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**Inferring about individual drug and schizotypy effects on cognitive functioning in polydrug using mephedrone users before and after clubbing**

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Review

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3 Inferring about individual drug **and schizotypy** effects on cognitive functioning in polydrug  
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5 using mephedrone users before and after clubbing  
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## Abstract

Objective: Mephedrone has been recently made illegal in Europe, but little empirical evidence is available on its impact on human cognitive functions. We investigated acute and chronic effects of mephedrone consumption on drug-sensitive cognitive measures, while also accounting for the influence of associated additional drug use and personality features.

Method: Twenty-six volunteers from the general population performed tasks measuring verbal learning, verbal fluency and cognitive flexibility **before and after a potential drug-taking situation (pre- and post-clubbing at dance clubs, respectively). Participants also provided information on chronic and recent** drug use, schizotypal (O-LIFE) and depressive symptoms (Beck depression inventory), sleep pattern and premorbid IQ.

Results: We found that i) mephedrone users performed worse than **non-users pre-clubbing, and deteriorated from the pre-clubbing to the post-clubbing assessment, ii) pre-clubbing cannabis and amphetamine (not mephedrone) use predicted relative cognitive attenuations, iii) post-clubbing, depression scores predicted relative cognitive attenuations,** and iv) schizotypy was largely unrelated to cognitive functioning, apart from a negative relationship between cognitive disorganisation and verbal fluency.

Conclusion: **Results suggest that polydrug use and depressive symptoms in the general population negatively affect cognition. For schizotypy, only elevated cognitive disorganisation showed potential links to a pathological cognitive profile previously reported along the psychosis dimension.**

**Keywords:** New-wave drugs, **mephedrone**, cognition, psychosis spectrum, substance dependence, cathinone

## Introduction

Drugs are feared to threaten our mental health facilitating politics that criminalise their distribution and use (Nutt et al., 2010). While we increasingly know about the clinical, cognitive, and physical implications when individuals use “conventional” licit and illicit psychoactive substances (Fernández-Serrano et al., 2011, e.g. heroine, cocaine, nicotine; Fernandez-Serrano et al., 2010, Nutt et al., 2010), we are yet to accumulate a comparable knowledge on so called “new wave” designer drugs. New wave designer drugs encompass a range of modern psychoactive substances, which have been both specifically marketed and synthesized for the aim of providing an intoxicating high. Since they are new, legislations have not yet been established, making the use of many of these substances officially legal and therefore attractive (Dargan et al., 2010).

The most popular of these drugs are based on the substance **cathinone**, a compound found in the khat plant (see Schifano et al., 2010 for overview). One derivate of cathinone is a substance widely referred to as **mephedrone**, (colloquially known as “4-MMC, MMCat, Meow/Miaow Miaow, Bubbles, Meph, Rush, Drone, Plant Feeder”) which has been relatively popular in the clubbing scene in recent years (Winstock et al., 2011, Wood et al., 2012).

Cathinone substances have a chemical structure similar to amphetamine (Hoffman and Al'Absi, 2010, Dal Cason et al., 1997, Prosser and Nelson, 2012), a similarity that is also reflected in the observation that they seem to mimic the physiological and psychological actions of amphetamines (Kalix, 1992, Schifano et al., 2010). For instance, both cathinones and amphetamines prevent the uptake and stimulate the presynaptic release of dopamine, serotonin and noradrenalin (see Kalix, 1992 for overview). Importantly, similarly to amphetamines, high doses of mephedrone can induce hallucinations (ACMD, 2010, Vardakou et al., 2011, James et al., 2010). To assess the physiological and psychological effects of cathinones, Brenneisen et al.

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2  
3 (1990) investigated the effects of intravenous administration of cathinone in human participants  
4 and discovered that the drug markedly increased heart rate and blood pressure in comparison to  
5 placebo. Furthermore, participants reported an increased sense of euphoria and sociability, which  
6 is comparable to independent reports on the psychological effects of mephedrone (Morris, 2010).  
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8 Reports such as these facilitated a fierce debate on the potential risks and harmfulness of  
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10 mephedrone, and its use was recently made illegal in the UK (see Vardakou et al., 2011 for  
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12 overview, Winstock et al., 2011) and other European countries (EMCDDA, 2010a, EMCDDA,  
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14 2011, EMCDDA, 2012).

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23 Despite some scientific explorations on the physiological and psychological effects of cathinones  
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25 (Brenneisen et al., 1990, James et al., 2010, Vardakou et al., 2011, ACMD, 2010, Morris, 2010,  
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27 Wood and Dargan, 2012), studies on the cognitive effects of these substances are surprisingly  
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29 sparse (Hoffman and Al'Absi, 2010), and to our knowledge have only recently started to be  
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31 investigated. For instance, **that use has been found to relate to impairments in working**  
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33 **memory and cognitive flexibility (Colzato et al., 2011b), increased response conflict**  
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35 **(Colzato et al., 2012) and decreased inhibitory control (Colzato et al., 2011a).** Given the  
36  
37 similarities between amphetamines and cathinones in chemical structure (Dal Cason et al., 1997)  
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39 and subjective reports (Brenneisen et al., 1990, James et al., 2010, Vardakou et al., 2011,  
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41 ACMD, 2010, Morris, 2010, Wood and Dargan, 2012), it seems justified to expect cathinone use  
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43 to result in similar cognitive peculiarities to those reported after amphetamine use. If this  
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45 reasoning is indeed considered feasible, we can infer from previous experimental research into  
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47 the cognitive harms of amphetamines (see Fernández-Serrano et al., 2011, Kalechstein et al.,  
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49 2007 for overview) that mephedrone (and other derivatives of cathinones) might negatively affect  
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51 various aspects of cognition such as working memory (Curran and Travill, 1997), verbal fluency  
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3 (Hanson and Luciana, 2004), cognitive flexibility (King et al., 2010), verbal learning (Gonzalez  
4 et al., 2004, Laws and Kokkalis, 2007, McCardle et al., 2004, Parrott and Lasky, 1998), and  
5 mood (Curran and Travill, 1997, Parrott and Lasky, 1998). Given that these predictions are based  
6 on inferences from research on amphetamines, we here aimed to test more directly whether  
7 cognitive impairments reported from amphetamine use might also be observed for **mephedrone**  
8 **use** or other drug use more broadly.  
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11 While the question on cognitive impairments as a function of drug use seems straightforward, it  
12 misses out on the equally important question on who would be most prone to use such drugs in  
13 the first place, or who might have a higher risk of experiencing harmful consequences from drug  
14 consumption. Knowing about these influential factors should indeed be of interest to clinicians  
15 and society more broadly, because early detection might help reduce negative long-term  
16 consequences for mental health (Bird et al., 2010, Marshall and Rathbone, 2006, Larsen et al.,  
17 2011). One factor associated with enhanced drug use is schizotypy (see Barkus and Murray,  
18 2010 for overview), a personality construct that has also been associated with an enhanced risk  
19 for psychiatric conditions (Chapman et al., 1994, Gooding et al., 2005).  
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22 Schizotypy is thought to describe subjective experiences in the general population that are  
23 reminiscent of those reported from patients with schizophrenia, but in a milder form (Meehl,  
24 1962). Such similarities are not only evident on the phenomenological level, but are also found  
25 for cognitive functions. In more detail, cognitive impairments that are common in patients with  
26 psychosis are also found along the psychosis dimension, although less severe, such as in  
27 individuals with a schizotypal personality disorder [see Reichenberg & Harvey (2007) for  
28 overview], and individuals from the general population scoring relatively high on self-report  
29 schizotypy questionnaires (Krabbendam et al., 2005, Poreh et al., 1995, Burch et al., 2004,  
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3 Laurent et al., 2001, Vollema and Postma, 2002). Most important to the present study, cognitive  
4 functions relying on the frontal lobes such as cognitive flexibility (Diforio et al., 2000, Laurent et  
5 al., 2000, Voglmaier et al., 1997, Blanchard et al., 2010), working memory (Voglmaier et al.,  
6 1997, Voglmaier et al., 2005, Park and McTigue, 1997, Kopp et al., 2002), **verbal memory**  
7 (Kaczorowski et al., 2009, Burch et al., 2006) and verbal fluency (Laurent et al., 2000,  
8 Tsakanikos and Claridge, 2005) seem attenuated along the psychosis spectrum including  
9 schizotypy (see also Reichenberg and Harvey, 2007 for overview).

