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Prevalence of self-reported movement dysfunction among young adults with a history of ecstasy and methamphetamine use

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ABSTRACT

Background: Illicit stimulant use is associated with long-lasting changes in movement and movement-related brain regions. The aim of our study was to investigate the prevalence of movement dysfunction in this population. We hypothesized that prevalence of self-reported movement dysfunction is higher among stimulant users than non-stimulant users.

Methods: Three groups of adults completed a survey containing questions about demographics, health, drug use, and movement. The groups consisted of ecstasy users with no history of methamphetamine use (ecstasy group, n = 190, 20 ± 3 yrs.), methamphetamine users (methamphetamine group, n = 331, 23 ± 5 yrs.), and non-stimulant users (control group, n = 228, 25 ± 8 yrs.). Movement data was analyzed with logistic regression.

Results: In the unadjusted logistic regression model, group had a significant effect on fine hand control, tremor, and voice/speech questions, but not on other movement domain questions. The prevalence of tremor and abnormal fine hand control was significantly higher in the ecstasy and methamphetamine groups than in the control group ($p < 0.018$), and changes in voice/speech was more prevalent in the ecstasy group than in the control group ($p = 0.015$). Age and use of cannabis and hallucinogens were confounding variables. However, inspection of chi-square tables suggests that the effect of these parameters on the movement data is likely to be minor.

Conclusions: The prevalence of self-reported tremor and changes in fine hand control and voice/speech is significantly higher in stimulant users than in non-stimulant users. Inclusion of these common and noticeable changes in body function may aid public health campaigns that target prevention or harm minimization.

1. Introduction

Use of methamphetamine and ecstasy (3,4-methylenedioxymethamphetamine or MDMA) is a significant health problem in many countries. The United Nations Office of Drugs and Crime estimates that, each year, 34 million people use amphetamine and/or methamphetamine and 20 million people use ecstasy (UNODC, 2018).

Methamphetamine and the metabolites of ecstasy are toxic to primarily dopaminergic and serotonergic neurons, respectively (for review see Green et al., 2003; Steele et al., 1994; Yamamoto and Bankson,

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2005). The toxicity can lead to long-lasting changes in neurotransmission that persist for months to years after cessation of drug use. Mechanisms that play a role in the neurotoxicity include oxidative stress and mitochondrial dysfunction, as well as excitotoxicity and neuroinflammation for methamphetamine and hyperthermia for ecstasy (for review see Capela et al., 2009; Carvalho et al., 2012; Green et al., 2003; Yamamoto et al., 2010).

One manifestation of the long-lasting changes in monoamine neurotransmission are alterations in movement and the structure and function of movement-related brain regions. For example, adults with a history of methamphetamine use exhibit clinical signs of parkinsonism and abnormal substantia nigra morphology (Rumpf et al., 2017; Todd et al., 2016b), and use of methamphetamine is associated with increased risk of Parkinson's disease (Callaghan et al., 2010). In addition, adults with a history of ecstasy use exhibit an abnormally large tremor during movement (Downey et al., 2017; Flavel et al., 2012a) and altered hand function (King et al., 2010; Pearson-Dennett et al., 2014; Toomey et al., 2003), and an abnormally high level of excitability in the motor cortex and descending motor projection to the hand (Flavel et al., 2012b) has been observed in adults with a history of methamphetamine and/or ecstasy use. However, learning of new fine motor skills appears to be largely unaffected (Todd et al., 2016a). The above changes were observed months to years after cessation of drug use. However, the prevalence of movement dysfunction in people with a history of illicit stimulant use has not yet been investigated.

The aim of the current study was to address this knowledge gap by investigating the prevalence of self-reported movement dysfunction in young-to-middle aged adults with a history of illicit stimulant use. Several movement domains were investigated including gait, balance, hand function, and speech. It was hypothesized that the prevalence of movement dysfunction would be higher in people with a history of illicit stimulant use than in people with no history of illicit stimulant use, and higher in people that use methamphetamine than in people that use ecstasy for most movement domains (except tremor). Evidence that supports the hypothesis is the association between methamphetamine use (but not ecstasy use) and parkinsonism (Todd et al., 2016b) and ecstasy use and tremor during movement and postural tasks (Downey et al., 2017; Flavel et al., 2012a).

The current study focuses on a noticeable long-lasting consequence of illicit stimulant use and one which may resonate with young people in public health campaigns that target prevention or harm minimization. Knowing the prevalence of specific drug effects on health can improve the relevance, and aid development, of informative drug education messages.

2. Methods

The prevalence of self-reported movement problems was investigated in three groups of participants aged 18–50 years. The two target groups consisted of i) 190 adults with a history of ecstasy use but no use of methamphetamine ('ecstasy group') and ii) 331 adults with a history of methamphetamine and ecstasy use ('methamphetamine group'). It is not possible to have a methamphetamine-alone group because up to 93% of people that have used methamphetamine also have a history of ecstasy use (e.g. Scholey et al., 2004; Todd et al., 2016b). The control group consisted of 228 adults with no history of illicit stimulant use (i.e. no history of use of ecstasy, amphetamine/methamphetamine, and/or cocaine). Recruitment of people with a history of illicit stimulant use occurred through the 2016 National Ecstasy and Related Drugs Reporting System - an annual national survey in Australia that investigates emerging trends in illicit drug markets (for full study details, see Stafford and Breen, 2017). Additional inclusion criteria for the ecstasy and methamphetamine groups was use of an illicit stimulant drug on six or more occasions during the preceding six months and > 12 months residency within the capital city in which the survey took place (Stafford and Breen, 2017). Recruitment of non-stimulant users occurred via community advertisement and participants were offered the chance to win one of twenty $100 gift vouchers upon completion of the survey. The study was approved by the Human Research Ethics Committee at the University of South Australia and University of New South Wales. The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Written or electronic informed consent was obtained from each participant prior to participation in the study.

