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Use of illicit amphetamines is associated with long-lasting changes in hand circuitry and control

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HIGHLIGHTS

- Elevated corticomotoneuronal excitability is present in abstinent male amphetamine users.
- Abstinent amphetamine users overestimate the grip force required to manipulate novel objects.
- Elevated excitability and grip force overestimation is present months to years after ending drug use.

ABSTRACT

Objective: The study aim was to determine if use of illicit amphetamines or ecstasy is associated with abnormal excitability of the corticomotoneuronal pathway and manipulation of novel objects with the hand.

Methods: Three groups of adults aged 18–50 years were investigated: individuals with a history of illicit amphetamine use, individuals with a history of ecstasy use but minimal use of other stimulants, and non-drug users. Transcranial magnetic stimulation was delivered to the motor cortex and the electromyographic response (motor evoked potential; MEP) was recorded from a contralateral hand muscle. Participants also gripped and lifted a novel experimental object consisting of two strain gauges and an accelerometer.

Results: Resting MEP amplitude was larger in the amphetamine group (6M, 6F) than the non-drug and ecstasy groups ($p < 0.005$) in males but not females. Overestimation of grip force during manipulation of a novel object was observed in the amphetamine group ($p = 0.020$) but not the ecstasy group.

Conclusions: History of illicit amphetamine use, in particular methamphetamine, is associated with abnormal motor cortical and/or corticomotoneuronal excitability in males and abnormal manipulation of novel objects in both males and females.

Significance: Abnormal excitability and hand function is evident months to years after cessation of illicit amphetamine use.

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1. Introduction

Use of illicit stimulant drugs is associated with long-lasting changes in movement and movement-related brain regions. Adults with a history of illicit stimulant use exhibit an abnormally high level of excitability of the motor cortex and descending motor projection to the hand (Flavel et al., 2012b), and altered hand function (King et al., 2010, Pearson-Dennett et al., 2014). Examples of the latter include overestimation of the grip force required to manipulate novel objects (Pearson-Dennett et al., 2014) and taking longer to complete the grooved pegboard test than non-drug using controls (King et al., 2010, c.f. Pearson-Dennett et al., 2014). However, the class of stimulant drug associated with these changes is not yet known. Participants in the studies by Flavel et al. (2012b) and Pearson-Dennett et al. (2014) had a history of primarily methamphetamine (average occasions of use >192) and ecstasy (average occasions of use >60) use, with lesser use of cocaine (average of 6–8 occasions of use). Thus, it is conceivable that the abnormal excitability and hand function is associated with use of amphetamines (including methamphetamine) or ecstasy, rather than use of cocaine.

Separating the long-lasting effects of amphetamines (including methamphetamine) from those of ecstasy is challenging in humans because a high percentage of amphetamine users have a history of ecstasy and other drug use (e.g. Darke et al., 2012, Todd et al., 2016b). An experimental approach that enables separation of the long-lasting effects of amphetamines from those of ecstasy involves comparison of individuals with a history of ecstasy use but minimal use of amphetamines, with individuals who have a history of amphetamine and ecstasy use. Use of this experimental approach has led to the discovery of abnormal substantia nigra morphology and symptoms of parkinsonism in abstinent amphetamine users (but not ecstasy users) and abnormal tremor in ecstasy users (Flavel et al., 2012a, Todd et al., 2016b). However, this experimental approach is challenging for participant recruitment because few regular ecstasy users have no or minimal use of amphetamines and/or cocaine (Palamar et al., 2017).

The primary aim of the current study was to use the above experimental approach to determine (i) if history of use of amphetamines or ecstasy is associated with abnormal hand function and excitability of the motor cortex and descending projection to hand muscles, and (ii) if the abnormal excitability and hand function in this population are related to one another. Amphetamines and ecstasy (3,4–methylenedioxymethamphetamine or 'MDMA') disrupt monoamine neurotransmission and are toxic to predominantly dopaminergic and serotonergic neurons, respectively (Green et al., 2003, Yamamoto and Bankson, 2005). We hypothesised that use of illicit amphetamines but not ecstasy would be associated with (i) increased excitability of the motor cortex and/or corticomotoneuronal projection and (ii) abnormal manipulation of novel objects (i.e. abnormal manipulation of an object during the first trial but not in subsequent trials). Evidence that supports a role for amphetamines comes from the literature on patients with Parkinson's disease, a disease characterised by degeneration of predominantly dopaminergic neurones (Fearnley and Lees, 1991). Both young-to-middle aged abstinent stimulant users and patients with Parkinson's disease exhibit increased resting motor cortical and/or corticomotoneuronal excitability (Cantello et al., 1991, Flavel et al., 2012b) and overestimation of the grip force required to lift a novel object (Fellows and Noth, 2004, Pearson-Dennett et al., 2014). There is also overlap between the pathophysiology of Parkinson's disease and methamphetamine-induced toxicity (e.g. oxidative stress, mitochondrial dysfunction, and excitotoxicity, Yamamoto and Bankson, 2005, Ambrosi et al., 2014), and use of methamphetamine is a significant risk factor for developing Parkinson's disease later in life (Callaghan et al., 2010, Todd et al., 2016b). Evidence that supports a role for abnormal manipulation of a novel object, but not subsequent handling of the same object, is preservation of motor learning in individuals with a history of illicit stimulant use (e.g. Pearson-Dennett et al., 2014, Todd et al., 2016a).