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21 A potential problem of the above described literature is that only few investigated cognition,  
22 drug use and schizotypy simultaneously, i.e. studies either investigated the influence of a  
23 particular drug on cognition, the link between drug use and schizotypy, or the relationship  
24 between schizotypy and cognitive functioning. Yet, in the latter case, individuals with elevated  
25 schizotypy are also likely to be subject to relative enhanced polydrug use, without this drug  
26 consumption being accounted for. We found **14 studies investigating the link between**  
27 **schizotypy and cognitive flexibility, verbal memory and verbal fluency; seven of them did**  
28 **not report on drug use** (Laws et al., 2011, Giraldez et al., 1999, Dinn et al., 2002, Lenzenweger  
29 and Korfine, 1994, Park et al., 1995, Tsakanikos and Claridge, 2005, Burch et al., 2006), and the  
30 others varied in their drug control criteria (Poreh et al., 1995, Daneluzzo et al., 1998, Kim et al.,  
31 2011, Suhr, 1997, Koychev et al., 2011, Kaczorowski et al., 2009, Matheson and Langdon,  
32 2008). It is thus possible that substance use (e.g. illicit as well as licit substances) influenced the  
33 relationship between schizotypal symptoms and the cognitive functions assessed (Herzig et al.,  
34 2010, Herzig and Mohr, 2012). As will be shown in the following, the present study took this  
35 reasoning into account.

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3 We investigated the potential role of current mephedrone use (but also of other common drugs)  
4 on cognitive functioning, and how this relationship might be influenced by individuals'  
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6 schizotypy. In particular, we adopted a "natural" design in which a group of participants was  
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8 tested twice, before (pre-clubbing) and after (post-clubbing) their clubbing experience. Because  
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10 mephedrone was a preferred clubbing drug at the time of testing, we expected that some  
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12 participants would consume new wave designer drugs such as mephedrone. This experimental  
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14 design not only allowed to account for changes of cognitive functioning over the course of a  
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16 clubbing experience (short-term) but also whether individuals using mephedrone have a more  
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18 severe overall drug history (polydrug use) potentially implying that their cognitive functioning is  
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20 already relatively impaired at the pre-clubbing stage (long-term effects).  
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28 Given the similarity between the physiological and emotional effects of cathinones and  
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30 amphetamines, we predict that mephedrone users as compared to non-users should show  
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32 relatively impaired cognitive functioning as reported from amphetamine users (cognitive  
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34 flexibility, verbal learning and verbal fluency). Moreover, we considered the possibility that drug  
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36 use rather than schizotypy would be the dominant predictor of these relatively impaired cognitive  
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38 functions (Herzig et al., 2010, Herzig and Mohr, 2012). Because of the reported links between  
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40 various drugs of abuse, mood and sleep patterns on cognition we also controlled for possible  
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42 influential variables such as depression (Deykin et al., 1987, Davison and Parrott, 1997, Curran  
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44 and Travill, 1997, MacInnes et al., 2001) and sleep (Curran and Travill, 1997, Carhart-Harris et  
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46 al., 2008). By accounting for these variables a 'purer' measure of the effects of drug use on  
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48 cognition is expected to derive.  
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## 54 55 **Methods**

### 56 57 *Participants*



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3 Participants were recruited using a combination of snowballing sample method and  
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5 advertisements, distributed at local businesses and university departments in the Bristol area. It  
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7 was made explicitly clear that only members of the clubbing community (**those going to dance**  
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9 **clubs**) were eligible to take part in the study, although no mention was made of drug use.

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12 Participants were excluded if they reported any major psychiatric illness or chronic health  
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14 problems. Furthermore, participants were excluded if they were currently taking psychoactive  
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16 medication (such as antidepressants, analgesics or neuroleptics), and/or had suffered from any  
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18 form of organic head injury according to self-report. No pressure was placed on participants to  
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20 consume psychoactive drugs at any point during the research, and no reimbursement was given  
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22 for participants' time. Instead, they were entered into a prize draw to win £100 worth of vouchers  
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24 to spend in a Bristol based business enterprise. We were able to recruit 26 native English  
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26 speakers (**all educated to at least degree level**) who were willing to participate shortly before  
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28 and after their clubbing experience. **All participants provided written informed consent.** The  
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30 study was approved by the ethics committee of the University of Bristol, Department of  
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32 Experimental Psychology.  
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### 39 *Procedure*

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42 Participants completed a total of two experimental sessions, lasting approximately an hour each.  
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44 The pre-clubbing session took place (mostly) on the Friday, in a quiet laboratory in the  
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46 Department of Experimental Psychology, University of Bristol. This session acted as a baseline  
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48 for measuring participants' cognitive performance when abstinent from current psychoactive  
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50 drugs (baseline cognitive functioning). Drug use information was not analysed during this  
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52 session, rendering the experimenter blind to participants' drug history. During this session  
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54 participants completed all of the cognitive tasks and questionnaires (details are given below).  
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3 Following completion of these tasks participants were instructed to engage in their usual  
4 clubbing experience. It is important to note that participants were not aware that the study was  
5 assessing the link between mephedrone use and cognition, therefore preventing to stimulate  
6 participants' motivation to consume drugs to be eligible for this study. The post-clubbing session  
7 was arranged approximately 48 hours after the night that they went clubbing (e.g. if they went  
8 clubbing on Friday the next testing session would be on Sunday). Participants were considered  
9 mephedrone users if they reported mephedrone use in the 48 hours between the pre-clubbing and  
10 post-clubbing testing session. The post-clubbing testing session involved exactly the same  
11 cognitive measures and tests that were completed in session 1. Considering the likely polydrug  
12 use of clubbers, participants also filled out additional questionnaires that measured their current  
13 and past psychoactive drug use (including any drugs taken in the period between testing  
14 sessions).