General exclusion criteria for participation in the study were i) diagnosed with a mental disorder prior to onset of illicit drug use, ii) current use of a prescribed medication for treatment of a diagnosed mental disorder, iii) current use of a prescribed medication that may affect movement (e.g. beta-blocker), iv) current or previous history of antipsychotic use, v) diagnosed with a condition, disease, or disorder that may affect movement (e.g. rheumatoid arthritis, brain tumor, or restless legs syndrome), and vi) history of illicit opioid use (e.g. heroin or methadone).

2.1. Experimental protocol

Each participant completed an anonymous survey containing questions about demographics (e.g. age, sex, education, employment), health, movement, and drug use. The first page of the survey explained the study aim and that all answers would remain anonymous and confidential. Participants were also informed that consent was implied by completion of the questionnaire. The questionnaire took 20 − 60 min to complete and contained a mix of open and closed questions.

The health questions in the survey focused primarily on diagnosed diseases/disorders or conditions that affect the brain, spinal cord, or nerves. Participants were provided with a list of examples that included 16 mental disorders, 46 neurological diseases/disorders/injuries (e.g. stroke, brain injury, epilepsy), and 5 other diseases/conditions (e.g. back injury) that may affect movement. Participants were asked to name the disease/disorder/injury/condition and to note how old they were when the diagnosis was received.

Information about movement was obtained from 9 questions derived from a published and validated questionnaire designed to investigate the prevalence of undiagnosed movement disorders in adults aged > 50 years (Chan et al., 2000) and a World Health Organization guideline and questionnaire on the epidemiology of neurological disorders (WHO, 1981). The questions included:

1) Have you noticed that you have become clumsier or have more difficulty with tasks that involve fine hand control (e.g. doing up your buttons or using a screwdriver)? Yes/No
2) Do you feel that you move slowly or stiffly? Yes/No
3) Do you walk with a stooped posture or shuffle? Yes/No
4) Have you noticed that you don't swing your arms when you walk, as much as you used to? Yes/No
5) Have you noticed a tremor (shaking) in your hands, arms, legs, or head? Yes/No
6) Have you noticed any changes in your voice or the way that you speak? Yes/No
7) Have you noticed that your balance isn't as good as it used to be? Yes/No
8) Have you had other unusual movements or weakness in your arms or legs? Yes/No. If yes, please describe.
9) Have you ever had a loss of sensation (feeling) or abnormal sensation affecting your arms or legs? Yes/No

The collective response to questions 2, 3, and 4 has been previously shown to have a high sensitivity (84.4%) and specificity (86.3%) for Parkinson's disease in hospital and community settings in Australia (Chan et al., 2000), the country within which the current study was performed. Questions 4 and 5 have also been shown to effectively

Table 1
Participant characteristics for the non-stimulant-using control group, ecstasy group, and methamphetamine group. Age is presented as mean ± SD. Education data is the percentage of participants who have completed (finished) secondary school (Year 12) and/or post-school training (e.g. university, college, trade, or technical qualification). Only education data for control participants that completed the online survey (n = 181) is presented for parity across groups ([a]). Drug treatment data is the percentage of participants who are currently undergoing treatment for drug use (counselling or detox). Drug use parameters are presented as the percentage of participants who have used that class of drug and mean ± SD for the number of days that these participants used the drug over the past 6 months in brackets. The term 'ecstasy and related drugs' includes MDMA (3,4-methylenedioxymethamphetamine), MDA (3,4-methylenedioxyamphetamine), 5MAPB (1-(benzofuran-5-yl)-*N*-methylpropan-2-amine), mephedrone, methylone, 4-MEC (4-methylethcathinone), MDAI (5,6-methylenedioxy-2-aminoindane), 5-IAI (5-iodo-2-aminoindane), Benzo Fury (or 6-APB), PMA (para-methoxyamphetamine), and/or MDEA (3,4-methylenedioxy-*N*-ethylamphetamine). The term 'methamphet and related drugs' describes methamphetamine, alpha PVP (α-pyrrolidinopentiophenone), MDPV (methylenedioxypyrovalerone), BZP (benzylpiperazine), 4-FA (4-fluoroamphetamine), and/or other substituted cathinone. The term 'pharmaceutical stimulant' includes illicit use of methylphenidate, dexamphetamine, amphetamine sulfate, modafinil, and/or duromine (phentermine). The term 'hallucinogens' includes LSD (lysergic acid diethylamide), LSA (d-lysergic acid amide), 'magic mushrooms', mescaline, methoxetamine, DOI (2,5-dimethoxy-4-iodoamphetamine), DMT (dimethyltryptamine), 5-MeO-DMT (5-methoxy-*N,N*-dimethyltryptamine), 4-AcO-DMT (*O*-Acetylpsilocin), 2C-I (2,5-dimethoxy-4-iodophenethylamine), 2C-B (4-bromo-2,5-dimethoxyphenylethanamine), 2C-C ((4-chloro-2,5-dimethoxyphenethyl)amine), 2C-D (2,5-dimethoxy-4-methylphenethylamine), 2C-E (4-ethyl-2,5-dimethoxyphenethylamine), 2C-P (2,5-dimethoxy-4-*N*-propylphenethylamine), 2C-T-2 (2-[4-(Ethylsulfanyl)-2,5-dimethoxyphenyl]ethan-1-amine), ketamine, dextromethorphan, NBOMe (*N*-methoxybenzyl), DOC (Dimethoxy-4-chloroamphetamine), 4 − HO-MET (4-hydroxy-*N*-methyl-*N*-ethyltryptamine, metocin, or methylcybin), DOM (2,5-Dimethoxy-4-methylamphetamine), Moby Shine (glass cleaner), synthetic cannabinoids, herbal high, changa, salvia divinorum, ayahuasca, and datura. The term 'inhalants' includes amyl nitrate and nitrous oxide. The term 'sedatives' includes GHB/GBL/1,4B/fantasy and illicit use of benzodiazepines, etizolam, antihistamines, and antidepressants. The term 'opioids' describes illicit use of oxycodone, buprenorphine, tramadol, and/or codeine. * Significantly different from the control group ($p < 0.05$). § Significant difference between the ecstasy and methamphetamine groups ($p < 0.05$).

