Impaired decision-making in opiate-dependent subjects: Effect of pharmacological therapies

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Abstract

Cognitive dysfunction is a major feature of drug addiction. In the present paper, we compared the decision-making ability using the Iowa gambling task of methadone- and buprenorphine-maintained individuals to non opiate-dependent drug-free controls. Buprenorphine-maintained individuals performed better than methadone-maintained individuals, and not differently than non opiate-dependent controls. In addition, methadone-maintained individuals had more perseverative errors on the Wisconsin card sorting task (WCST) as compared with non opiate-dependent drug-free controls whereas buprenorphine-maintained individuals had intermediate scores. Scores on Weschler adult intelligence scale (WAIS-R) were similar for methadone- and buprenorphine-maintained individuals whereas drug-free controls had significantly higher scores. In addition, both opiate-dependent groups performed more poorly than drug-free controls on the Benton visual retention test (BVRT). The results suggest that buprenorphine in contrast to methadone improves decision-making, and thus may be more effective in rehabilitation programs of opiate-dependent subjects and this improvement may be related to its distinct pharmacological action as a δ antagonist.

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1. Introduction

Drug addiction is a brain disease (Pulvirenti and Diana, 2001; Melis et al., 2005) accompanied by cognitive dysfunction. Accordingly, the DSM IV (APA, 1994) includes continued use in spite of knowledge of negative consequences and loss of control over intake in the diagnostic criteria for substance dependence, in which impaired decision-making is widely recognized as an important contributing factor. In particular, methadone-maintained participants perform worse on the Iowa gambling task (GT; Bechara et al., 1998) compared to non drug users (Mintzer and Stitzer, 2002). The GT has been developed as an instrument for functional assessment in neurological patients with lesions of the ventromedial prefrontal cortex who exhibit poor decision-making in every day life (Bechara et al., 1994, 1998, 2000). This card game task requires participants to choose between options with larger short-term gains offset by greater long-term losses and those with smaller short-term gains and long-term losses, i.e., greater overall gain. This instrument has also been useful in demonstrating impairments in research participants who reported use of other drugs such as of cocaine (Bartzokis et al., 2000; Grant et al., 2000; Bechara et al., 2001) and alcohol (Mazas et al., 2000; Bechara et al., 2001). Further, part of the prefrontal cortex (i.e., the orbitofrontal cortex, OFC) has been suggested to be involved in drug addiction processes, possibly through a reduced inhibition of impulsive behaviors (Kringelbach and Rolls, 2004; Volkow et al., 2004). Neuroimaging studies have shown activation during the GT (Ernst et al., 2002) in healthy adults and higher normalized metabolic rates in temporal and frontal areas, including orbitofrontal cortex, in human drug users (Stapleton et al., 1995; London et al., 2000), consistent with a primary role of OFC. All these findings support the notion that prefrontal cortical cellular mechanisms, including orbitofrontal, are crucial in cognitive function...
in general and decision-making in particular (Fukui et al., 2005).

Among the various pharmacological treatments currently available for opiate addiction, methadone and buprenorphine are among the most widely employed. While methadone is a pure and unselective opiate agonist, buprenorphine is currently classified as a mixed agent (i.e., μ agonist and κ antagonist) (Reesink and Pasternak, 1995). In addition, κ receptors are located in cortical areas of several species including rats (Morris and Herr, 1986), rabbits (Meunier, 1982) and humans (Cross et al., 1987), raising the possibility that pharmacological manipulation of this receptor may affect cellular mechanisms crucial for cognitive (dis)function in opiate-dependent individuals. In the present paper, we sought to evaluate decision-making using the GT in individuals maintained on methadone compared to individuals maintained on buprenorphine as well as non drug-dependent controls.