### 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 *Tasks*

#### 34 35 Cognitive tests<sup>1</sup>

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37 Premorbid verbal intelligence: The national adult reading test (NART)

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39 To ensure groups were matched on IQ, participants completed the NART at the beginning of the  
40 pre-clubbing session. The NART is designed to provide a measure of verbal IQ, through the  
41 visual presentation of a list containing 50 irregular words, which the participant is required to  
42 pronounce in serial order (Nelson, 1982). The NART is a widely used and reliable test that takes  
43 advantage of the correlation between reading ability and intelligence in the normal population  
44 (Wiens et al., 1993). The greater the number of correctly pronounced words the higher a  
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57 <sup>1</sup> We measured a computerised Go NoGo task as well. Due to an overall ceiling performance, we omitted this task  
58 from all further analysis. Detailed information on this task can be requested from the first author.  
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3 participant's verbal IQ. Normative values for the English version in healthy adults can be found  
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5 in Crawford et al. (1989).  
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10 Verbal learning and memory: The Rey Auditory verbal memory task (RAVLT)

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12 The RAVLT (e.g. Spreen and Strauss, 1998) is an easy to administer task assessing verbal  
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14 learning as well as immediate and delayed recall. A series of 15 nouns are read aloud to the  
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16 participant (separated by one second intervals) for five consecutive trials. Each trial is followed  
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18 by an immediate free recall test. We assessed the number of correctly recalled words over the  
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20 five trials (maximum 75). Finally, after a delay of 25 minutes, participants were again asked to  
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22 recall the original word list (delayed recall). We calculated percentages of the correctly recalled  
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24 words for both immediate and delayed recall. Pre-clubbing and post-clubbing, participants  
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26 received alternative versions with the order of the two versions counterbalanced between  
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28 participants. Normative values for both versions can be found in Badcock et al. (2011).  
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35 Verbal fluency (COWAT)

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37 The COWAT (Controlled Word Association Task) was originally developed by Bechtold,  
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39 Benton et al. (1962), and is a measure of left frontal lobe functioning (Newman et al., 2007,  
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41 Wood et al., 2001). It tests participants' ability to produce as many words as they can that begin  
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43 with pre-determined sequentially presented letters (in this study: F, A and S) or categories (in  
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45 this study: animals, vegetables and fruit) within a minute. In the present study, only letters were  
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47 presented. We assessed the number of correctly generated words across all three letters. Proper  
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49 nouns and changing of suffixes and prefixes were not included (for example 'See' would be  
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51 correct but subsequently saying 'seeing' would not). The test has been found to have reasonable  
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3 test-retest reliability (Ruff et al., 1996), and updated normative data can be found in Ruff et al.  
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5 (1996).  
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### 8 Trail making task (TMT)

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10 The TMT is used to test cognitive flexibility. It was originally part of the Army Individual Test  
11 Battery (1944), and was incorporated into the Halstead–Reitan Battery (Reitan and Wolfson,  
12 1985). In the TMT participants are presented with a sheet of paper depicting circles. These  
13 circles are either filled with numbers (TMT A), or with numbers and letters (TMT B). In version  
14 A, participants have to draw a line from circle 1 to circle 25 in chronological order, as fast as  
15 possible. In TMT B participants have to draw a line in chronological order from 1 to 13, and A to  
16 L, but to switch back and forth between numbers and letters. Therefore, participants draw a line  
17 from 1 to A, from A to 2, from 2 to B etc. The reaction time (RT) of both tasks are recorded, and  
18 an index subtracting RT's of TMT A from RT's of TMT B results in an estimate of cognitive  
19 flexibility (Lezak, 1995) adjusted for individual differences in motor functioning and visual  
20 search strategies (Reitan and Wolfson, 1985). Norm values are available from Tombaugh (2004).  
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### 40 *Questionnaires*

#### 41 The Beck Depression Inventory (BDI)

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43 The BDI (Beck et al., 1961) is a 21 item questionnaire designed to measure depressive  
44 symptoms. Each item comprises a 4 choice statement differing in the extent of depressive  
45 loading. For example (0) I don't have thoughts of killing myself, (1) I have thought of killing  
46 myself but I would not carry them out, (2) I would like to kill myself, (3) I would kill myself if I  
47 had the chance. Each of the 4 choice statements provides a score that indicates how depressed  
48 the person feels from 0 to 3. The total depression score is the sum of the scores of each of the 21  
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3 items. Scores between 0–9 indicate that a person is not depressed, 10–18 indicates mild-  
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5 moderate depression, 19–29 indicates moderate-severe depression and 30–63 indicates severe  
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7 depression (Sotiropoulos et al., 2008, Beck et al., 1961). In this experiment, we asked  
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9 participants to answer the questionnaire by referring to how they generally felt in the past two  
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11 weeks (pre-clubbing) and to how they feel currently (post-clubbing).  
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16 The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; short version)

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18 The short O-LIFE questionnaire (Mason et al., 2005) is a validated 43-item self-report  
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20 questionnaire assessing schizotypy in terms of four dimensions. Positive schizotypy is assessed  
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22 by 12 items pertaining to Unusual Experiences (UnEx, maximum score 12, including items such  
23  
24 as ‘Are your thoughts sometimes so strong that you can almost hear them?’), negative schizotypy  
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26 is assessed by 10 items pertaining to Introvertive Anhedonia (IntAn, maximum score 10,  
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28 including items such as ‘Do you prefer watching television to going out with people?’), and  
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30 Cognitive Disorganization is assessed by 11 items (CogDis, maximum score 11, including items  
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32 such as ‘Are you easily confused if too much happens at the same time?’). Finally, 10 items  
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34 assess Impulsive Nonconformity (ImpNC, maximum score 10), which does not represent a  
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36 schizotypy dimension (Mason et al., 1995), but will be accounted for in the present study  
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38 because of the significant link between impulsivity and addiction (Crews and Boettiger, 2009).  
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40 For each item, participants have to indicate whether the statement is true or false. The number of  
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42 positive responses (some items are reversely formulated) is summed so that higher scores  
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44 indicate higher schizotypy. Normative values can be found in Mason et al. (2005) and the scale  
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46 has shown good internal consistency as well as high correlations with the original O-LIFE  
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48 questionnaire (Mason et al., 2005, Mason et al., 1995).  
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### Drug use and sleep patterns

On the post-clubbing testing session participants were asked to fill in the drug questionnaires of the national household survey on drug abuse (NHSDA; 1998). The NHSDA questionnaire gives detailed data of respondents' prior drug use, and an adapted version was administered to assess use of nicotine, alcohol, cannabis, mephedrone, amphetamine, cocaine, ketamine and benzodiazepine use during the clubbing experience (amount used), and in the past 30 and seven days (times used). Additionally, participants indicated their total amount of average hours of sleep, as well as how much they slept between the pre- and the post-clubbing experience (total amount of hours).

### *Data analysis Mephedrone use vs. Control*

In a first set of analysis, in which we focused on recent mephedrone use, we calculated separate 2 x 2 mixed sample ANOVAs with day (pre-clubbing, post-clubbing) as the related samples factor and drug use group (mephedrone, control) as the independent samples factor on the total % correct responses in the RAVLT (measuring verbal learning) as well as total amount correct items named in the COWAT (measuring verbal fluency). In the TMT (measuring cognitive flexibility) an index (TMT B – TMT A) was calculated and used as an outcome measure, with higher values indicating reduced cognitive flexibility. Post-hoc tests were performed using paired samples tests. Effect sizes are reported for all ANOVA results.

In order to establish if schizotypy explained an additional amount of variance on top of drug use and demographic / control variables, we firstly explored which variables are relevant to the regression models. We correlated age, BDI scores, hours of sleep (average and total hours between pre- and post-clubbing), NART-scores, drug use variables and schizotypy sub-scale

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3 scores with the outcome measures of the cognitive tasks. For regression analyses, we only kept  
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5 variables that were significantly related to at least one outcome measure. Subsequently, two  
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7 separate regression models were run, corresponding to the two times of assessment (see result  
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9 section for details). Blocks of predictors were entered into the regression model, with the first  
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11 one containing control variables (if none of these correlated with the outcome measures, this step  
12  
13 was omitted), the subsequent step including drug use information, and the final step containing  
14  
15 schizotypy measures. These blocks were entered in nested blocks, meaning that each subsequent  
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17 block contained all prior predictors and the additional predictors from the current block.  
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19 Presentation of results however will only include significant predictors as in Fridberg et al.  
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21 (2011), for economy of presentation. Because all tolerance values were above .2 (Menard, 1995),  
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23 and all independent variables were mean-centered, multi-collinearity between the independent  
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25 variables was considered negligible. The dependent variables were i) total percentage correctly  
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27 recalled items in the RAVLT, for immediate and delayed recall, ii) the total amount of correctly  
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29 named items in the verbal fluency task, and iii) TMT index scores.  
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36 Kolmogorov–Smirnov tests for the groups separately revealed normal distribution for all  
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38 behavioral measures, NART, BDI and schizotypy scores. All  $p$ -values were two-tailed and the  $\alpha$ -  
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40 level was set at .05.  
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## 45 **Results**

### 46 *Participants and self-report questionnaires*

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48 The first major analysis concerned the grouping of people in the mephedrone and control group.  
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50 Of the 26 participants, 10 reported having used mephedrone between test sessions.  
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3 In the 30 days prior to testing, eight of the 10 mephedrone users reported having used nicotine,  
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5 one had used cannabis, eight had used alcohol, and four had used amphetamines. In the 30 days  
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7 prior to testing, 14 of the 16 non-mephedrone using controls used alcohol, four had used  
8  
9 cannabis and five had used nicotine.