Characteristic	Control	Ecstasy	Methamphetamine
Sample size	228	190	331
Age (years)	25 ± 8	20 ± 3 *	23 ± 5 *§
Sex	77 M, 151 F	121 M, 69 F *	186 M, 145 F *
Education	School: 91% [a] Post-School: 61% [a]	School: 86% Post-School: 26%	School: 77% Post-School: 52%
Employed and/or studying	82% [a]	96%	89%
Drug treatment	0%	2%	1%
Tobacco	42% (18 ± 49 days)	89% * (76 ± 73 days) *	93%* (98 ± 80 days) *§
e-cigarettes	7% (5 ± 8 days)	53% * (14 ± 37 days) *	51% * (9 ± 19 days) *§
Alcohol	88% (22 ± 29 days)	99% * (45 ± 34 days) *	99% * (63 ± 47 days) *§
Cannabis	30% (16 ± 41 days)	96% * (58 ± 63 days) *	99% *§ (63 ± 70 days) *
Ecstasy and related drugs	0%	100% (16 ± 15 days)	100% (18 ± 15 days)
Methamphet and related drugs	0%	0%	100% (6 ± 19 days)
Cocaine	0%	61% (4 ± 5 days)	80% § (6 ± 8 days) §
Pharmaceutical stimulants	0%	45% (10 ± 18 days)	53% (11 ± 25 days)
Hallucinogens	9% (1 ± 1 days)	76% * (5 ± 7 days) *	89% *§ (6 ± 10 days) *
Inhalants	3% (5 ± 10 days)	67% * (12 ± 14 days)	69% * (9 ± 11 days)
Sedatives	2% (1 ± 3 days)	40% * (5 ± 9 days)	51% *§ (9 ± 20 days) *
Opioids	0%	27% (11 ± 26 days)	28% (10 ± 22 days)

discriminate patients with idiopathic Parkinson's disease from healthy adults aged > 40 years (arm swing: Youden's index = 0.73, sensitivity = 75%, specificity = 98%; tremor: Youden's index = 0.77, sensitivity = 87%, specificity = 90%) (Fereshtehnejad et al., 2014).

Information about drug use was obtained by asking participants if they had ever tried licit drugs (alcohol or tobacco), e-cigarettes, or 39 listed illicit drugs (e.g. ecstasy, methamphetamine, cocaine, cannabis, LSD, amyl nitrate, GHB). Participants were also asked if they had ever tried other illicit drugs not listed or capsules with unknown contents. Participants were also asked if they had ever tried one or more of 10 listed classes of medications without a prescription (i.e. for recreational use, e.g. pharmaceutical stimulants, opiates, benzodiazepines). For each drug tried, participants were asked about age of first use and/or the number of days used in the past six months. The survey also contained questions about use of medications that participants had a prescription for (e.g. pharmaceutical stimulants, opiates, benzodiazepines, antipsychotics, antidepressants) to identify any other potential mental disorders not mentioned elsewhere in the survey. Participants were also asked if they had suffered a drug overdose or sought help from a health professional/service for any issues related to drug or alcohol use. Participants also completed the Alcohol Use Disorders Identification Test (AUDIT), to identify indicators of hazardous and harmful alcohol use (AUDIT score ≥8) (Babor et al., 2001), and the Severity of Dependence Scale (Gossop et al., 1995) to identify potential dependence on ecstasy or methamphetamine (score ≥4) within the sample (Bruno et al., 2009; Topp and Mattick, 1997).

For the ecstasy and methamphetamine groups, the survey was administered in 2016 during a face-to-face structured interview conducted by trained interviewers as part of the 2016 National Ecstasy and Related Drugs Reporting System. For the control group, the survey was administered between 2015 and 2018 in a face-to-face structured interview conducted by trained interviewers (n = 47) or via an online survey (n = 181) using SurveyMonkey (San Mateo, USA). Participant responses were immediately documented on paper or a digital device. It was not possible to check if online respondents completed the questionnaire more than once as IP tracking was turned off to protect anonymity.

2.2. Statistics

Group data are presented using a combination of means, standard deviations, and percentages. One-way analysis of variance (ANOVA) was used for between-group comparison of age and recent consumption (days used in past 6 months) of alcohol, tobacco, cannabis, and e-cigarettes, in participants that reported use of these drugs. Post-hoc testing between means was made with the Tukey procedure. Kolmogorov-Smirnov and Levene's tests were performed on recent consumption (days used in past 6 months) of cocaine, opioids, pharmaceutical stimulants (used illicitly), hallucinogens, sedatives, and inhalants. Mann-Whitney U test was subsequently performed on recent use of cocaine, opioids, and pharmaceutical stimulants in the ecstasy and methamphetamine groups, and one-way ANOVA on ranks was performed on recent use of hallucinogens, sedatives, and inhalants. Unpaired Student's *t*-test was used to investigate recent consumption (days used in past 6 months) of ecstasy in the ecstasy and methamphetamine groups. Between-group (ecstasy versus methamphetamine)

comparison of the prevalence of drug overdose and ecstasy dependence was performed with Pearson's chi-square test. Between-group (ecstasy versus methamphetamine) comparison of the prevalence of drug injecting behaviour was performed with Fisher's exact test (IBM SPSS Statistics 25, Armonk NY, USA). For sex and each categorical outcome measure (e.g. history of use of each class of drug), a crude logistic regression model with just group as the predictor variable was conducted. For each movement outcome measure separately, each potential confounding variable on its own was added to the model. Tobacco was not included in the model because it is difficult to distinguish the effects of tobacco from those of cannabis (77–91% of European cannabis smokers and 52% of Australian cannabis smokers mix tobacco with cannabis prior to consumption, Hindocha et al., 2016). Greenland's change in coefficient method was used to determine variables that were confounding, with a criterion of a 20% change or more in either coefficient (Greenland, 1989). Finally, for each movement outcome measure, a multivariate logistic regression was undertaken including all confounding variables (Stata v.14, StataCorp, Texas, USA). Significance was set at $p < 0.05$.

