (Lee et al., 2019; Yücel et al., 2019a). In that context, we believe the present study can help advance a neuroscience-informed approach of diagnosis and treatment of opioid dependence.

In conclusion, as hypothesised, heroin, methadone, buprenorphine and abstinent groups exhibited impairment in aspects of impulsivity. Heightened compulsivity persisted in the heroin, buprenorphine and abstinent groups. Higher morphine equivalent dosage correlated negatively with compulsivity and the compulsivity/ impulsivity ratio. These results improve understanding of the development and maintenance of opioid dependence and suggest potential future studies of vulnerability, maintenance and relapse associated with opioid addiction (Tolomeo, 2020; Tolomeo et al., 2020).

Declaration of Competing Interest

Dr Tolomeo has received unrestricted educational grants from Indivior, Lundbeck and Merck Serono. Prof. Steele has received funding from the MRC, Wellcome Trust, Indivior and Wyeth. Prof Baldacchino has received funding from the MRC, CSO, and unrestricted educational grants from Schering-Plough, Merck Serono and Indivior. Dr Davey and the authors declare no conflicts of interest with regard to this work.

Contributors

Dr Tolomeo designed the study, analysed the data and wrote the first draft of the current manuscript. Dr Davey recruited the participants. Profs Steele and Baldacchino designed the study and significantly contributed to the final manuscript. All authors approved the final manuscript.

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Figure legends

Figure 1. Recruitment Flow Chart.

Flowchart of study stages and participants. H=Heroin group; MMT= Methadone Maintenance group; BMT=Buprenorphine Maintenance Treatment group; ABS= Abstinent group; HC= Healthy Control group.