A secondary aim was to investigate the effect of sex on excitability and hand control because amphetamine dependency and the effect of amphetamines on the brain can differ between males and females (for review see Dluzen and Liu, 2008). Female methamphetamine users report a greater severity of psychiatric and drug problems, and a more rapid transition from first use to problem use, than male methamphetamine users (Simpson et al., 2016). However, this does not translate to consistently greater abnormalities in brain structure and/or function in females. For example, widespread reductions in gray matter volume has been observed in abstinent female methamphetamine users but not in abstinent males (Regner et al., 2015) whereas male methamphetamine users exhibit more hypoperfused areas of the frontal and parietal lobes than female methamphetamine users (Chang et al., 2002), and greater severity of white-matter signal hyperintensities (Bae et al., 2006). We hypothesised that the magnitude of change in the excitability of the motor cortex and/or corticomotoneuronal projection to the hand, and application of grip force during manipulation of novel objects, would be greater (more abnormal) in male amphetamine users than female amphetamine users. This hypothesis is based on the observation that testosterone is toxic to dopaminergic neurons experiencing oxidative stress (Holmes et al., 2016), and oxidative stress is present in dopaminergic neurons that are exposed to amphetamine and/or methamphetamine (Yamamoto and Bankson, 2005). The results of the current study will further understanding of the long-lasting consequences of amphetamine and ecstasy use on the control of movement, and may broaden discussion on treatment and rehabilitation practices in this population.

2. Methods

Ninety-eight participants completed one or two studies to investigate hand function (Study 1) and excitability of the motor cortex and descending pathway to the hand (Study 2; 32 participants completed both studies). Each study involved three groups of adults aged 18–50 years. The target group consisted of adults with a history of illicit amphetamine and/or methamphetamine use ($\geq$5 occasions of use; 'amphetamine' group). The two control groups consisted of (i) adults with a history of ecstasy use ($\geq$5 occasions) but minimal use of amphetamine and/or methamphetamine ($\leq$3 occasions; 'ecstasy' group) and (ii) adults with a history of minimal cannabis use ($\leq$2 occasions) and no other illicit drug use ('non-drug' group). We sought to match the three groups for sex and handedness, and to match history of post-drug use depression and/or anxiety in the amphetamine and ecstasy groups. Some of the data has been published in a different form (Flavel et al., 2012b, Pearson-Dennett et al., 2014). The study was approved by the University of South Australia Human Research Ethics Committee and conducted according to the World Medical Association Code of Ethics (Declaration of Helsinki). Written informed consent was obtained.

2.1. Screening

Each participant completed several screening tests including a urine drug screen (PSCupA-6MBAU; US Diagnostics Inc.), transcranial magnetic stimulation (TMS) safety screen (Rossi et al., 2009),

neuropsychological assessment (Verbal Trails, Logical Memory I and II, Verbal Fluency, Digit Span forwards and backwards; Wechsler, 1981, Benton and Hamsher, 1983, Wechsler, 1987, Grigsby and Kaye, 1995), and questionnaires to document recent symptoms of depression (Beck Depression Inventory-II; Beck et al., 1996), hand dominance (Edinburgh Handedness Inventory; Oldfield, 1971), and lifetime history of licit (alcohol and tobacco) and illicit drug use (Flavel et al., 2012b, Pearson-Dennett et al., 2014). For each licit and illicit drug used, age of first use, duration and frequency of use, dose (if known), and time since last use were documented. The number of drug overdoses experienced and treatment for drug dependency were also noted.