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11  
12 In the seven days prior to testing, only one mephedrone user had used amphetamines and  
13  
14 cannabis once. For all other mephedrone users recency of use for other illicit substances  
15  
16 (including mephedrone) exceeded seven days. None of the mephedrone non-users had used  
17  
18 cannabis or other illicit substances within the last seven days prior to testing.

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21 As is evident from Table 1, mephedrone users used more amphetamine, mephedrone, and  
22  
23 nicotine as compared to the control group in the past 30 days, more nicotine in the past seven  
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25 days prior to testing, and more mephedrone and alcohol during the clubbing experience.

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28 Furthermore, mephedrone users as compared to controls scored higher on BDI scores, CogDis  
29  
30 and ImpNC. A mixed-samples ANOVA with BDI scores pre-clubbing and post-clubbing as the  
31  
32 repeated measures, and group (mephedrone, control) as the between subjects factor indicated that  
33  
34 there was a significant effect of day of testing [ $F(1,24)=6.69, p=.02, \text{partial } \eta^2= .22$ ], with BDI  
35  
36 scores being generally lower pre-clubbing than post-clubbing (see Table 1). There also was a  
37  
38 significant interaction between group \* day of testing [ $F(1,24)=17.83, p<.001, \text{partial } \eta^2= .43$ ].  
39  
40 Post-hoc paired samples t-tests split by group revealed that this rise in BDI scores was only  
41  
42 significant in the mephedrone using group [ $t(9)=-3.70, p<.01$ ], but not in the control group  
43  
44 [ $t(15)= 1.50, p=.16$ ; see Table 1]. All other measures did not differ between groups (Table 1).  
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52 **-Table 1 about here-**

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55 *Results in the behavioural tasks*  
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## RAVLT

For the immediate recall measure, we found that mephedrone users performed worse than controls ( $F(1,24) = 10.43, p < .01, \text{partial } \eta^2 = .30$ ; see Table 2). The interaction between group and day ( $F(1,24) = .85, p = .37, \text{partial } \eta^2 = .03$ ) and the effect of day ( $F(1,24) = 1.99, p = .17, \text{partial } \eta^2 = .08$ ; see Table 2) were both not significant. For the delayed recall measure, we found that mephedrone users performed significantly worse than controls ( $F(1,24) = 12.33, p < .01, \text{partial } \eta^2 = .34$ ; see Table 2). Whereas the effect of day ( $F(1,24) = .73, p = .40, \text{partial } \eta^2 = .03$ ; see Table 2) was not significant, the analysis revealed a significant interaction between group and day ( $F(1,24) = 7.72, p = .01, \text{partial } \eta^2 = .24$ ). Post-hoc paired samples t-tests split by group revealed that in the control group there was no difference in scores between pre- and post clubbing [ $t(15) = -1.30, p = .21$ ]. However, the mephedrone group showed a significant decrease in delayed recall performance between pre- and post-clubbing [ $t(9) = 4.33, p < .01$ ; see Table 2].

**-Table 2 about here-**

## COWAT

There was a significant main effect for group ( $F(1,24) = 5.32, p = .03, \text{partial } \eta^2 = .18$ ), with mephedrone users performing significantly worse than controls (see Table 2). Additionally, there was a significant effect of day ( $F(1,24) = 6.77, p = .02, \text{partial } \eta^2 = .22$ ; see Table 2), and interaction between group and day ( $F(1,24) = 13.11, p < .01, \text{partial } \eta^2 = .35$ ). Post-hoc paired samples t-tests split by group revealed that in the mephedrone group values significantly decreased from pre- to post-clubbing [ $t(9) = 5.00, p < .01$ ; see Table 2), whereas there was no day difference in the control group [ $t(15) = -.74, p = .47$ ; see Table 2).

## TMT

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3 There were no significant findings (group:  $F(1,24) = .39$   $p = .54$ ,  $partial \eta^2 = .02$ ; day:  $F(1,24) =$   
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There were no significant findings (group:  $F(1,24) = .39$   $p = .54$ ,  $partial \eta^2 = .02$ ; day:  $F(1,24) =$   
.60,  $p = .45$ ,  $partial \eta^2 = .02$ , interaction between group \* day:  $F(1,24) = 1.31$ ,  $p = .26$ ,  $partial \eta^2$   
=.05; see Table 2).

*Regressions: Severity of drug use and schizotypy as predictors of performance*

To further investigate the possibility that schizotypy may be relevant to cognitive functioning on  
top of drug use, multivariate step-wise regressions were conducted. Exploratory correlation  
analyses (Table 3) showed that pre-clubbing amphetamine, mephedrone and cannabis use in the  
past 30 days, as well as CogDis scores correlated with cognitive functioning. Therefore, for the  
pre-clubbing session amphetamine, mephedrone and cannabis use in the past 30 days was  
entered in the first step, and CogDis scores in the second step.

**-Table 3 about here-**

For the post-clubbing session (Table 4) BDI scores, total hours of sleep between test sessions,  
mephedrone use and schizotypy scores (UnEx, CogDis and ImpNC scores) were correlated with  
at least one of the outcome measures. Therefore, BDI scores post-clubbing and total hours of  
sleep between test sessions were entered in the first step, mephedrone use between test sessions  
in the second, and schizotypy subscales (UnEx, CogDis and ImpNC) in the third step.

**-Table 4 about here-**

The results from the regression on pre-clubbing session are displayed in Table 5. We found that  
immediate recall in the RAVLT was reduced with increasing cannabis use and delayed recall in

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3 the RAVLT was reduced with increasing amphetamine use. Additionally, increasing CogDis  
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5 scores related to a decreasing number of words produced in the COWAT.  
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9 **-Table 5 about here-**  
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11 The results from the regression on post-clubbing session are presented in Table 6. Results  
12  
13 indicate that increasing BDI scores predicted lower RAVTL performance (immediate and  
14  
15 delayed recall) as well as less words produced in the COWAT. Additionally, a higher amount of  
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17 hours slept between test-sessions related to lower immediate recall performance in the RAVTL  
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19 and less words produced in the COWAT. Adding drugs or schizotypy in later steps did not  
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21 explain additional variance in cognitive functioning.  
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27 **-Table 6 about here-**  
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## 32 **Discussion**