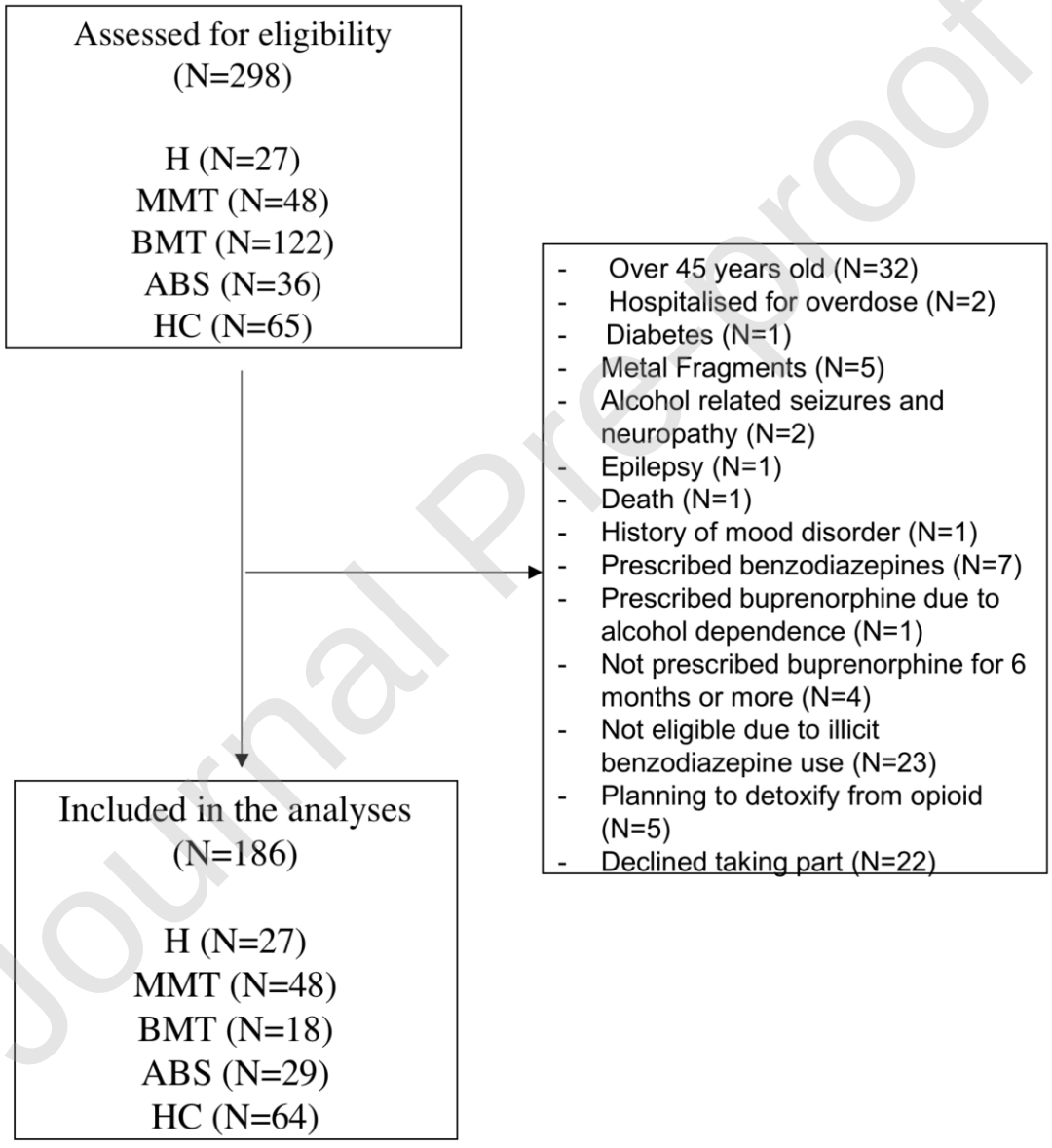

Figure 2.

(A)The heroin and buprenorphine groups made significantly more errors compared to healthy control during the Pre-ED errors; (B) Regression plot between extra-dimensional set shifting errors and morphine dosage. The regression gradient is statistically significant [t = -2.9, *p*=0.006]; (C) Regression plot between extra-dimensional set shifting – total errors. The regression gradient is statistically significant [t = -2.8, *p*=0.007]; (D) Regression plot between compulsivity/impulsivity ratio and morphine. The regression gradient was statistically significant [t =-2.4, *p*=0.02].