General exclusion criteria included (i) contraindications for TMS, (ii) prior diagnosis of a neurological trauma or disease/disorder that affects movement, (iii) current use of a medication that alters motor cortical excitability, (iv) frequent illicit opioid use (i.e. >5 times per year) and (v) poor performance on three or more of the tested cognitive domains (for details see Pearson-Dennett et al., 2014). Drug-using participants who had been diagnosed with depression and/or anxiety after first use of an illicit drug, and who were not currently being medicated for the condition, were allowed to participate due to the association between drug use and affective disorders (Dyer and Cruickshank, 2005, Taurah et al., 2014). Participants were also excluded if they returned a positive urine test for amphetamine, methamphetamine, MDMA, opioids, cocaine, and/or benzodiazepines. Participants who had a positive urine test for cannabis (tetrahydrocannabinol) were allowed to participate if self-reported use of cannabis occurred >12 hours prior to testing. This exemption was required because the body can retain tetrahydrocannabinol for up to 80 days after last use (Grotenhermen, 2003). Participants with a non-neurological condition that may affect hand function (e.g. arthritis or prior finger injury) were excluded from participating in Study 1.

2.2. Experimental protocol

In Study 1, participants (n = 46 non-drug group, n = 24 ecstasy group, n = 19 amphetamine group) completed one experiment involving tests of hand function, using a previously published protocol (Pearson-Dennett et al., 2014). The experiment began with placement of two surface electromyographic (EMG) electrodes (Ag-AgC1, 10 mm diameter, inter-electrode distance: 3 cm) over the tendon and belly of the first dorsal interosseous (FDI) muscle on the dominant hand. EMG activity was amplified (300 or 1000 times), sampled at 2000 Hz, and filtered (20–1000 Hz) using a data acquisition system (1902 with Power 1401 Interface and Signal software, Cambridge Electronic Design, Cambridge, UK).

Participants sat on a chair in front of a table and performed three tasks with their dominant hand. The first task involved gripping and lifting an experimental apparatus (Fig. 1A) that consisted of two load cells (model MPL-100; Transducer Techniques, Temecula, CA, USA) and a dual axis accelerometer (±2 g, model ADXL311J, RS Components Pty Ltd, Smithfield, Australia). The load cells were mounted at 90° to one another for measurement of horizontal grip force and vertical load force and the total mass of the experimental apparatus was 342 g. Participants touched the apparatus on two polished brass disks mounted 35 mm apart, on opposing sides of the grip load cell. Participants were instructed to use their index finger and thumb (pinch grip) to 'lift the object off the table to the height indicated (~10 cm), hold the object there for 3 s, and then place it back on the table'. The task duration was ~6 s and lifting the apparatus occurred predominantly through elbow flexion. The experimenter demonstrated the task before the participants' first attempt and practice was not allowed. Participants performed two trials with 3–5 s rest between trials.

The second task involved three brief (2–3 s) maximal voluntary contractions (MVCs) to allow for normalization of certain parameters measured during the grip and lift task. MVCs were completed with a pinch grip and participants were not required to lift the apparatus off the table. Each MVC was separated by ~1 min of rest to minimize fatigue. The experimenter provided visual feedback of force and verbal encouragement during MVCs.

In the final task, participants completed three trials of the grooved pegboard test. The task involved placing key-shaped pegs into corresponding holes (model 32025, Lafayette Instrument Company, Lafayette IN, USA), as fast as possible and in a set sequence. The time to complete each trial was recorded and a 1-min rest was provided between trials.

In Study 2, participants (n = 18 non-drug group, n = 11 ecstasy group, n = 12 amphetamine group) completed one experiment involving TMS, using a previously published protocol that successfully differentiated stimulant users from non-drug users and cannabis users (Flavel et al., 2012b). The age-range of participants in Study 2 was restricted to 18–33 years to minimise the effect of age on motor cortical excitability (Pitcher et al., 2003). Two surface electromyographic (EMG) electrodes (Ag-AgC1, 10 mm diameter, inter-electrode distance: 3 cm) were positioned on the dominant hand, over the first dorsal interosseous muscle belly and tendon. EMG activity was recorded with the same data acquisition system as that described in Study 1. Single-pulse TMS was delivered (~0.2 Hz) to the first dorsal interosseous representation of the contralateral motor cortex using a Magstim 200^2 stimulator, BiStim^2 UI controller, and a figure-of-eight coil (90-mm external diameter with handle pointing posteriorly at ~45° to the midline and tangentially to the skull; Magstim Co., Whitland, UK). Resting motor threshold was measured first and was defined as the minimum intensity that evoked a motor evoked potential (MEP) of >50 μV in amplitude in five out of ten consecutive stimuli (Rossini et al., 1994). A further fifteen stimuli were then delivered during relaxation, at an intensity of 130% resting motor threshold, to assess resting motor cortex and/or corticomotoneuronal excitability. Fifteen stimuli were then delivered, at the same intensity, during weak contraction of the target first dorsal interosseous muscle (via abduction of the index finger against a 53 g mass suspended from the distal interphalangeal joint). Stimuli delivered during weak contraction enabled measurement of the silent period (an index of $GABA_B$-mediated intracortical inhibition) and movement-induced facilitation of motor cortex and corticomotoneuronal excitability (Ziemann, 2004).