3. Results

Table 1 shows participant characteristics for each group. A small but significant difference in age was observed between the groups ($p < 0.001$) and the ratio of males to females also differed between the groups. The control group had a lower male to female ratio than the ecstasy ($\chi^2 = 43.48$, OR = 0.29, $p < 0.001$) and methamphetamine group ($\chi^2 = 43.48$, OR = 0.40, $p < 0.001$) but the male to female ratio did not differ between the drug-using groups. The groups also significantly differed in alcohol, tobacco, e-cigarette, and cannabis consumption. The prevalence of use of these drugs was significantly higher in the ecstasy and methamphetamine groups than in the control group, and the prevalence of cannabis use was greater in the methamphetamine group than in the ecstasy group. Recent consumption of these drugs (number of days used in past 6 months) was also higher in the ecstasy and methamphetamine groups than in the control group. Indicators of hazardous and harmful alcohol use (AUDIT score ≥ 8) were common in the ecstasy (75% of participants) and methamphetamine (74% of participants) groups and rare in the control group (13% of participants).

Table 1 also shows the prevalence of use and recent consumption (number of days used in past 6 months) of illicit drugs and Tables 2 and 3 present the results of the logistic regression models and one-way ANOVA showing the main effects and post-hoc analysis of group. All participants in the ecstasy and methamphetamine groups had used ecstasy or an ecstasy-related drug in their lifetime and the two groups did not differ in recent consumption of these drugs, or indicators of ecstasy dependence (Severity of Dependence Scale score ≥ 4; ecstasy group = 16% of participants, methamphetamine group = 18% of participants). The prevalence of use and recent consumption of cocaine was higher in the methamphetamine group than in the ecstasy group but, the ecstasy and methamphetamine groups did not differ in illicit use of pharmaceutical stimulants. The prevalence of use of hallucinogens, inhalants, sedatives, and opioids was greater in the ecstasy and methamphetamine groups than in the control group but, recent consumption of these drugs did not differ between the ecstasy and methamphetamine groups. Few participants in the methamphetamine group (9%) displayed indicators of methamphetamine dependence (Severity of Dependence Scale score ≥ 4). The percentage of participants in the ecstasy and methamphetamine groups that had experienced a drug overdose was comparable (ecstasy group: 2% on a new psychoactive substance, 23% on a stimulant, 24% on a depressant; methamphetamine group: 2% on a new psychoactive substance, 25% on a stimulant, 23% on a depressant) but, the prevalence of drug injecting behaviour was higher in the methamphetamine group (8%) than in the ecstasy group (1%; $p < 0.001$).

Fig. 1 shows group data for participant responses to the movement questions. For all movement questions, except the question on voice/speech, a 'yes' response is indicative of a self-reported negative (abnormal) change in movement. In the control group, the prevalence of self-reported movement abnormalities was low, with abnormal fine motor control (2.6%) and unusual movement or weakness (3.1%) reported less frequently than changes in the other movement domains (7.9–10.5%). Fig. 1 suggests that the prevalence of self-reported tremor and abnormal changes in fine motor control is higher in the ecstasy and methamphetamine groups than in the control group, and that the ecstasy group has a higher prevalence of self-reported changes in voice/speech and abnormal gait and posture compared to the other groups.

Statistical between-group comparison of the participant responses to the movement questions was performed with logistic regression. In the unadjusted model, group had a significant effect on the answer to the fine hand control, tremor, and voice/speech questions (Table 4). The prevalence of self-reported tremor and abnormal changes in fine hand control was significantly higher in the ecstasy and methamphetamine groups than in the control group ($p < 0.018$). The prevalence of changes in voice/speech was also significantly higher in the ecstasy group than in the control group ($p = 0.015$). No other significant between-group differences were observed in the other movement domains.

For the fine hand control, tremor, and voice/speech questions, each potential confounding variable on its own was added to the logistic regression model. The results of the adjusted models are presented in Table 4. A significant between-group effect on the response to the tremor and voice/speech questions was still evident after accounting for age. However, no significant between-group differences were observed in the response to the fine hand control or tremor questions after accounting for history of use of cannabis and hallucinogens.

Table 5 contains a chi-square table to assist interpretation of the adjusted logistic regression models. As expected, cannabis use in the ecstasy and methamphetamine groups was very common and only 8 participants in the ecstasy group and 2 participants in the methamphetamine group had not used cannabis. In the control group, non-cannabis users accounted for 33% of participants that reported an abnormal change in fine hand control and 67% of participants that reported a tremor. Furthermore, in the control group, non-hallucinogen users accounted for 83% of participants that reported an abnormal change in fine hand control, 87.5% of participants that reported tremor, and 90.5% of participants that reported a change in voice/speech. The effect of alcohol use on voice/speech is difficult to investigate because only one participant in the ecstasy group and two participants in the methamphetamine group had not used alcohol.

4. Discussion

The results of the current study demonstrate, for the first time, that the prevalence of self-reported tremor and changes in fine hand control and voice/speech, is significantly higher in young-to-middle aged adults with a history of illicit stimulant use than in non-stimulant-using controls. The prevalence of perceived abnormal changes in other movement domains, such as gait, posture, balance, sensation, and movement speed and stiffness, did not differ between the groups.