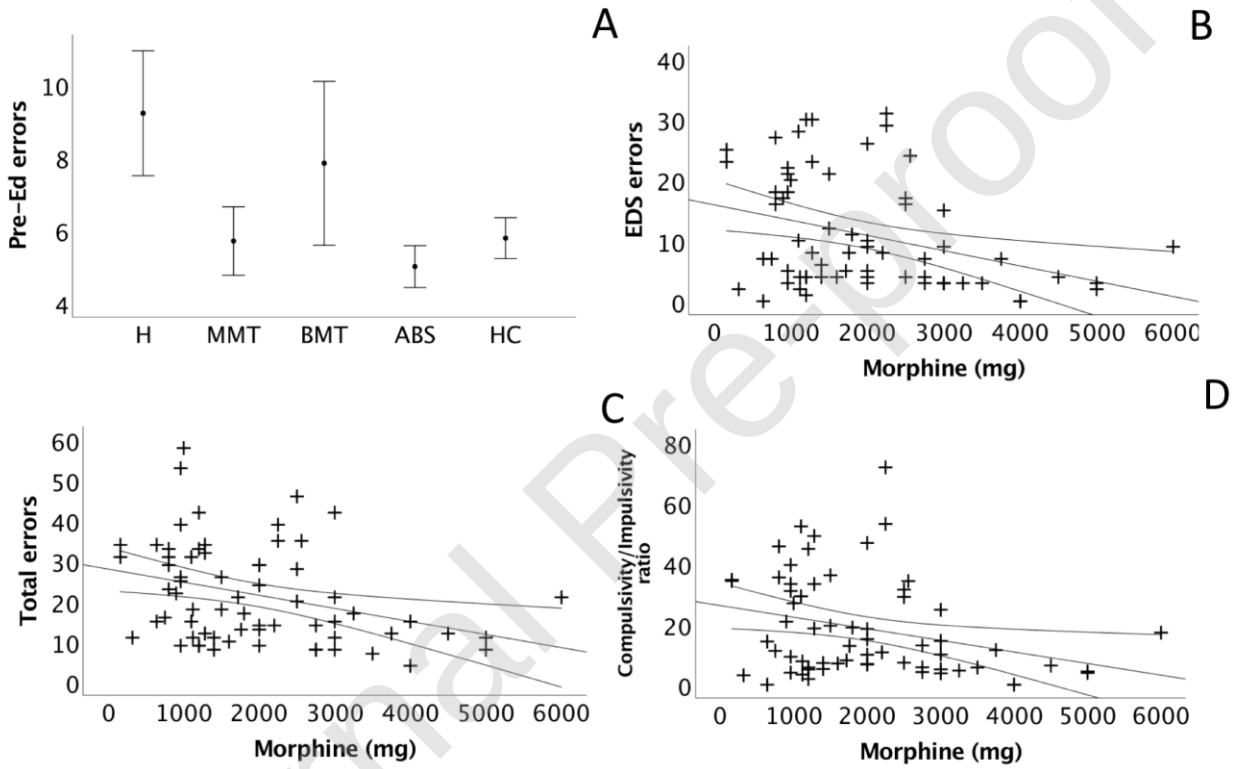

Figure 3.

(A–B) H, MMT, BMT and ABS took more time at deliberation time and risk adjustment in comparison to HC group. (C) H and ABS performed worse in delay aversion than the HC group. (D) Regression plot between CGT risk adjustment and IED total errors. The regression gradient was statistically significant [t =-2.6, *p*=0.01].