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34 Drug policies are aimed to prevent harm to people by making access to these drugs more  
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36 difficult. To avoid the problem of the illegality of drugs, new drugs are frequently developed that  
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38 are little or not yet regulated. Among those drugs are popular new wave designer drugs such as  
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40 mephedrone. These provide “legal highs” without knowing much about their harmfulness or  
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42 factors that might predict it. We here investigated whether mephedrone use might have a  
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44 negative impact on cognitive functioning, and whether any such relationship might be influenced  
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46 by individuals’ schizotypal features and other drug use. We tested cognitive functions that were  
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48 formerly associated with amphetamine use and elevated schizotypy, i.e. cognitive flexibility,  
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50 verbal learning and verbal fluency. Importantly, we were able to recruit volunteers in a “natural”  
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52 setting, i.e. before and after a clubbing experience during which drugs such as mephedrone are  
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3 commonly consumed. The advantage of this design consists in the assessment of i) participants'  
4 baseline functioning (i.e. the cognitive level at which individuals with different drug histories  
5 entered the study), and ii) how the drug use of the clubbing experience affected their cognitive  
6 performance (i.e. short-term effects). The main findings of the present study were that i)  
7 mephedrone users performed worse than controls at baseline and their performance decreased  
8 pre- to post-clubbing in tasks measuring cognitive functioning, ii) cannabis and amphetamine use  
9 related to decreased cognitive performance in the pre-clubbing session, whereas mephedrone did  
10 not, iii) depression rather than drug use or schizotypy was the most consistent predictor of  
11 cognitive attenuations in the post-clubbing session, and iv) schizotypy did not explain variance in  
12 cognitive functioning (apart from CogDis in the pre-clubbing session) when controlling for drug  
13 use. These findings will be discussed in the following sections.  
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32 We argued that the cognitive consequences of mephedrone use should mirror those of  
33 amphetamine use, because studies reported on physiological, chemical and psychological  
34 similarities between the consequences of amphetamine (such as ecstasy) and cathinone use (Dal  
35 Cason et al., 1997, Kalix, 1992, Schifano et al., 2010, ACMD, 2010, Vardakou et al., 2011,  
36 James et al., 2010, Morris, 2010, Brenneisen et al., 1990, Hoffman and Al'Absi, 2010, Wood and  
37 Dargan, 2012). For our pre-clubbing session, we observed that mephedrone users performed  
38 worse than the control group for immediate and delayed verbal recall, and verbal fluency. Our  
39 group results also showed that performance in all but the TMT task became worse over the pre-  
40 clubbing to post-clubbing session in our mephedrone users as compared to controls. These group  
41 comparison results would suggest that recent mephedrone use negatively affects cognitive  
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3 functioning. We have, however, obtained more detailed information on other drug use as well,  
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5 and this additional drug use was important to cognitive functioning.  
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10 Firstly, we found that mephedrone users as compared to controls had consumed more  
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12 amphetamines and nicotine in the 30 days prior to testing. Secondly, when looking at the  
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14 individual contribution of drug use (regression analysis) on cognitive functioning, we found that  
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16 enhanced cannabis and amphetamine use was related to memory impairments, whereas  
17  
18 mephedrone use was not. These latter results are in line with studies on the cognitive effects of  
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20 amphetamines (Hoshi et al., 2007, Morgan, 2000, see Gouzoulis-Mayfrank and Daumann, 2009,  
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22 Rogers et al., 2009 for overview, Kuypers and Ramaekers, 2005), cathinones (Colzato et al.,  
23  
24 2011b), and cannabis (Fernández-Serrano et al., 2011) indicating impairments in verbal recall,  
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26 verbal learning and/or fluency as a function of these drugs' consumption. Our findings and the  
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28 previous literature would thus suggest that mephedrone consumption does not necessarily exert a  
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30 negative impact on cognitive functioning by itself. Instead, mephedrone users are likely those  
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32 individuals who are **prone to consuming** other psychoactive drugs in conjunction with  
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34 mephedrone. It might be this polydrug use that makes these individuals more vulnerable to the  
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36 observed attenuations in the cognitive tasks. In line with this **rationale**, it seems difficult to find  
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38 pure users of any one substance alone (Fernández-Serrano et al., 2011), and our sample has been  
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40 no exception.  
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50 The implication of polydrug use when trying to understand the influence of a particular drug on  
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52 cognition is thus far-reaching. For instance, polydrug users may suffer exacerbated negative  
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54 implications of drug use on mental health when compared to individual drug users (Bondi et al.,  
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3 1998, Hakansson et al., 2011). Consequently, findings from psychopharmacological studies  
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5 which pre-selected their participants according to drug naivety might not provide very  
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7 representative results for a clinically relevant population. Moreover, when individual drug use is  
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9 targeted (see Fernández-Serrano et al., 2011 for overview), we might neglect and miss out on the  
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11 influence of other drugs frequently consumed simultaneously on the relationship we are  
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13 interested in. Based on these considerations, we here conjecture that it is impossible to infer  
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15 about the impact of a single drug on cognition in a research context using a sample of typical  
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17 recreational drug users. Instead, we should take polydrug use more thoroughly into account, as  
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19 former polydrug use might also influence cognitive functioning in substance users in the long-  
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21 term.  
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29 Polydrug use and not only single drug use **might be** relevant for cognition and mood in the  
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31 short-term, as was found here when considering post-clubbing performance and mood. In the  
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33 regression analysis, we explored additional factors that could influence cognitive measures post-  
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35 clubbing more thoroughly. Strikingly, we found that higher BDI scores and prolonged sleep  
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37 (rather than drug use or schizotypy) predicted a relative drop in cognitive performance. While  
38  
39 not our a priori focus, the role of depression is worthwhile considering. To start with, our  
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41 mephedrone users as compared to controls showed higher BDI scores both pre-clubbing and  
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43 post-clubbing. Moreover, schizotypy scores showed no additional influence on cognitive  
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45 functioning post-clubbing, and the influence of actual drug use seemed to become marginal when  
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47 BDI scores were considered. We thus conjecture that depression might be a major confound in  
48  
49 previous schizotypy and drug studies that targeted cognitive functions, because depression levels  
50  
51 are commonly not assessed (e.g. Herzig et al., 2010, Skosnik et al., 2001). The same can be said  
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3 for studies testing non-clinical populations (and thus non-clinical depression) on the influence of  
4 particular drugs, where potentially relevant depression ratings have not been reported in  
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6 relatively pure cannabis users (Fried et al., 2005), alcohol users (Ratti et al., 2002) or  
7  
8 psychostimulant users (Bolla et al., 2003). Depression rates are, however, relatively elevated in  
9  
10 e.g. amphetamine users (Morgan, 2000, Rogers et al., 2009 for overview), alcohol users (Wood  
11  
12 and Dargan, 2012) and cannabis users (Hayatbakhsh et al., 2007, Patton et al., 2002).  
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15 Consequently, if depression is a major confound in studies such as the present one, we would  
16  
17 expect that depression influences cognitive functioning directly (primary influence) or indirectly  
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19 (secondary influence through e.g. loss of motivation), much as we have originally expected this  
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21 to be the case for drug use and / or schizotypy.  
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29 Studies that tested the link between depression and cognitive functioning indeed report that  
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31 clinical depression in young adults is accompanied by relatively impaired cognitive functioning  
32  
33 including those we tested here (see Castaneda et al., 2008 for overview). Even in healthy  
34  
35 subjects, negative mood can lead to reduced brain activity during verbal (not spatial) working  
36  
37 memory tasks (Aoki et al., 2011). Finally, the mood-behavior model (Gendolla, 2000) predicts  
38  
39 that negative mood results in disengagement and little resource mobilization when facing  
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41 difficult tasks, as demands would be perceived as being too high (Silvestrini and Gendolla,  
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43 2009). Given that negative mood is frequently a characteristic of depression, it is possible that  
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45 task performance decreases the more individuals are depressed, due to decreased motivation  
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3 Another possibility, though not necessarily independent of motivational factors, could be that the  
4 clubbing experience (including the drug consumption) resulted in neurochemical changes related  
5  
6 to depression via serotonergic pathways, or more specifically through an attenuation of  
7  
8 serotonergic functioning (Bhagwagar et al., 2006, Meyer et al., 2003, Meyer et al., 2004).  
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10