2.3. Data analysis and statistics

Group data are presented as mean ± standard deviation, except for the output of regression analyses which are reported as mean ± standard error. All data were assessed for normality with Shapiro-Wilks test. One-way analysis of variance (ANOVA) was used for between-group comparison of participant characteristics, and alcohol and tobacco use. Data were analysed in Stata v.14 software (StataCorp, Texas, USA). Statistical significance was set at $p < 0.05$.

In Study 1, the grip and lift task was divided into a lift (0 s (lift onset)–1.5 s) and hold (1.5–2.5 s) phase (for example see Fig. 1B-D). Fifteen parameters were measured in the lift phase to provide information about grip strategy, kinematics and kinetics of the lifting action, and the coupling between grip and load force. In the lift phase, measurement of grip and lift onset involved applying a low-pass filter (20 Hz) to the raw force traces and then calculation of the rate of change in grip force (dGF/dt) and load force (dLF/dt). The onset was defined as the time of the initial increase in the derivative of force (above the noise level) that lead to attainment of the maximum derivative. The preload duration (grip onset

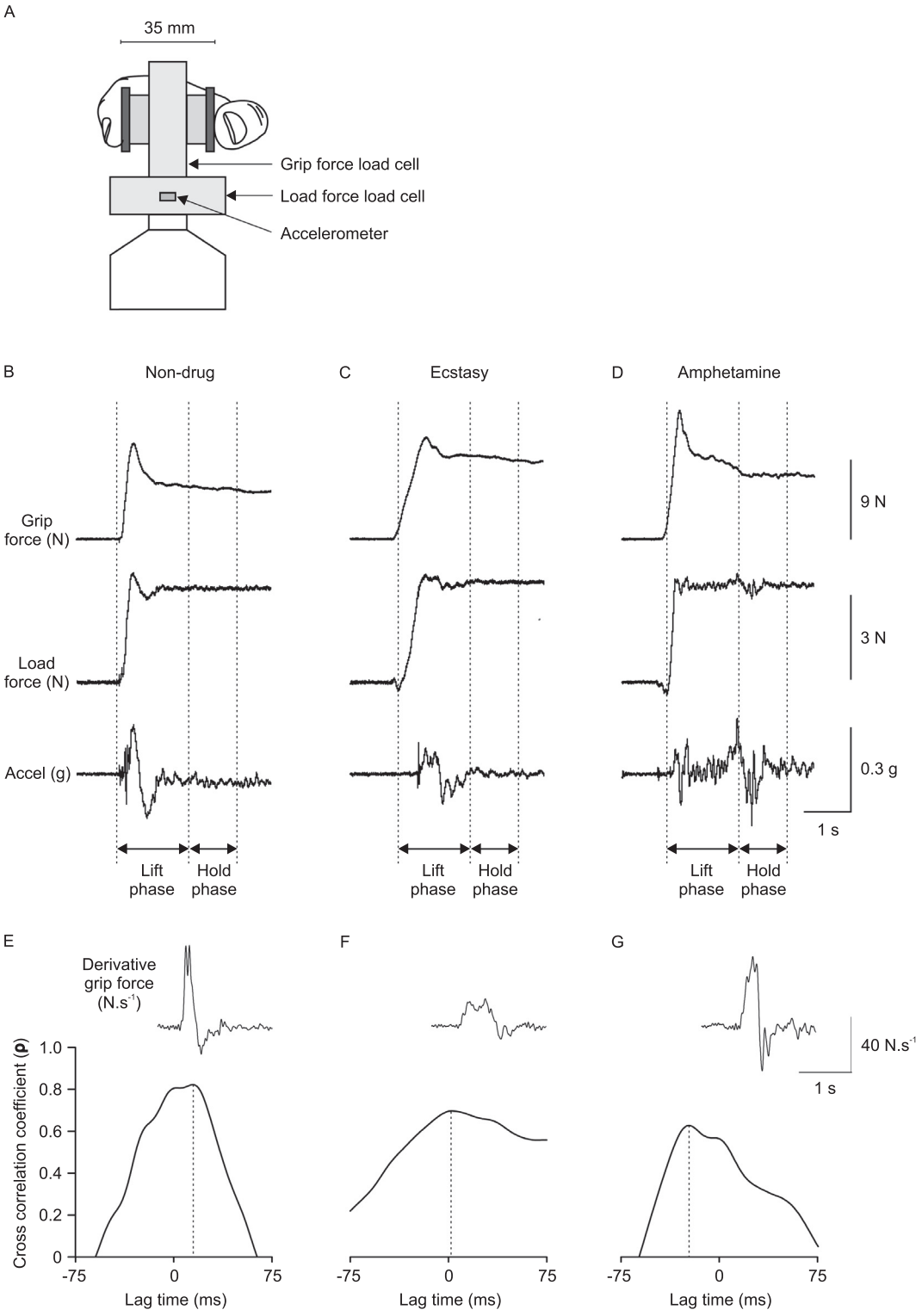

Fig. 1. Study 1 experimental apparatus and data from three participants in the grip and lift task. (A) Experimental apparatus for the grip and lift task. The index finger and thumb contacted the experimental apparatus on two polished brass disks positioned 35 mm apart. (B-D) Raw traces of grip force (top panel), load force (middle panel), and acceleration (bottom panel) for one participant in the non-drug-using group (B), ecstasy group (C), and amphetamine group (D) during the first trial of the grip and lift task. Vertical dotted lines show the start and end of the lift phase (0 s (lift onset)–1.5 s) and hold phase (1.5–2.5 s). (E-G) Temporal characteristics of the grip force and load force derived from the raw data presented in B-D. The derivative of grip force (dGF/dt, inset) was correlated with the derivative of load force (dLF/dt) and the resultant cross-correlogram is shown for each participant. Vertical dotted lines in E-G represents the time shift required to achieve the maximal cross-correlation coefficient.

relative to lift onset) and the maximum rate of change in force (dGF/dtmax and dLF/dtmax) were also calculated. The temporal relationship between the grip force and load force was measured by cross-correlating the rate of change in grip force (dGF/dt) and load force (dLF/dt) (Flanagan and Wing, 1997). dLF/dt was moved in 2.5 ms increments (sampling resolution) relative to dGF/dt until the maximal cross-correlation coefficient (ρ) was attained (IBM SPSS Statistics 20, Armonk NY, USA). The shift in time required to