The prevalence of abnormal changes in fine hand control was 4–5 times higher in individuals with a history of illicit stimulant use than in non-stimulant-using controls. One in seven participants in the ecstasy group reported an abnormal change in fine hand control and one in nine participants in the methamphetamine group reported an abnormal change in this movement domain. The prevalence of self-reported tremor was also higher in stimulant users than in non-stimulant-using controls, by a factor of 1.7 and 2.2 times in the ecstasy and methamphetamine groups, respectively. One in four participants in the ecstasy group had noticed a tremor in their hands, arms, legs, or head, and one in five participants in the methamphetamine group reported a tremor.

Table 2
Results of the logistic regression models showing the main effects of group on prevalence of drug use. Statistical comparison of the prevalence of ecstasy use in the ecstasy and methamphetamine groups was not possible because all participants in the ecstasy and methamphetamine groups had a history of ecstasy use. Abbreviations: Meth, methamphetamine.

		Prevalence of use					
		Control as base			Methamphetamine as base		
		OR	95% CI	Sig	OR	95% CI	Sig
Tobacco	Group [a]						
	v Control				0.05	0.03, 0.09	< 0.001
	v Ecstasy	11.07	6.55, 18.69	< 0.001	0.57	0.31, 1.07	0.082
	v Meth	19.31	11.64, 32.04	< 0.001			
e-cigarettes	Group [a]						
	v Control				0.07	0.04, 0.13	< 0.001
	v Ecstasy	14.72	8.22, 26.36	< 0.001	1.08	0.75, 1.54	0.680
	v Meth	13.66	7.86, 23.72	< 0.001			
Alcohol	Group [a]						
	v Control				0.05	0.01, 0.19	< 0.001
	v Ecstasy	25.38	3.42, 188.68	0.002	1.15	0.10, 12.76	0.910
	v Meth	22.10	5.20, 93.92	< 0.001			
Cannabis	Group [a]						
	v Control				0.003	0.0006, 0.0109	< 0.001
	v Ecstasy	52.42	24.46, 112.36	< 0.001	0.14	0.03, 0.66	0.013
	v Meth	379.1	91.76, 1565.94	< 0.001			
Ecstasy	Group [a]						
	v Meth				–	–	–
Cocaine	Group [a]						
	v Ecstasy				2.65	1.78, 3.94	< 0.001
Pharmaceutical stimulants	Group [a]						
	v Ecstasy				1.39	0.97, 1.99	0.072
Hallucinogens	Group [a]						
	v Control				0.012	0.007, 0.021	< 0.001
	v Ecstasy	32.56	18.48, 57.36	< 0.001	0.39	0.25, 0.63	< 0.001
	v Meth	82.64	46.63, 146.45	< 0.001			
Inhalants	Group [a]						
	v Control				0.012	0.005, 0.028	< 0.001
	v Ecstasy	76.39	32.14, 181.56	< 0.001	0.933	0.64, 1.37	0.721
	v Meth	81.90	35.23, 190.41	< 0.001			
Sedatives	Group [a]						
	v Control				0.021	0.009, 0.054	< 0.001
	v Ecstasy	29.73	11.70, 75.56	< 0.001	0.64	0.45, 0.92	0.015
	v Meth	46.53	18.69, 115.83	< 0.001			
Opioids	Group [a]						
	v Ecstasy				1.07	0.71, 1.59	0.758

[a] Groups are compared to the set base group (either control or methamphetamine).

The tremor data supports the findings of Parrott et al (2002) who report that 20% of moderate ecstasy users (10 − 99 occasions of use) and 38% of heavy ecstasy users (+100 occasions of use) self-report problems with tremor and/or twitches (Parrott et al., 2002). The higher prevalence of tremor observed in the current study may be linked to the higher prevalence of abnormal fine hand control if the reported tremor was present in the hands.

Identifying the underlying cause of the higher prevalence of tremor and abnormal changes in fine hand control in the ecstasy and methamphetamine groups is challenging. It is reasonable to assume that use of ecstasy and/or methamphetamine is responsible for the higher prevalence and there are several lines of evidence to support this view. For example, abnormal manipulation of novel objects has been observed in abstinent young-to-middle aged adults with a history of methamphetamine and/or ecstasy use (Pearson-Dennett et al., 2014) and use of transcranial magnetic stimulation in this population has demonstrated abnormal excitability in the pathway between the motor cortex and hand muscles (Flavel et al., 2012b). In rodents and primates, there is rich dopaminergic innervation of the motor cortex (Awenowicz and Porter, 2002; Goldman-Rakic et al., 1989), and local application of dopamine decreases spontaneous discharge of pyramidal tract neurons (Awenowicz and Porter, 2002). Thus, methamphetamine-induced changes in dopaminergic neurotransmission could alter basal excitability of the motor cortex and/or corticomotoneuronal pathway and control of the hand. Changes in manipulation of novel objects and the excitability of the neural pathway to the hand has also been observed in older adults with Parkinson's disease, a disease characterized by degeneration of primarily dopaminergic neurons (e.g. Fearnley and Lees, 1991) and intracellular mechanisms that share some similarities with methamphetamine neurotoxicity (e.g. oxidative stress, mitochondrial dysfunction, and neuroinflammation: Obeso et al., 2017; Yamamoto and Bankson, 2005). Use of accelerometry has also demonstrated augmented tremor during hand movement and postural tasks in abstinent young adults with a history of ecstasy use and minimal amphetamine use, but not in young adults with a history of cannabis use but no stimulant use (Flavel et al., 2012a). Augmented tremor has also been observed in young-to-middle aged adults that were currently using, or had previously used, stimulant drugs (amphetamine, ecstasy, cocaine, or mephedrone) for two or more times a week for a minimum of two years (Downey et al., 2017). However, there are several factors, other than use of ecstasy and/or methamphetamine that could contribute to the increased prevalence of tremor and abnormal changes in fine hand control. Examples of other factors include poly-drug use, higher consumption of alcohol and tobacco, and higher rates of affective symptoms in stimulant-using populations.