11 Serotonin is a neurotransmitter, importantly linked to depression, to amphetamine use (see  
12  
13 Walstab et al., 2010 for overview), and the interaction between depression and amphetamine use  
14  
15 (see Darke et al., 2008 for overview, McCardle et al., 2004, Rogers et al., 2009, Morgan, 2000).  
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18 In all cases, a reduction in serotonin availability seems to have negative consequences. For  
19  
20 instance, taking amphetamines such as ecstasy is related to a drop in mood, observable about two  
21  
22 days after its consumption (Curran and Travill, 1997, Parrott and Lasky, 1998), presumably via  
23  
24 reductions in serotonin-receptor density and binding [McCann et al. (1998, 2008)]. These  
25  
26 changes in serotonin functioning have also been related to verbal memory performance  
27  
28 (Reneman et al., 2001). Interestingly, serotonin receptor functioning has been implicated in the  
29  
30 rewarding effects of THC as well (Maldonado et al., 2011), and some studies suggest that the  
31  
32 effect of amphetamine and cannabis on memory functions is accumulative when consumed in  
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34 parallel (see Mohamed et al., 2011 for overview). Taken together, these findings suggest that  
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36 amphetamine and cannabis use may have altered susceptibility to mood-related cognitive  
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38 attenuations, either via motivational factors, neurochemical modulations, or both.  
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48 To summarize, drug use was a consistent predictor of task performance in the long-term (pre-  
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50 clubbing), and may have induced mood-related attenuations in cognitive functioning in the short-  
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52 term (post-clubbing). Schizotypy, on the other hand, was largely irrelevant to cognitive  
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54 functioning on top of (poly-)drug use. The only significant schizotypy finding was that enhanced  
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3 CogDis scores related to reduced verbal fluency. If we consider this single significant finding to  
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5 be meaningful, the question arises whether some schizotypy dimensions are pathologically more  
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7 relevant than others. Indeed, several researchers have indicated that CogDis is related to  
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9 unpleasant evaluation of unusual experiences (Schofield and Claridge, 2007), or cognitive  
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11 attenuations and poor emotional processing (Kerns and Becker, 2008, Cappe et al., 2012). A  
12  
13 problem is certainly the lack of consideration of disorganised symptoms in studies that found  
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15 attenuated cognitive functioning relating to positive symptoms (Laws et al., 2011, Lenzenweger  
16  
17 and Korfine, 1994), and that most of the psychometric tools used in these studies do not  
18  
19 distinguish between the two symptom dimensions (Chapman et al., 1976, Eckblad and Chapman,  
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21 1983, Chapman et al., 1978, Eysenck and Eysenck, 1975, Winterstein et al., 2011, Peters et al.,  
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23 1999).

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32 If cognitive disorganisation is considered to be a separate symptom dimension, it seems more  
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34 relevant to cognitive performance than the positive symptom dimension. For instance, in a study  
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36 by Rawlings and Goldberg (2012) performance in a continuous performance task was affected  
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38 by higher cognitive disorganization, but not as consistently by other schizotypy dimensions.  
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40 Similar conclusions on the role of symptom dimensions have also been drawn from studies in  
41  
42 other schizotypal samples (Szöke et al., 2009, Chan et al., 2011, Colzato et al., 2011a, Cappe et  
43  
44 al., 2012) and in schizophrenia patients (Kebir et al., 2008, Lucas et al., 2004). With regard to  
45  
46 schizotypy, positive symptoms have even been associated with performance benefits such as in  
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48 creativity tasks (Nelson and Rawlings, 2010, Mohr et al., 2001, Batey and Furnham, 2008). It  
49  
50 might be the case that scoring high on positive schizotypy only relates to a well-adapted  
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52 cognitive profile, while high scores in CogDis alone or in combination with high scores in  
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3 positive schizotypy might yield the most disadvantageous cognitive profile (Schofield and  
4 Claridge, 2007, Cappe et al., 2012). Our results would support this notion.  
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#### 10 Study limitations and implications

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12 Our study population consisted of volunteers who were willing to come to the laboratory twice,  
13 shortly before and after a clubbing night. Moreover, testing had to be completed within two  
14 months. These study constraints reduced the number of possible participants, and by inference  
15 the overall sample size. Given our naturalistic designs, we nevertheless argue that our results are  
16 informative (Fernández-Serrano et al., 2011), and stress that we could retain a considerable  
17 number of participants despite their clubbing activity, and decreased mood. These volunteers  
18 committed themselves to be tested twice around their clubbing experience, turning this sample  
19 and the measurements into a valuable data pool. Only with this naturalistic design were we able  
20 to assess the long-term (pre-clubbing) and short-term (post-clubbing) effects of drug use as it  
21 might occur in everyday situations. We suggest that the current study, its design and results  
22 revealed important new findings that should be followed up in future studies, including  
23 laboratory ones (the role of depression, mediation of results by the emotional consequences of  
24 the clubbing / drug experience not observable in laboratory tests of drug exposure, the problem  
25 of poly-drug use).  
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48 Illicit drug use and depression are associated, but so are licit drugs. For instance, alcohol  
49 negatively influences mood, and the accumulation of this effect could be related to the  
50 depression rate increase seen in mephedrone users as well. According to recent meta-analyses,  
51 alcohol increases the risk for depression (Boden and Fergusson, 2011), is related to impairments  
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3 in memory and verbal fluency (see Fernández-Serrano et al., 2011 for overview, Zeigler et al.,  
4 2005, Manning et al., 2008, Wendt and Risberg, 2001), and hangovers are usually associated  
5 with low mood (Howland et al., 2010). Moreover, alcohol seems to affect serotonin-receptor  
6 functioning, similarly to amphetamines (McHugh et al., 2010, Vengeliene et al., 2008). Given  
7 that alcohol has been used more frequently between test sessions in mephedrone users, we  
8 assume important interaction effects with alcohol.  
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11 It is also possible that the effects of mephedrone become more pronounced in chronic users, or  
12 those that use the drug at a high frequency, as in our sample use was relatively low (about 1.5  
13 times/month). **Another possibility is that unreported (intentionally taken) or unknown (e.g.**  
14 **participants consumed impure mephedrone) substances were taken, influencing cognitive**  
15 **performance. We did not confirm individuals' self-report with objective drug tests.**  
16  
17 **However, we here suggest that the likelihood is high that participants actually consumed**  
18 **mephedrone when assuming to do so. The current study was completed within five months**  
19 **shortly after the ban for mephedrone had been implemented in the UK and other**  
20 **European countries (see Vardakou et al., 2011 for overview, Winstock et al., 2011,**  
21 **EMCDDA, 2010a, EMCDDA, 2011, EMCDDA, 2012). Very likely, participants consumed**  
22 **mephedrone that had been widely available and bought online before the implementation**  
23 **of the ban (EMCDDA, 2011, EMCDDA, 2012). Even though there is a debate about the**  
24 **quality of mephedrone purchased from internet portals (Davies et al., 2010), many reports**  
25 **would agree on its high purity (Gibbons and Zloh, 2010, EMCDDA, 2010b). Consequently,**  
26 **we assume that our participants actually consumed mephedrone of relatively high purity.**  
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3 Furthermore, it could have been advantageous to test the effects of mephedrone use in a sample  
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5 of less educated subjects. IQ may have the potential to protect from adverse situations in e.g.  
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7 psychiatric illnesses (MacCabe and Murray, 2004, Moore et al., 2007, Sørensen et al., 2010) or  
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9 substance use (Pope et al., 2003, Zammit et al., 2010). However, in our sample most participants  
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11 were students, or educated to at least degree level. Therefore, more variance in subjects'  
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13 educational level/IQ could be informative in subsequent studies.  
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## 20 Conclusion