attain the maximum cross-correlation coefficient reflects the difference in time between the change in load force and the change in grip force, and is indicative of grip strategy. A negative time shift (grip force leads load force) indicates a primarily anticipatory grip strategy and a positive time shift (grip force lags load force) indicates a primarily reactive grip strategy. Peak force, time-to-peak force, peak acceleration, time-to-peak acceleration, minimum load force (degree of downward force application before lifting the object), and the root mean square (RMS) EMG were also measured in the lift phase from raw traces. Three parameters were measured in the hold phase. These included RMS EMG, mean grip force, and the grip force coefficient of variation (%). For brief maximal voluntary contractions, RMS EMG and mean grip force were calculated over a 1 s period.

Data from the grip and lift task and grooved pegboard test were analysed with mixed effects models in Stata v.14 software (StataCorp, Texas, USA). The models included fixed effects of 'Group', 'Trial' and their interaction ('Group' × 'Trial'). A random-effects intercept was included to account for between-participant variability. Maximal pinch grip strength was analysed with linear regression analysis. Raw data that violated model assumptions (i.e. distribution and homoscedasticity of the residuals) were transformed and the models run on the transformed data. The effects of sex, age, and lifetime alcohol use were investigated on hand function parameters. Age and lifetime alcohol use were not predictors of any hand function parameters and therefore excluded from all models. Sex was found to be a significant predictor of maximal pinch grip strength and performance on the grooved pegboard test, and thus was included in the final analysis of these parameters. Planned contrasts were performed on trial one for peak grip force (raw) and maximal rate of change in grip force, and trial one of the grooved pegboard test. Contrasts were used to calculate the main effects of 'Group', 'Trial', 'Group' × 'Trial', and/or 'Sex' and are reported as either Chi square (grip and lift task, grooved pegboard task) or F-statistic (maximal pinch grip strength). Results of the models are reported (in the text and Supplementary Table S1) as transformed coefficient ± standard error. All graphs show raw data to aid interpretation. Pearson Product Moment or Spearman Rank Order correlation were used to investigate the relationship between hand function and amphetamine drug-use parameters (age of onset of use, number of occasions of use, duration of abstinence) in the amphetamine group (SigmaPlot 11.0; Systat Software Inc).