2. Methods

2.1. Participants

Three groups of participants were recruited. Participants in the first group were methadone-maintained outpatients (MMP; \(n = 30\)) and participants in second group were buprenorphine-maintained outpatients (BMP; \(n = 18\)). Both groups were diagnosed as opiate-dependent according to DSM IV-R criteria and had attended the local drug addiction clinic (Servizio Tossicodipendenze ASL 7 – Iglesias) for at least 12 months. Participants in the third group were non opiate-dependent controls (CS; \(n = 21\)) with no history of drug dependence, matched socially and demographically (age, gender, employment, etc., see Table 1) with other groups. Exclusion criteria for all groups included organic CNS pathology, diagnosis of any axis 1 disorder, head trauma resulting in loss of consciousness for longer than 5 min, dementia, current therapy with medications known to affect cognitive function, and past and present alcohol and other illicit substance dependencies.

### Table 1

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>MMP ((n = 30))</th>
<th>BMP ((n = 18))</th>
<th>CS ((n = 21))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>29/1</td>
<td>17/1</td>
<td>14/7</td>
</tr>
<tr>
<td>Age</td>
<td>35 (25–44)</td>
<td>33 (22–46)</td>
<td>34 (20–53)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8.37 ± 0.58 (5–18)</td>
<td>8.72 ± 0.91 (5–18)</td>
<td>10.66 ± 0.88 (8–18)</td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td></td>
<td>18/3</td>
</tr>
<tr>
<td>Yes/no</td>
<td>19/11</td>
<td>11/7</td>
<td></td>
</tr>
<tr>
<td>Duration of dependence (years)</td>
<td>15.53 ± 1.7 (2–29)</td>
<td>13.28 ± 1.28 (6–26)</td>
<td></td>
</tr>
<tr>
<td>Drug-treatment dose (mg/day)</td>
<td>66 ± 7.45 (2–150)</td>
<td>9 ± 1.34 (2–20)</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment (years)</td>
<td>8.3 ± 0.69 (1–12)</td>
<td>5.4 ± 1.01 (1–12)</td>
<td></td>
</tr>
<tr>
<td>Number of positive urinalysis/12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>3.6 ± 1.02 (0–23)</td>
<td>1.56 ± 0.66 (0–11)</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>2.33 ± 0.94 (0–24)</td>
<td>2.11 ± 0.61 (0–8)</td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>1.43 ± 0.55 (0–11)</td>
<td>2.81 ± 0.69 (0–9)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as means ± S.E.M. and ranges.*

### 2.2. General procedures

Unpaid volunteers who met study criteria based on the results of an initial screening interview were informed about the objectives and details of the study by the project director and they signed a written consent form acknowledging their understanding of the protocol prior to enrollment. All participants were older than 18 years of age. General demographic information, background characteristics and treatment history were collected and drug abuse severity was detailed for all participants by a drug history survey and medical examination. All participants were clinically evaluated for psychiatric status according to DSM IV-R criteria both for drug abuse and psychiatric disorders. Urinalyses were conducted weekly during a 12-month period for occasional use of heroin (cut-off 300 ng/ml), cocaine (cut-off 300 ng/ml) and cannabis (cut-off 50 ng/ml). Tests were performed using an automated (ILab 600) immunoenzymatic assay purchased from Instrumentation Laboratory (Milano, Italy).

### 2.3. Experimental procedures

#### 2.3.1. Gambling task

All participants were tested with the GT to assess decision-making ability. The GT was administered by a computer program, as in some other studies (Ernst et al., 2002, 2003). Participants were instructed to accumulate as much (play) money as possible by picking one card at a time from each of the four decks. Participants selected 100 cards from four decks with the goal of obtaining the highest payout of virtual money. Each card choice provided a reward of virtual money or a potential penalty, which was revealed only after turning up the card. Two of the decks yielded higher payouts with higher penalties (disadvantageous decks). The remaining two decks resulted in lower payouts with lower penalties (advantageous decks). However, while the reward of the disadvantageous decks was twice as high as the advantageous decks, the punishment was two times as high. The advantageous decks generated smaller rewards more frequently while the disadvantageous decks generated larger rewards less frequently (Bechara et al., 1994, 1998, 2001, Grant et al., 2000; Ernst et al., 2002, 2003; Bolla et al., 2003).
2.3.2. Neuropsychological test battery. Prior to neurocognitive testing sessions with the GT, participants completed a neuropsychological test battery to assess specific dysfunction(s).