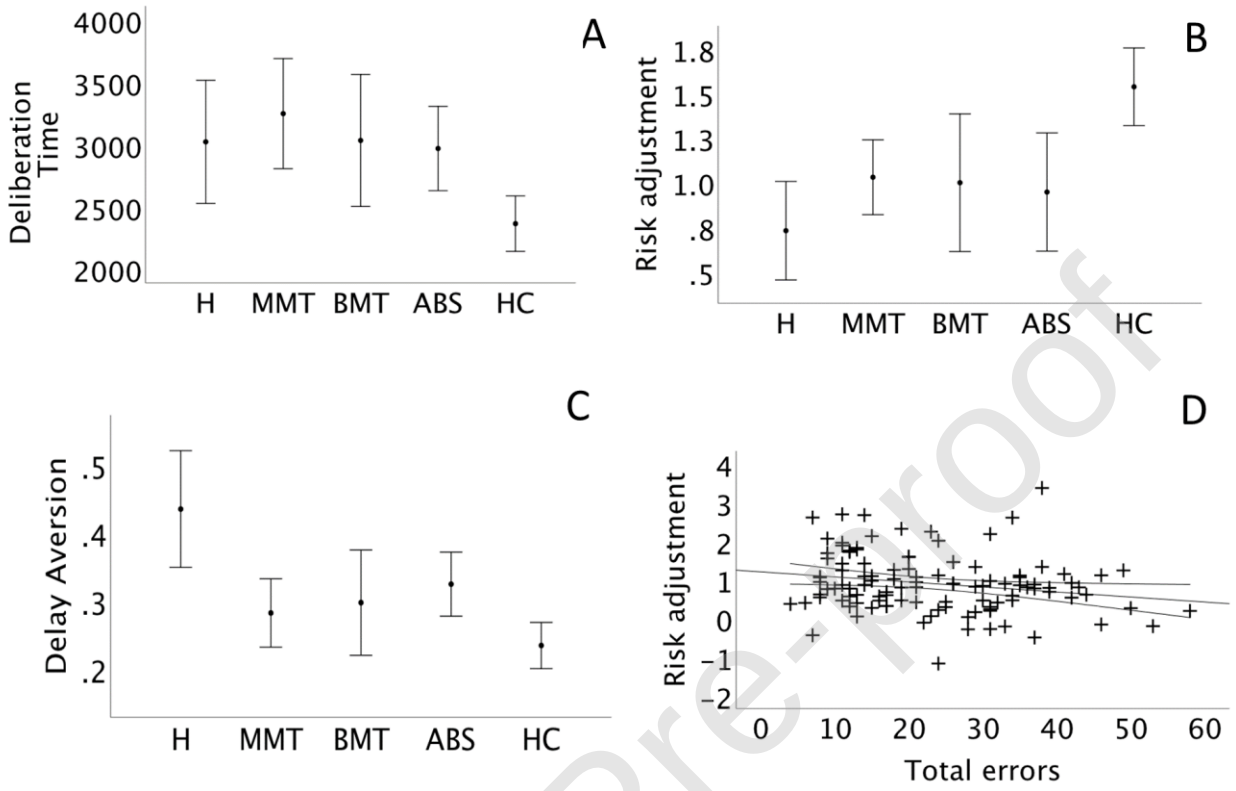

Table 1. Demographic and Clinical Information

	H (n=27)	MMT (n=48)	BMT (n=18)	ABS (n=29)	HC (n=64)	Significance*
Age in years	26.3 (3.45)	30.2 (4.7)	36.8 (6.2)	36.5 (5)	28.7 (7.3)	P<0.001 H<BMT, ABS***
NART	108.6 (12.2)	111.15 (7.3)	98.8 (13.6)	109 (9.8)	117.55 (6.5)	P<0.001 H,BMT<HC***
Daily OD (methadone or buprenorphine) in mg)*	-	117 (60.8)	11 (6.7)	-	-	P<0.001 H,MMT>BMT***
Daily intake expressed as morphine equivalent dose in mg*	-	2341.25 (1216)	888.0 (533)	-	-	P<0.001 MMT>BMT***
Age when first used heroin in years*	19.4 (4.1)	20.2 (4.4)	21.7 (5.4)	20.0 (4.7)	-	ns
Age when dependent on opioids in years*	20.5 (3.9)	20.2 (4.4)	23.6 (5.9)	22.9 (8.5)	-	ns
Age when injecting opioids in years*	20.5 (4)	21.8 (4.2)	24.8 (6)	22.7 (6.9)	-	ns
Years of opioid use*	6.1 (2.9)	12.9 (4.4)	13.4 (6.7)	13.4 (7.6)	-	ns
Age when first used benzodiazepine in years*	16.8 (3.3)	17.2 (5.8)	21.7 (7.7)	15.6 (6.6)		P<0.05 HC<BMT
Days of benzodiazepine use in the last 30 days*	3.0(4.6)	-	-	-	-	-
Age when first used cocaine in years*	17.7(2.3)	17.3 (1)	21.9 (6.6)	18.3 (4.2)	-	ns
Days of cocaine use in last 30 days*	-	-	-	-	-	-
Age when first used cannabis in years*	12.8 (1.6)	13.3 (3.8)	15.8 (5.3)	13.1 (1.2)	-	ns
Days of cannabis use in last 30 days*	12.3 (13.4)	-	-	-	-	-
Age when first used alcohol in years*	12.5 (1.3)	10.5 (7.9)	15.1 (3)	13.0 (1.9)	-	ns
Days of alcohol use in last 30 days*	2.2 (6.1)	-	-	-	-	-
Duration abstinence	-	-	-	Between six weeks to seven months	-	-

Values are mean (SD); H= Heroin group, MMT= Methadone Maintenance Treatment group, BMT= Buprenorphine Maintenance Treatment group, ABS=Abstinent group, HC= Healthy Control group; N= total number; NART= National Adult Reading Test; Significant ***=p<0.001, mg= milligrams, OD=opioid dose (methadone or buprenorphine).* mean (standard deviation); ns=not significant.