Poly-drug use is common in individuals with a history of ecstasy and/or methamphetamine use. This is evidenced in Table 1 and in the results of national drug monitoring surveys (e.g. Stafford and Breen,

Table 3
Results of the statistical analysis showing the effect of group on the number of days of drug use in the past 6 months. Abbreviations: Meth, methamphetamine.

		Days of use (past 6 months)				
			Control as base		Methamphetamine as base	
		Main effect	95% CI	Sig	95% CI	Sig
Tobacco	Group [a]	$F_{2,562} = 45.19$, $p < 0.001$ [b]				
	v Control				61.62, 102.19	< 0.001
	v Ecstasy		−80.58, -36.32	< 0.001	6.93, 39.98	0.003
	v Meth		−102.19, -61.62	< 0.001		
e-cigarettes	Group [a]	$F_{2,562} = 45.19$, $p < 0.001$ [b]				
	v Control				61.62, 102.19	< 0.001
	v Ecstasy		−80.58, -36.32	< 0.001	6.93, 39.98	0.003
	v Meth		−102.19, -61.62	< 0.001		
Alcohol	Group [a]	$F_{2,709} = 66.98$, $p < 0.001$ [b]				
	v Control				32.53, 49.13	< 0.001
	v Ecstasy		−32.37, -13.66	< 0.001	9.36, 26.28	< 0.001
	v Meth		−49.13, -32.53	< 0.001		
Cannabis	Group [a]	$F_{2,577} = 14.71$ $p < 0.001$ [b]				
	v Control				26.33, 66.86	< 0.001
	v Ecstasy		−62.96, -19.69	< 0.001	−8.87, 19.40	0.656
	v Meth		−66.86, -26.33	< 0.001		
Ecstasy	Group [a]					
	v Meth				−5.07, 0.32	0.084 [e]
Cocaine	Group [a]					
	v Ecstasy				−3.72, -0.41	0.008 [d]
Pharmaceutical stimulants	Group [a]					
	v Ecstasy				−8.51, 5.67	0.401 [d]
Hallucinogens	Group [a]	$F_{2,457} = 9.518$, $p < 0.001$ [c]				
	v Control				55.70, 189.22	< 0.001
	v Ecstasy		−174.58, -36.29	0.001	−13.70, 47.75	0.394
	v Meth		−189.22, -55.70	< 0.001		
Inhalants	Group [a]	$F_{2,233} = 2.643$, $p = 0.073$ [c]				
	v Control					
	v Ecstasy					
	v Meth					
Sedatives	Group [a]	$F_{2,167} = 4.429$, $p = 0.013$ [c]				
	v Control				8.28, 111.30	0.018
	v Ecstasy		−100.74, 4.21	0.078	−6.83, 29.89	0.301
	v Meth		−111.30, -8.28	0.018		
Opioids	Group [a]					
	v Ecstasy				−6.77, 9.78	0.696 [d]

[a] Groups are compared to the set base group (either control or methamphetamine).
[b] One-way ANOVA with Tukey post hoc testing.
[c] One-way ANOVA performed on rank transformed data with Tukey post hoc testing.
[d] Mann-Whitney U test.
[e] Unpaired Student's *t*-test.

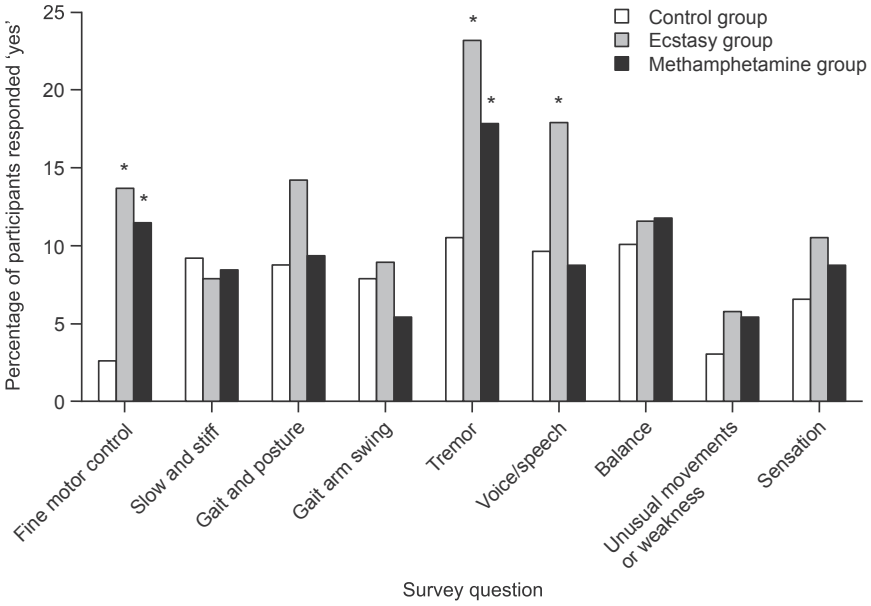

Fig. 1. Group data showing the percentage of participants that responded 'yes' to each movement question. For all questions, except the voice/speech question, a yes response indicates a negative (abnormal) change in movement. White bars, control group (n = 228). Grey bars, ecstasy group (n = 190). Black bars, methamphetamine group (n = 331). * Significantly different to control group in the unadjusted logistic regression model ($P \leq 0.018$).

Table 4
Results of the logistic regression models for the fine hand control, tremor, and voice/speech movement questions. Results of the unadjusted logistic regression models are presented first. For each movement question, Greenland's change in coefficient method was used to determine the variables that were confounding, and only the confounding variables are listed in the table. A multivariate logistic regression was then undertaken including all confounding variables for each movement question. Abbreviations: Meth, methamphetamine.