2.3.2.1. Wechsler adult intelligence scale-revised (WAIS-R). The Wechsler adult intelligence scale-revised (Norman, 1966; Benoff, 1970) designed as a comprehensive test of cognitive ability for adults, is a general test of intelligence, which Wechsler defines as "... the global capacity of the individual to act purposefully, to think rationally, and to deal effectively with his environment" (Wechsler, 1981).

2.3.2.2. The Wisconsin card sorting test (WCST). The WCST is a measure of abstract conceptual skills, cognitive flexibility and ability to test hypotheses and utilizes error feedback (Tien et al., 1996). The test is sensitive to the effects of frontal lobe injury and may be a useful indicator of brain damage. The WCST requires sorting 128 cards that depict colored numbered shapes into four categories using accuracy feedback (Tien et al., 1996) given after each trial. The criterion for correct categorization (color, number or shape) changes whenever 10 consecutive cards are sorted correctly. Standard scoring procedures yield six measures of performance (Spreen and Strauss, 1991).

2.3.2.3. Benton visual retention test (BVRT). The BVRT is a measure to assess visual perception, visual memory and visual constructive abilities. It provides three alternative, almost equivalent forms (forms C-E) of the task. Each form consists of 10 drawings and each drawing contains one or more figures. It can be administered in four different ways: in our study the subject had to look at the figure for 10s and after that to reproduce it. The performance is evaluated by two different scores: number of correct designs (out of 10) and number of errors.

2.3.3. Data analysis. Differences in performance on the GT, IQ scores measured by WAIS, WCST performance and BVRT among the three groups were evaluated with analysis of covariance (ANCOVA) using years of education and number of years enrolled in the substitution treatment program as covariates. Dependent measures for GT were choices made from advantageous vs. disadvantageous decks and "net score" (i.e. number of cards selected from the advantageous decks minus number of cards selected from disadvantageous decks). The dependent measure of IQ was the "full scale IQ" obtained on the WAIS test, whereas the dependent measure for WCST was "perseverative errors" defined as two consecutive errors upon change of categorization and for BVRT the number correct out of 10. To improve the normal distribution of IQ and WSCT scores, the data set was transformed to a logarithmic scale. Pair-wise comparisons between groups were made with the least significant difference post hoc test (LSD). Statistical analyses for demographic data were obtained with ANOVA and LSD post hoc test where appropriate, using the software SPSS for Windows, Version 10.1, SPSS Inc., Chicago, IL. All tests considered a minimum alpha level of $p<0.05$.

3. Results

3.1. Participants

The total sample of the present study is composed of 69 subjects, aged between 20 and 53 years. All were nicotine-dependent. Demographic characteristics of the three experimental groups are shown in Table 1. The groups did not differ significantly with respect to mean age ($p > 0.05$ one-way ANOVA). Years of education were similar for the MMP and BMP groups (LSD post hoc $p = 0.744$) and the BMP and CS groups (LSD post hoc $p = 0.072$) whereas for the MMP and CS groups the difference was statistically significant (LSD post hoc $p = 0.019$) ($F_{3,66} = 3.121, p = 0.051$). In addition, the MMP and BMP groups were not significantly different on the mean number of times of positive urinalysis for heroin ($t_{66.6} = 1.683, p = 0.095$), cocaine ($t_{66} = 0.170, p = 0.866$) or cannabis ($t_{66} = -1.382, p = 0.174$).