In Study 2, peak-to-peak MEP amplitude was measured in each trial. Resting MEPs with voluntary EMG activity prior to the stimulus were excluded from the analysis. During weak contractions, the duration of the silent period and the amount of voluntary EMG activity prior to the stimulus (RMS EMG amplitude over a 100 ms period) were also measured in each trial. MEP characteristics, silent period duration, and RMS EMG were analysed with a linear regression analysis in Stata v.14 software (StataCorp, Texas, USA). The resting and active TMS conditions were analysed separately. MEP latency partly depends on the distance between the motor cortex and target muscle. Thus, height was included as a factor in the analysis of MEP latency. The effects of sex, age, and lifetime alcohol use were investigated on TMS parameters. Age and lifetime alcohol use were not predictors of any TMS parameters and thus were excluded from all models. Sex was found to be a significant predictor of MEP amplitude, and was therefore included in the final analysis of this parameter. Raw data that violated model assumptions (i.e. distribution and homoscedasticity of the residuals) were transformed and the models run on transformed data. Contrasts were used to calculate the main effects of 'Group', 'Sex', and 'Group' × 'Sex' and are reported as the F-statistic. All graphs show raw data to aid interpretation. Results of the models are reported (in the text and tables) as transformed mean ± standard error. Pearson Product Moment or Spearman Rank Order correlation were used to investigate the relationship between TMS parameters and drug use characteristics in the amphetamine group. Pearson Product Moment or Spearman Rank Order correlation were also used to investigate the relationship between TMS and hand function parameters in participants in the amphetamine group who completed both Study 1 and 2 (n = 9; SigmaPlot 11.0; Systat Software Inc).

3. Results

3.1. Participant characteristics

Table 1 shows participant characteristics for each group in Study 1 and 2. The groups were matched for handedness (laterality quotient) and years of education, and performance on the neuropsychological tests did not significantly differ between the non-drug and drug-using groups. The groups were also matched for sex, except for the ecstasy group in Study 2 which had fewer females. The groups did, however, significantly differ in age (Study 1: $F_{2,86} = 13.37$, $p < 0.001$, Study 2: $F_{2,38} = 5.27$, $p = 0.010$). The average age of the amphetamine group was 4–9 years older than the non-drug (Study 1: $p < 0.001$, Study 2: $p = 0.038$) and ecstasy (Study 1: $p < 0.001$, Study 2: $p = 0.013$) groups. The groups also differed significantly on the Beck Depression Inventory II (Study 1: $F_{2,86} = 3.32$, $p = 0.041$, Study 2: $F_{2,38} = 8.56$, $p < 0.001$). More symptoms of depression were reported in the ecstasy (Study 1: $p = 0.036$, Study 2: $p = 0.005$) and amphetamine (Study 2: $p = 0.003$) groups than in the non-drug group.

Lifetime use of alcohol (Study 1: $F_{2,77} = 46.80$, $p < 0.001$, Study 2: $F_{2,30} = 9.82$, $p < 0.001$) and tobacco (Study 1: $F_{2,86} = 37.40$, $p < 0.001$, Study 2: $F_{2,24} = 4.10$, $p = 0.029$) also differed significantly between the groups. Use of alcohol and tobacco was greatest in the amphetamine group and least in the non-drug group (Table 1). Poly-drug use was common in the ecstasy and amphetamine groups, but lifetime use of ecstasy and hallucinogens did not differ between the drug-using groups. The amphetamine group reported significantly greater lifetime use of cannabis than the ecstasy group ($p = 0.002$) in Study 1 but not Study 2. In the ecstasy group, the average duration of abstinence from cannabis was 0.4 ± 0.7 years in Study 1 and 0.2 ± 0.3 years in Study 2 and the average duration of abstinence from ecstasy was 0.5 ± 0.8 years in Study 1 and 0.5 ± 0.6 years in Study 2. In the amphetamine group, the average duration of abstinence from cannabis was 0.7 ± 2.3 years in Study 1 and 0.3 ± 0.5 years in Study 2 and the average duration of abstinence from ecstasy was 3.9 ± 4.4 years in Study 1 and 2.2 ± 2.7 years in Study 2. The average duration of abstinence from amphetamines was 3.5 ± 4.6 years in Study 1 and 1.8 ± 2.2 years in Study 2. Urine data is missing for one control participant due to mislabelling (Study 1) and a small number of drug-using participants tested positive for THC, but none reported use of cannabis in the 12 hours prior to testing (Study 1: n = 5 ecstasy group, n = 3 amphetamine group, Study 2: n = 3 ecstasy group, n = 2 amphetamine group).