	Unadjusted model			Adjusted model		
	β	95% CI	Sig	β	95% CI	Sig
Fine hand control						
Intercept	−3.61	−4.42, -2.80	< 0.001	−4.54	−5.94, -3.13	< 0.001
Group						
Control vs Ecstasy	1.77	0.86, 2.68	< 0.001	0.51	−0.62, 1.63	0.376
Control vs Meth	1.57	0.69, 2.45	< 0.001	0.20	−0.93, 1.33	0.726
Cannabis				1.60	−0.05, 3.24	0.057
Hallucinogens				0.77	−0.05, 1.59	0.067
Tremor						
Intercept	−2.14	−2.56, -1.71	< 0.001	−0.39	−1.61, 0.83	0.535
Group						
Control vs Ecstasy	0.94	0.40, 1.48	0.001	0.31	−0.49, 1.12	0.446
Control vs Meth	0.61	0.10, 1.12	0.018	0.15	−0.66, 0.96	0.710
Age				−0.08	−0.13, -0.03	0.002
Cannabis				0.27	−0.54, 1.08	0.515
Hallucinogens				0.27	−0.30, 0.84	0.358
Voice/speech						
Intercept	−2.24	−2.68, -1.80	< 0.001	−0.08	−1.67, 1.52	0.924
Group						
Control vs Ecstasy	0.71	0.14, 1.30	0.015	0.41	−0.36, 1.18	0.299
Control vs Meth	−0.11	−0.70, 0.48	0.720	−0.26	−1.06, 0.55	0.529
Age				−0.07	−0.13, -0.01	0.018
Alcohol				−0.63	−1.69, 0.43	0.243
Hallucinogens				0.22	−0.44, 0.88	0.512

2017) and previously published studies (McCann et al., 1994; Scholey et al., 2004). Thus, it is not possible to differentiate the effects of ecstasy or methamphetamine alone from the combined effects of these stimulants and other drugs. The results of the adjusted models presented in Table 4 demonstrates the potential importance of other drugs. No significant between-group differences were observed in the response to the fine hand control or tremor questions after accounting for history of use of cannabis and hallucinogens. However, exploration of these confounding variables with chi-square tables (see Table 5) suggests that the contribution of cannabis and hallucinogens to the increased prevalence of tremor and abnormal changes in fine hand control is likely to be minor. In the control group, non-cannabis and non-hallucinogen users accounted for a large percentage of participants that reported tremor or an abnormal change in fine hand control. This suggests that use of these drugs is unlikely to have made a meaningful contribution to the higher prevalence of tremor and abnormal changes in fine hand control in the ecstasy and methamphetamine groups.

Individuals that use ecstasy and/or methamphetamine also consume

Table 5
Stratified chi square table showing confounding variables on the response to the fine hand control, tremor, and voice/speech questions in each group. For the fine hand control and tremor questions, a yes response indicates a negative (abnormal) change in movement. The number of participants are reported and the data is also expressed as a percentage of the sample (in brackets).

Group		Control			Ecstasy			Methamphetamine		
Fine hand control										
Response		Yes	No	Sig	Yes	No	Sig	Yes	No	Sig
Cannabis	Yes	4 (1.8%)	65 (28.5%)	0.070 [a]	26 (13.7%)	156 (82.1%)	0.601 [a]	38 (11.5%)	290 (87.6%)	1.000 [a]
	No	2 (0.9%)	157 (68.9%)		0 (0%)	8 (4.2%)		0 (0%)	2 (0.6%)	
Hallucinogens	Yes	1 (0.4%)	19 (8.3%)	0.427 [a]	25 (13.2%)	119 (62.6%)	0.006 [a]	34 (10.3%)	259 (78.2%)	1.000 [a]
	No	5 (2.2%)	203 (89.0%)		1 (0.5%)	45 (23.7%)		4 (1.2%)	33 (10.0%)	
Tremor										
Response		Yes	No	Sig	Yes	No	Sig	Yes	No	Sig
Age (yrs)	≤25	20 (8.8%)	130 (57.0%)	0.069 [a]	44 (23.2%)	134 (70.5%)	0.072 [a]	47 (14.2%)	202 (61.0%)	0.384 [b]
	> 25	4 (1.8%)	74 (32.5%)		0 (0%)	12 (6.3%)		12 (3.6%)	70 (21.1%)	
Cannabis	Yes	8 (3.5%)	61 (26.8%)	0.815 [b]	43 (22.6%)	139 (73.2%)	0.684 [a]	59 (17.8%)	270 (81.6%)	1.000 [a]
	No	16 (7.0%)	143 (62.7%)		1 (0.5%)	7 (3.7%)		0 (0%)	2 (0.6%)	
Hallucinogens	Yes	3 (1.3%)	17 (7.5%)	0.450 [a]	37 (19.5%)	107 (56.3%)	0.164 [b]	51 (15.4%)	243 (73.4%)	0.649 [b]
	No	21 (9.2%)	187 (82.0%)		7 (3.7%)	39 (20.5%)		8 (2.4%)	29 (8.8%)	
Voice/speech										
Response		Yes	No	Sig	Yes	No	Sig	Yes	No	Sig
Age (yrs)	≤25	19 (8.3%)	131 (57.5%)	0.034 [a]	34 (17.9%)	144 (75.8%)	0.129 [a]	25 (7.6%)	224 (67.7%)	0.181 [a]
	> 25	3 (1.3%)	75 (32.9%)		0 (0%)	12 (6.3%)		4 (1.2%)	78 (23.6%)	
Alcohol	Yes	17 (7.5%)	184 (80.7%)	0.154 [a]	34 (17.9%)	155 (81.6%)	1.000 [a]	29 (8.8%)	300 (90.6%)	1.000 [a]
	No	5 (2.2%)	22 (9.6%)		0 (0%)	1 (0.5%)		0 (0%)	2 (0.6%)	
Hallucinogens	Yes	3 (1.3%)	17 (7.5%)	0.420 [a]	26 (13.7%)	118 (62.1%)	1.000 [b]	26 (7.9%)	268 (81.0%)	1.000 [a]
	No	19 (8.3%)	189 (82.9%)		8 (4.2%)	38 (20.0%)		3 (0.9%)	34 (10.3%)	