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22 We set out to investigate the effects of mephedrone use on cognition, and elucidate the  
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24 relationship between drug use, schizotypal symptoms and cognitive functioning. Results showed  
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26 that even before clubbing (and after recent drug use) mephedrone users performed worse than  
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28 non-users on cognitive tasks. In mephedrone users but not in controls, performance in verbal  
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30 learning and fluency decreased over the clubbing experience. Additional analysis on the use of  
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32 other drugs and psychological factors, however, indicated that the changes in cognitive  
33  
34 functioning were likely due to prior polydrug use (amphetamine, cannabis and alcohol use in  
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36 particular), and related psychological consequences (enhanced depression rates). Schizotypal  
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38 traits were rather unrelated to cognitive performance, apart from CogDis. This schizotypy  
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40 subscale may therefore represent a pathologically more relevant symptom dimension. The  
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42 present study shows that polydrug use should be considered in future studies on drug effects on  
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44 cognition, as well as relevant associated psychological concepts (depression, schizotypy). Given  
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46 the political interest in preventing the population from harmful drug effects, knowing which  
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48 conditions increase risk is warranted, particularly because a more regulated drug policy has been  
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50 called for from various professional domains (Nutt et al., 2010, Bennett and Holloway, 2010).  
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For Peer Review

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## Tables

**Table 1.** T-test values and descriptives for demographic variables, average sleep and total hours sleep between test sessions, BDI scores, schizotypy scores, and substance use in mephedrone users (n = 10 participants) and non-mephedrone using controls (n = 16 participants). Significant values are highlighted in bold.

Variable	Total		Mephedrone (N=10)		Control (N=16)		T-test statistics	
	Mean	SD	Mean	SD	Mean	SD	t(24)	p
Age	23.42	5.54	21.40	0.84	24.69	6.80	-1.91	0.07
Verbal IQ	32.96	5.44	33.60	5.42	32.56	5.59	0.47	0.65
Average hours sleep	7.58	1.03	7.60	1.06	7.56	1.03	0.09	0.93
Total hours sleep between sessions	19.35	4.99	19.80	4.10	19.06	5.58	0.36	0.72
BDI <sup>a</sup> pre <sup>b</sup>	8.15	7.25	11.90	5.53	5.81	7.36	2.24	<b>0.03</b>
BDI post <sup>c</sup>	8.77	7.63	14.50	5.70	5.19	6.48	3.73	<b>0.00</b>
UnEx <sup>d</sup>	3.35	2.71	4.60	2.41	2.56	2.66	1.97	0.06
CogDis <sup>e</sup>	5.15	3.46	6.80	3.26	4.13	3.26	2.03	<b>0.05</b>
IntAn <sup>f</sup>	1.73	1.80	2.00	1.89	1.56	1.79	0.59	0.56
ImpNC <sup>g</sup>	3.42	2.48	5.30	1.57	2.25	2.24	3.76	<b>0.00</b>
Amphetamine past 30 days	0.19	0.49	0.50	0.71	0.00	0.00	2.24	<b>0.05</b>
Mephedrone past 30 days	0.62	1.10	1.60	1.26	0.00	0.00	4.00	<b>0.00</b>
Nicotine past 30 days	12.77	14.33	22.00	13.17	7.00	12.08	2.98	<b>0.01</b>

Cannabis past 30 days	2.31	4.35	4.80	6.12	0.75	1.53	2.05	0.07
Alcohol past 30 days	9.62	6.54	9.20	5.29	9.88	7.37	-0.25	0.80
Amphetamine past seven days	0.04	0.20	0.10	0.32	0.00	0.00	1.00	0.34
Nicotine past seven days	2.96	3.36	5.00	3.23	1.69	2.85	2.74	<b>0.01</b>
Cannabis past seven days	0.04	0.20	0.10	0.32	0.00	0.00	1.00	0.34
Alcohol past seven days	1.54	1.61	1.30	1.49	1.69	1.70	-0.59	0.56
Mephedrone between test sessions	0.54	0.76	1.40	0.52	0.00	0.00	8.57	<b>0.00</b>
Cannabis between test sessions	0.27	1.00	0.70	1.57	0.00	0.00	1.41	0.19
Alcohol between test sessions	16.08	7.03	20.50	7.75	13.31	5.02	2.88	<b>0.01</b>
Age of first use:								
Amphetamine	18.75	1.86	19.00	1.66	18.00	2.65	0.79	0.45
Age of first use: Mephedrone	n/a	n/a	20.67	0.50	n/a	n/a	n/a	n/a
Age of first use: Nicotine	16.00	3.12	15.38	1.19	16.63	4.31	-0.79	0.44
Age of first use: Cannabis	17.56	4.06	16.60	1.78	18.75	5.75	-1.12	0.28
Age of first use: Alcohol	14.85	1.93	14.70	1.57	14.94	2.17	-0.30	0.77

*Note:* <sup>a</sup> Beck's Depression Inventory; <sup>b</sup> Pre-clubbing experience; <sup>c</sup> Post-clubbing experience; <sup>d</sup> Unusual Experiences; <sup>e</sup> Cognitive Disorganisation; <sup>f</sup> Introvertive Anhedonia; <sup>g</sup> Impulsive Nonconformity;



**Table 2:** Means and standard deviations (SD) of task performance for the total sample and the two groups separately.

	All		Mephedrone		Control	
	Mean	SD	Mean	SD	Mean	SD
RAVLT <sup>a</sup> % Immediate <sup>b</sup> pre <sup>c</sup>	79.85	10.07	74.50	11.37	83.19	7.78
RAVLT % Immediate post <sup>d</sup>	78.27	9.09	71.30	8.60	82.63	6.38
RAVLT % Delayed <sup>e</sup> pre	82.81	17.03	74.60	19.39	87.94	13.60
RAVLT % Delayed post	82.27	19.27	66.00	19.18	92.44	10.54
COWAT <sup>f</sup> pre	45.88	9.09	42.40	10.29	48.06	7.81
COWAT post	44.69	10.20	38.20	8.70	48.75	9.07
TMT <sup>g</sup> index pre	16.49	9.39	14.61	5.80	17.66	11.10
TMT index post	15.62	7.41	14.92	5.81	16.06	8.41

*Note:* <sup>a</sup> Rey Auditory verbal memory task; <sup>b</sup> Immediate Recall; <sup>c</sup> Pre-clubbing; <sup>d</sup> Post-clubbing; <sup>e</sup> Delayed Recall; <sup>f</sup> Verbal Fluency Task; <sup>g</sup> Trail Making Task;

**Table 3.** Correlations between potential predictor variables and outcome measures pre-clubbing.

Significant values are highlighted in bold.