3.2. Gambling task

The three groups scored differently on decision-making performance measured by the GT (Table 2). The BMP group selected an average of about 60 cards from advantageous decks versus about 40 cards from disadvantageous decks. Similarly, the CS group selected an average of about 58 and 42. In contrast, the MMP group selected an average of about 52 cards from advantageous decks versus 48 from disadvantageous decks. Thus, the MMP group’s performance was significantly different (lower) from both the BMP and CS groups. In addition, differences among groups were also evaluated by using the mean "net score" (number of cards selected from the advantageous decks minus number of cards selected from disadvantageous decks). The MMP group scored significantly lower than both the BMP and CS groups (Table 2). However, because a statistical difference was observed in years of education and length of treatment between the MMP and BMP groups, an ANCOVA using these two variables as covariates for the net score was performed with the results confirming a difference ($F_{3,66} = 2.934; p = 0.05$).

Out of the total 69 subjects, 22 (32%) performed in the negative range i.e., selected disadvantageous decks over advantageous ones. Interestingly, among all subjects performing in the negative range, 12 belonged to the MMP group (40%), whereas only 4 were in the BMP group (22%) and 6 were in the CS group (29%) (Fig. 1).

3.3. Neuropsychological Battery

In Table 2 are reported the values of the WAIS, WCST and BVRT. Both MMP and BMP IQ scores were significantly lower than CS ($F_{2,66} = 13.078, p < 0.01$), but not significantly different from each other. WCST scores (perseverative errors) were significantly different between MMP vs. BMP and MMP vs. CS ($F_{2,66} = 8.175, p = 0.01$). Furthermore both MMP and BMP were significantly different when compared with control subjects on BVRT scores (correct) ($F_{2,66} = 11.684, p < 0.001$).
Data are expressed as means ± SEM and ranges. $p < 0.05$: net scores (vs. MMP; n.s. vs. CS); perseverative errors (vs. CS; n.s. vs. BMP); full scale IQ (vs. MMP and BMP); correct (vs. MMP and BMP).

**F** net scores ($F_{2,65} = 3.707$); perseverative errors ($F_{2,65} = 13.913$); correct ($F_{2,65} = 10.072$).

4. Discussion

Cognitive and behavioral changes may develop subsequent to drug use (Petry et al., 1998). Research demonstrates that acute substance use results in myopic behavior, or focusing of attention on more salient features of a situation and ignoring long-term consequences or less-salient information (Josephs and Steele, 1990; Steele and Josephs, 1990). Chronic drug use may lead (or exacerbate pre-existing) structural or functional damage that manifests in cognitive deficits including long-term heroin and polysubstance abuse (Zacny, 1995). Regardless of whether these deficits result from drug use itself or from a condition that is associated with drug abuse, previous work suggests that treatment and drug abstinence may reverse or partially reverse these deficits (Petry et al., 1998).

From a behavioral point of view, drug addicts share certain characteristic with patients who have suffered neurological damage to the ventromedial prefrontal cortex, such as the persistent making of choices based upon immediate reward, even though they may be fully aware of long-term negative consequences of their actions. This “myopia for the future” has been demonstrated in patients with ventromedial prefrontal cortex lesions (Bechara et al., 1994) using a gambling task that is able to detect and measure the decision-making impairment, testing the ability to balance immediate rewards against long-term negative consequences. Using this task, several studies have demonstrated decision-making impairments in other disorders, as well as in cocaine, opiate and alcohol abusers (Bechara et al., 2001; Grant et al., 2000; Mazas et al., 2001; Rogers, 2000), who have shown abnormalities in ventromedial prefrontal cortex during functional neuroimaging studies (Homer et al., 1997, Volkow et al., 1991).