3.2. Study 1: Hand function

Fig. 1B-D shows examples of raw data from the grip and lift task, for one participant in each group. Grip force and load force increased in parallel, and the initial increase in acceleration indicates the time at which the object began to accelerate. After peak grip force was attained, a slight decrease in grip force occurred and this was followed by a plateau while the object was held above the table in a stationary manner. During the plateau, grip force was 1.7–2.6 times higher than the load force, suggesting a modest

Table 1
Participant characteristics for the non-drug, ecstasy, and amphetamine groups in Study 1 and 2. Data presented are mean ± SD, except for lifetime drug use parameters which are presented as the percentage of participants who have used a class of drug and the mean ± SD for the lifetime occasions of use in brackets. 'Diagnosis' refers to the number of participants who had received a formal diagnosis of depression and/or anxiety after commencement of illicit drug use. The term 'ecstasy' includes MDMA (3,4–methylenedioxymethamphetamine) and MDA (3,4-methylenedioxyamphetamine). The term 'pharmaceutical stimulant' (pharmaceut) includes illicit use of methylphenidate and dexamphetamine. The term 'hallucinogens' includes LSD (lysergic acid diethylamide), LSA (d-lysergic acid amide), 'magic mushrooms', mescaline, DOI (2,5-dimethoxy-4-iodoamphetamine), DMT (dimethyltryptamine), JWHO18 (synthetic cannabis), 2CI/2CB (2,5-dimethoxy-4-iodophenethylamine or 2-(4-bromo-2,5-dimethoxyphenyl) ethanamine), ketamine, NBOMe (N-methoxybenzyl), salvia divinorum, and datura. The term 'inhalants' includes amyl nitrate, nitrous oxide, and ethyl chloride. The term 'sedatives' includes GHB/fantasy and illicit use of benzodiazepines, pregabalin, antihistamines, and antidepressants. The term 'opioids' describes opium and heroin and illicit use of methadone, oxycodone, buprenorphine, morphine, and/or codeine.

	Study 1: Hand function			Study 2: Excitability		
Parameter	Non-drug	Ecstasy	Amphet	Non-drug	Ecstasy	Amphet
Age (yrs)	24.4 ± 7.7	22.4 ± 2.5	31.4 ± 6.9*,§	22.8 ± 3.9	21.7 ± 2.5	26.3 ± 4.1*,§
Sex	28 M, 18 F	16 M, 8 F	12 M, 7 F	9 M, 9 F	9 M, 2 F	6 M, 6 F
Handedness	43 R, 3 L	23 R, 1 L	18 R, 1 L	18 R, 0 L	11 R, 0 L	11 R, 1 L
Educ (yrs)	15.5 ± 2.3	15.7 ± 2.2	14.6 ± 2.9	15.9 ± 2.5	16.2 ± 2.7	14.9 ± 2.3
BDI-II score	5.8 ± 7.4	9.4 ± 6.6*	7.0 ± 6.2	3.1 ± 2.8	10.4 ± 6.4*	10.5 ± 7.9*
Diagnosis	0	3	3	0	2	3
Alcohol (drinks)	(80%) 1042 ± 3525	(100%) 3222 ± 4218*	(100%) 8430 ± 8009*	(67%) 511 ± 804	(100%) 2584 ± 2727*	(100%) 5285 ± 4608*,§
Tobacco (cigarettes)	(24%) 22 ± 53	(88%) 5124 ± 12706	(89%) 45,662 ± 52,085*,§	(22%) 5 ± 3	(100%) 4721 ± 7418*	(100%) 14,027 ± 16,229*,§
Ecstasy	(0%)	(100%) 38 ± 51	(89%) 97 ± 127	(0%)	(100%) 35 ± 50	(100%) 82 ± 64
Methamphet	(0%)	(38%) 1 ± 1	(89%) 636 ± 1252	(0%)	(45%) 1 ± 0	(92%) 449 ± 623
Cocaine	(0%)	(50%) 2 ± 2	(58%) 6 ± 8	(0%)	(27%) 2 ± 2	(58%) 8 ± 10
Pharmaceut	(0%)	(17%) 2 ± 0	(32%) 18 ± 36	(0%)	(18%) 2 ± 0	(25%) 34 ± 51
Cannabis	(7%) 1 ± 1	(100%) 457 ± 1036	(100%) 3031 ± 2971§	(0%)	(91%) 753 ± 1362	(100%) 1270 ± 1678
Hallucinogen	(0%)	(79%) 18 ± 32	(84%) 83 ± 164	(0%)	(91%) 18 ± 43	(92%) 60 ± 100
Inhalant	(0%)	(33%) 49 ± 69	(58%) 65 ± 98	(0%)	(45%) 69 ± 83	(75%) 19 ± 33
Sedative	(0%)	(17%) 2 ± 1	(47%) 12 ± 22	(0%)	(0%)	(67%) 3 ± 2
Opioid	(0%)	(13%) 3 ± 1	(42%) 4 ± 4	(0%)	(9%) 4	(33%) 2 ± 1

* Significantly different from the non-drug group ($P < 0.05$).
§ Significant difference between ecstasy and amphetamine groups ($P < 0.001$).

safety margin to prevent the object from slipping. Three examples of the temporal relation between grip force and load force are displayed in Fig. 1E-G. Data in Fig. 1 suggest that the participant in the amphetamine group performed the task with a higher grip force than the participant in the non-drug and ecstasy group.