[a] Fisher's exact test.
[b] Pearson chi-square.

more alcohol and tobacco than non-stimulant users (e.g. Scholey et al., 2004) and, in the current study, indicators of hazardous and harmful alcohol use were much more common in the ecstasy and methamphetamine groups than in the control group. Greater alcohol consumption could conceivably contribute to a higher prevalence of movement dysfunction in individuals with a history of illicit stimulant use. However, alcohol was not a confounding variable in the logistic regression model for fine hand control or tremor. A higher prevalence of affective symptoms in stimulant-using populations (for review see Darke et al., 2008) could also be associated with changes in movement, because for example, motor retardation can accompany major depression (for review see Bennabi et al., 2013). However, the effect of affective symptoms on the current movement data is likely to be minimal due to the strict participant exclusion criterion employed. Furthermore, previous studies on the long-lasting effects of illicit drug use on movement have shown disparate movement effects in different drug-using populations (cannabis, ecstasy, methamphetamine) with comparable recent symptoms of depression (e.g. Flavel et al., 2012a; Todd et al., 2016b).

It was hypothesized that the prevalence of abnormal changes in movement (except tremor) would be higher in the methamphetamine group than in the ecstasy group however this was not the case. The lack of a between-group difference could arise if both serotonergic and dopaminergic circuitry play a significant role in movement – where damage to either serotonergic (ecstasy) or dopaminergic (methamphetamine) neurons may lead to altered movement. Evidence derived from de novo patients with Parkinson's disease suggests that dopamine plays a key role in several movement domains, including fine motor function where abnormalities in grip force planning and application have been noted (Fellows and Noth, 2004). However, the role of serotonergic neurotransmission in fine motor function and other movement domains is not well understood.

The prevalence of self-reported changes in voice/speech was also significantly higher in the ecstasy group than in the control group ($p = 0.015$). Changes in speech content have been observed in patients with posttraumatic stress disorder while under the effects of MDMA (Corey et al., 2016) and changes in verbal fluency (involving access to long-term memory) have been documented in individuals with a history of predominantly ecstasy use (Montgomery et al., 2005). Although both features relate to language (what people say) rather than how they say it (motor speech production). It is unclear if the changes in voice and/or speech observed in the current study are positive or negative in nature, or whether the changes refer to speech timing, intonation, or articulation (i.e. speech motor function) or the formation of content used in communication (i.e. language). A detailed investigation of the speech profile of individuals in this population is warranted. It is also unclear if the increased self-reported changes in voice/speech is associated with use of ecstasy or other drugs. The results of the adjusted models presented in Table 4 suggests that use of alcohol and hallucinogens may play a role. No significant between-group differences were observed in the response to the voice/speech question after accounting for history of use of alcohol and hallucinogens. The effect of alcohol use on voice/speech is difficult to interpret because only one participant in the ecstasy group had not used alcohol. The effect of hallucinogens on voice/speech is likely to be minor given that, in the control group, non-hallucinogen users accounted for 90.5% of participants that reported a change in voice/speech.

The prevalence of abnormal changes in other movement domains, such as gait, posture, balance, sensation, and movement speed and stiffness, did not differ between the groups. This suggests that use of illicit stimulants does not affect these types of movement or that the effect is of a magnitude that is not discernible to the individual. These movement domains have not been quantitatively assessed in illicit stimulant users but, bradykinesia and abnormal finger tapping, subjectively assessed by a neurologist that specializes in movement disorders, have been observed in abstinent methamphetamine users (Todd et al., 2016b).

The study had three main limitations. First, we intended to match the groups for sample size, age, and sex but this was difficult to achieve due to the strict study inclusion and exclusion criterion employed. The average age in the control, ecstasy, and methamphetamine groups was 25 ± 8, 20 ± 3, and 23 ± 5 years, respectively. The effect of age on participant response to the movement questions is likely to be minor given that age was not a confounding variable for the fine hand control question and a significant between-group effect on the tremor and voice/speech questions was still evident after adjusting for age in the logistic regression model. The effect of sex on participant response to the movement questions is also likely to be minimal because sex was not a confounding variable in the logistic regression model. Second, the ecstasy and methamphetamine groups in the current study were delineated through self-reported use of methamphetamine. Participants in the ecstasy group had used ecstasy but not methamphetamine, and participants in the methamphetamine group had used methamphetamine and ecstasy. Recruiting a large sample of individuals that have used methamphetamine but not ecstasy is not possible in Australia, or many other western countries, because a very high percentage of people that have used methamphetamine also have a history of ecstasy use (Scholey et al., 2004; Stafford and Breen, 2017). Lastly, the current data set does not permit exploration of the relationship between prevalence of movement dysfunction and drug dose, cumulative use, or duration of abstinence. The reason for this is that the National Ecstasy and Related Drugs Reporting System survey has a large set of consistent questions that must be administered to participants each year, within an approximate one-hour appointment. Thus, it was not possible to add the 2–3 additional questions per drug that would have enabled quantification of these additional drug use parameters.

5. Conclusions

The results of the current study demonstrate, for the first time, that the prevalence of tremor, and abnormal changes in fine hand control and voice/speech, is significantly higher in young-to-middle aged adults with a history of illicit stimulant use than in non-stimulant-using controls. Further research is required to elucidate the underling mechanisms for the increased prevalence of self-reported changes in these movement domains. Establishment of a rigorous quantitative link between illicit stimulant use and movement dysfunction may aid public health campaigns that target prevention or harm minimization via use of a health effect that is common and noticeable among young people.

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Contributors

All authors contributed to study concept and design. VPD, PF, and GT were involved in acquisition of the data. VPD, AE, and GT were involved in analysis of the data and all authors contributed to interpretation of the data. GT drafted the manuscript and all authors contributed to critical revision of the manuscript for important intellectual content. All authors approved the final article.

Declaration of Competing Interest

APV is the Chief Science Officer of Redenlab, a speech testing service provider.

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