The observations reported in the present paper suggest that opiate-dependent patients maintained on buprenorphine perform significantly better than those maintained on methadone on the GT, an index of decision-making (Bechara et al., 1998). In fact, the BMP group performed similar to demographically-matched healthy drug-free subjects. Moreover, the difference between the BMP and MMP groups on GT performance cannot be ascribed to a general better intellectual capacity as IQ evaluations through administration of the WAIS and prefrontal cortical function examined through the WCST yielded similar results for both groups of opiate-dependent individuals. In addition, the finding cannot be ascribed to better visual perception and memory because the BMP and MMP groups showed similar results when assessed with BVRT.

Although WCST and GT may tap into the same cognitive resources (executive function, problem solving capacity, abstract conceptual skill, working memory) located in the same cortical area, the GT is a more sensitive measure of a specific function, namely decision-making ability requiring evaluation of long-term consequences. Therefore, it may not be surprising that MMP and BMP groups performed similarly in the WCST, suggesting similar capacities in modifying cognitive strategies when changing environmental circumstances, and in contrast, the MMP group scored more poorly than the BMP group on the GT, possibly owing to the reward component of this test. This
finding would suggest that individuals maintained on buprenor-
phine, compared to individuals maintained on methadone, would
be more aware of long-term consequences, rather than immedi-
ate reward or punishment (Ersche et al., 2005), thereby favoring
higher scoring in the GT. However, the present results await con-
firmation from different methods aimed at further evaluating
decision-making to draw firm conclusions on decision-making
abilities in real-life. Further studies, evaluating decision-making
performances during methadone therapy, followed by a substi-
tution with buprenorphine, would seem particularly helpful.

These results are part of a growing body of basic (Tszschentke,
2002, 2004) and clinical evidence (Fudala and Woody, 2005; Oreskovich et al., 2005; Verdejo et al., 2005) that suggest
that pharmacological antagonism of k opiate receptors, obtained with
buprenorphine, may improve response to treatment (Rothman
et al., 2000), reduce use of opiates (Fudala et al., 2003) and
highlight the role of cortical k opiate receptors in cognitive func-
tions in general and decision-making in particular. In addition,
the relative ratio between k and µ receptors may also underlie
buprenorphine-induced effects observed here. In line with this,
buprenorphine reduces drug-seeking behavior and self-reported
craving for heroin (Greenwald et al., 2002). Recent PET stud-
ies (Zubieta et al., 2000) have shown a reduction in µ receptors
after buprenorphine treatment in male heroin-dependent volun-
teers with major (between 46 and 85%) and dose-dependent
reductions in cortical areas (Zubieta et al., 2000; Greenwald et
al., 2003) known to be involved in cognitive processing, such
as the prefrontal cortex, crucial for decision (Bechara et al.,
1998). These possibilities await experimental testing and fur-
ther research aimed at investigating the relative roles of µ and k
receptors is warranted.

In conclusion, the present results in opiate addicts suggest that
buprenorphine-maintained patients on the GT that indexes decision-making ability. This effect cannot be ascribed to a general difference in intellectual capacity of the two groups, as both scored similarly in the WAIS and WCST. Further studies with larger numbers and different means of evaluating decision-making are needed to fur-
ther confirm the possibility that buprenorphine may be helpful in
some cognitive tasks reflecting real-life situations. Nevertheless,
the present observations suggest that pharmacological blockade
of k receptors and/or stimulation of µ with buprenorphine may
improve cognitive performance as measured by the GT in opiate-
dependent subjects.

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References


Fukun, R., Murai, T., Yokoyama, H., Hayashi, T., Hanakawa, T., 2005. Func-
tional activity related to risk anticipation during performance of the Iowa
gambling task. Neuroimage 24, 253–259.


phine maintenance dose on M-opioid receptor availability, plasma con-

Hommer, D., Andreasen, P., Rio, D., Williams, W., Rattuman, U., Mom-

Josephs, R.A., Steele, C.M., 1990. The two faces of alcohol myopia: atten-
tional mediated and psychological distress. J. Abnormal Psychol. 99, 115–126.