Table 2. Compulsivity

Compulsivity (IED measures)	H (n=27)	MMT (n=48)	BMT (n=18)	ABS (n=29)	HC (n=64)	Significance	Partial Eta Squared Value
Pre-ED errors	8.63 (8.4)	5.7 (3.2)	7.8 (4.7)	5.0 (1.5)	5.8 (2.3)	*p*=0.004 H>HC***, H>MMT***, H>ABS***, BMT>HC**	*DV=0.08 IV=0.07 CV=0.001*
Total EDS errors	12.7 (9.96)	9.5 (8.5)	14.6 (10)	13.7 (10.4)	8.4 (8.6)	*p*=0.03	*DV=0.12 IV=0.007 CV=0.07*
Total errors	26.7 (12.6)	19.7 (11.9)	26.8 (11.7)	24.5 (11.6)	16.1 (8.8)	*p*<0.001 H>HC**, BMT>HC**	*DV=0.121 IV=0.01 CV=0.06*
Total errors adjusted	48 (46.6)	23.3 (17.6)	31.7 (17)	30.6 (19.6)	19.1 (15.7)	*p*<0.001 H>HC***, H>MMT***	*DV=0.13 IV=0.004 CV=0.08*
Total stages completed	7.7 (2.1)	8.6 (0.7)	8.5 (0.8)	8.3 (0.9)	8.8 (0.7)	*p*=0.03 H<HC***, H<MMT**,	*DV=0.07 IV=0.001 CV=0.06*

Values are mean (SD); H= Heroin group, MMT= Methadone Maintenance Treatment group, BMT= Buprenorphine Maintenance Treatment group, ABS=Abstinent group, HC= Healthy Control group; n= total number; DV=dependent variable; IV=independent variable; CV=covariate variable *= p <0.05, **=p<0.01, ***=p<0.001; Pre-ED errors=number of errors made prior to the extra-dimensional shift of the task; EDS errors= errors made during the extra-dimensional stage when the participants make an extra-dimensional shift.

Table 3. Impulsivity

Impulsivity (CGT measures)	H (n=27)	MMT (n=48)	BMT (n=18)	ABS (n=28)	HC (n=64)	Significance	Partial Eta Squared Value
Quality of decision making	0.88 (0.1)	0.93 (0.08)	0.92 (0.09)	0.87 (0.1)	0.95(0.06)	$p<0.001$, H,ABS<HC***	*DV=0.003 IV=0.003 CV=0.002*
Deliberation of time	3021 (1223)	3247.6 (1520)	3032 (1064)	2968 (872)	2365 (889)	$p<0.001$, MMT>HC***	*DV=0.02 IV=0.01 CV=0.02*
Risk Taking	0.61 (0.1)	0.65 (0.1)	0.65 (0.1)	0.59 (0.1)	0.61 (0.1)	ns	*DV=0.001 IV=0.001 CV=0.001*
Risk Adjustment	0.73 (0.8)	1.029 (0.7)	0.99 (0.8)	1.1 (1.0)	1.5 (0.9)	$p<0.001$, H<HC***, MMT, BMT,ABS<HC**	*DV=0.003 IV=0.001 CV=0.001*
Delay aversion	0.43 (0.2)	0.28 (0.2)	0.29 (0.16)	0.29 (0.15)	0.23 (0.135)	$p<0.001$ H>HC***	*DV=0.03 IV=0.03 CV=0.01*
Overall Proportion of bet	0.58 (0.1)	0.609 (0.1)	0.59 (0.09)	0.58 (0.12)	0.57 (0.109)	ns	*DV=0.007 IV=0.005 CV=0.005*

Values are mean (SD); H= Heroin group, MMT= Methadone Maintenance Treatment group, BMT= Buprenorphine Maintenance Treatment group, ABS=Abstinent group, HC= Healthy Control group; *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$; CGT= Cambridge Gambling Task; ns= not significant.