	RAVLT <sup>h</sup> %	RAVLT %	TMT <sup>k</sup> index	COWAT <sup>l</sup> pre
	Immediate <sup>i</sup> pre	Delayed <sup>j</sup> pre	pre	
Age	0.30	0.04	0.23	0.24
NART <sup>a</sup>	0.15	0.08	-0.22	<b>0.35†</b>
BDI <sup>b</sup> pre <sup>c</sup>	-0.27	-0.26	-0.08	<b>-0.34†</b>
Average sleep	0.05	0.29	-0.02	-0.16
UnEx <sup>d</sup>	-0.22	-0.25	0.03	-0.25
CogDis <sup>e</sup>	<b>-0.47*</b>	-0.13	0.04	<b>-0.65***</b>
IntAn <sup>f</sup>	0.14	0.21	-0.13	0.17
ImpNC <sup>g</sup>	-0.17	-0.17	0.09	<b>-0.37†</b>
Amphetamine past seven days	-0.32	-0.27	-0.28	-0.18
Nicotine past seven days	-0.23	-0.32	-0.18	0.21
Cannabis past seven days	-0.32	-0.27	-0.28	-0.18
Alcohol past seven days	-0.30	-0.15	-0.12	0.07
Amphetamine past 30 days	<b>-0.49*</b>	<b>-0.52**</b>	-0.21	-0.30
Mephedrone past 30 days	<b>-0.48*</b>	-0.18	0.01	-0.29
Nicotine past 30 days	-0.21	-0.31	-0.18	0.04
Cannabis past 30 days	<b>-0.63***</b>	<b>-0.34†</b>	0.02	<b>-0.39*</b>
Alcohol past 30 days	0.20	-0.07	-0.12	0.28

†  $p \leq 0.10$ ; \* significant at  $p \leq 0.05$ ; \*\* significant at  $p \leq 0.01$ ; \*\*\* significant at  $p \leq 0.001$

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3 *Note:* <sup>a</sup> National Adult Reading Test; <sup>b</sup> Beck's Depression Inventory; <sup>c</sup> Pre-clubbing experience; <sup>d</sup>  
4 Unusual Experiences; <sup>e</sup> Cognitive Disorganization; <sup>f</sup> Introvertive Anhedonia; <sup>g</sup> Impulsive Non-  
5 conformity; <sup>h</sup> Rey Auditory verbal memory task; <sup>i</sup> Immediate Recall; <sup>j</sup> Delayed Recall; <sup>k</sup> Trail  
6 Making Task; <sup>l</sup> Verbal Fluency Task;  
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For Peer Review

**Table 4.** Correlations between potential predictor variables and outcome measures post-clubbing. Significant values are highlighted in bold.

	RAVLT <sup>h</sup> %	RAVLT %	TMT <sup>k</sup>	COWAT <sup>l</sup>
	Immediate <sup>i</sup>	Delayed <sup>j</sup>	index	post
	post	post	post	
Age	0.32	0.04	0.07	<b>0.36†</b>
NART <sup>a</sup>	0.24	-0.02	-0.32	0.30
BDI <sup>b</sup> post <sup>c</sup>	<b>-0.49*</b>	<b>-0.55**</b>	0.02	<b>-0.44*</b>
Total hours sleep	<b>-0.36†</b>	-0.22	0.13	<b>-0.39*</b>
between test sessions				
UnEx <sup>d</sup>	-0.31	<b>-0.54**</b>	0.09	-0.23
CogDis <sup>e</sup>	<b>-0.52**</b>	<b>-0.47*</b>	0.15	<b>-0.59**</b>
IntAn <sup>f</sup>	-0.23	0.05	0.03	0.19
ImpNC <sup>g</sup>	<b>-0.40*</b>	<b>-0.47*</b>	0.10	<b>-0.40*</b>
Alcohol between test	0.02	-0.22	-0.06	-0.08
sessions				
Cannabis between	-0.26	<b>-0.35†</b>	-0.29	-0.29
test sessions				
Mephedrone between	<b>-0.58**</b>	<b>-0.52**</b>	0.00	<b>-0.43*</b>
test sessions				

†  $p \leq 0.10$ ; \* significant at  $p \leq 0.05$ ; \*\* significant at  $p \leq 0.01$ ; \*\*\* significant at  $p \leq 0.001$

Note: <sup>a</sup> National Adult Reading Test; <sup>b</sup> Beck's Depression Inventory; <sup>c</sup> Post-clubbing; <sup>d</sup> Unusual Experiences; <sup>e</sup> Cognitive Disorganization; <sup>f</sup> Introverted Anhedonia; <sup>g</sup> Impulsive Non-conformity; <sup>h</sup> Rey Auditory verbal memory task; <sup>i</sup> Immediate Recall; <sup>j</sup> Delayed Recall; <sup>k</sup> Trail Making Task; <sup>l</sup> Verbal Fluency Task;

**Table 5.** Regression analysis assessing the effect of cannabis and amphetamine use (step 1) and CogDis (step 2) on cognitive functioning at the pre-clubbing session. Only significant  $\Delta R^2$ -values and their corresponding coefficients ( $\beta$ -values) are reported.

Outcome variables	Step	Significant predictor	$\beta$ -value	Total $R^2$	$\Delta R^2$	$F$ for $\Delta R^2$
RAVLT <sup>a</sup> % immediate <sup>b</sup>	1	Cannabis	<b>-0.60*</b>	<b>0.48**</b>	<b>0.48**</b>	<b>6.85**</b>
	1	Amphetamines	<b>-0.33†</b>	<b>0.48**</b>	<b>0.48**</b>	<b>6.85**</b>
RAVLT % delayed <sup>c</sup>	1	Amphetamines	<b>-0.53*</b>	<b>0.35*</b>	<b>.035*</b>	<b>3.99*</b>
COWAT <sup>d</sup>	2	CogDis <sup>e</sup>	<b>-0.58**</b>	<b>0.45**</b>	<b>0.26**</b>	<b>9.76**</b>

†  $p \leq .10$ ; \* significant at  $p \leq .05$ ; \*\* significant at  $p \leq .01$ ; \*\*\* significant at  $p \leq .001$   
 Note: <sup>a</sup> Rey Auditory verbal memory task; <sup>b</sup> Immediate Recall; <sup>c</sup> Delayed Recall; <sup>d</sup> Verbal Fluency Task; <sup>e</sup> Cognitive Disorganisation;

**Table 6.** Regression assessing the effect of total hours of sleep between test sessions and depression (Beck's Depression Inventory/BDI; step 1), mephedrone use between test sessions (step 2), and schizotypy (Unusual Experiences, Cognitive Disorganisation, and Impulsive Non-conformity; step 3) on cognitive functioning post-clubbing. Only significant  $\Delta R^2$ -values and their corresponding coefficients ( $\beta$ -values) are reported.

Outcome variables	Step	Significant predictor	$\beta$ -value	Total $R^2$	$\Delta R^2$	$F$ for $\Delta R^2$
RAVLT % <sup>a</sup> immediate <sup>b</sup>	1	BDI <sup>e</sup> post <sup>f</sup>	<b>-0.55**</b>	<b>0.42**</b>	<b>0.42**</b>	<b>8.45**</b>

	1	Total hours	<b>-0.43*</b>	<b>0.42**</b>	<b>0.42**</b>	<b>8.45**</b>
		of sleep				
		between test				
		sessions				
RAVLT % delayed <sup>c</sup>	1	BDI post	<b>-0.59**</b>	<b>0.39**</b>	<b>0.39**</b>	<b>7.40**</b>
COWAT <sup>d</sup>	1	BDI post	<b>-0.50**</b>	<b>0.39**</b>	<b>0.39**</b>	<b>7.49**</b>
	1	Total hours	<b>-0.46*</b>	<b>0.39**</b>	<b>0.39**</b>	<b>7.49**</b>
		of sleep				
		between test				
		sessions				

†  $p \leq 10$ ; \* significant at  $p \leq 05$ ; \*\* significant at  $p \leq 01$ ; \*\*\* significant at  $p \leq 001$

Note: <sup>a</sup> Rey Auditory verbal memory task; <sup>b</sup> Immediate Recall; <sup>c</sup> Delayed Recall; <sup>d</sup> Verbal Fluency Task; <sup>e</sup> Beck's Depression Inventory; <sup>f</sup> Post-clubbing;