Statistical analysis of group data for the grip and lift task and grooved pegboard task involved confirming learning across trials and then focusing on trial 1 (with planned contrasts) to investigate manipulation of novel objects (re an object is only novel during the first trial). Several grip and lift parameters improved across trials confirming preservation of motor learning in the drug-using groups. There was a significant main effect of trial on the raw ($\chi^2(1) = 57.43$, $p < 0.001$) and normalised ($\chi^2(1) = 58.14$, $p < 0.001$) peak grip force and maximum rate of change in grip force ($\chi^2(1) = 18.33$, $p < 0.001$) during the lift phase of the grip and lift task. The peak grip force (Fig. 2A) and maximum rate of change in grip force (Fig. 2C) decreased across trials. The mean grip force (raw force: $\chi^2(1) = 5.5$, $p = 0.019$, Fig. 2B, normalised force: $\chi^2(1) = 5.61$, $p = 0.018$), mean load force ($\chi^2(1) = 6.28$, $p = 0.012$, Fig. 2B), and the safety margin for error (mean grip force/load force; $\chi^2(1) = 5.19$, $p = 0.023$) during the hold phase also decreased significantly across trials, whereas the maximum cross-correlation coefficient increased significantly (i.e. better coupling between grip force and lift force, $\chi^2(1) = 39.76$, $p < 0.001$, Fig. 2D). Planned contrasts revealed a significant between-group difference in the raw peak grip force and maximum rate of change in grip force in trial one but not trial two. In trial one, raw peak grip force (Fig. 2A) and the maximum rate of change in grip force (dGF/dt; Fig. 2C) were significantly larger in the amphetamine group than in the non-drug (coefficient ± standard error; peak grip force: 0.233 ± 0.101, $p = 0.020$; dGF/dt: 0.295 ± 0.132, $p = 0.025$) and ecstasy (peak grip force: 0.227 ± 0.113, $p = 0.045$; dGF/dt: 0.274 ± 0.148, $p = 0.065$) groups. However, no between-group differences in raw peak grip force or the maximum rate of change in grip force were observed between the non-drug and ecstasy groups. No other significant effects of trial, group, or sex were observed for parameters measured during the grip and lift task.

In the grooved pegboard test, performance time decreased (i.e. performance improved) across trials ($\chi^2(2) = 338.99$, $p < 0.001$, Fig. 2E). Planned contrasts revealed a significant between-group difference in performance time between the amphetamine group and non-drug group in trial one (coefficient ± standard error: 0.081 ± 0.035, $p = 0.020$) but not in trial two or three. Sex was also found to be a significant predictor of performance on the grooved pegboard test. On average, males took 5 s longer to complete the pegboard task than females (60.9 ± 9.4 s versus 55.5 ± 3.8 s, $p < 0.001$). No other between-group differences were observed for the grooved pegboard test.

Maximal pinch grip strength significantly differed between the groups ($F_{2,83} = 8.76$, $p < 0.001$) and between males and females ($F_{1,83} = 45.40$, $p < 0.001$). The average force during the brief maximal voluntary contractions was larger in the amphetamine group (70.8 ± 18.9 N) than in the non-drug group (55.5 ± 15.3 N; $p = 0.002$) but did not differ to that of the ecstasy group (62.5 ± 14.3 N). The non-drug and ecstasy groups also did not differ in average force during the brief maximal voluntary contractions. As expected, males (68.1 ± 15.9 N) had a greater pinch grip strength than females (48.1 ± 9.2 N, $p < 0.001$) but, there was no group-by-sex interaction on maximal pinch grip strength.

There was no correlation between amphetamine drug-use parameters (age of first use, number of occasions of use, duration of abstinence) and hand function parameters in the amphetamine group.

3.3. Study 2: Motor cortical excitability

Fig. 3A shows averaged resting EMG traces recorded in a typical participant from each group, and the size of the MEP following stimulation. The amplitude of the resting MEP was larger in the amphetamine participant than in the non-drug-using and ecstasy-using participants. Fig. 3B shows group data for resting MEP amplitude. There was no main effect of group on resting MEP amplitude but there was a significant group-by-sex interaction ($F_{2,35} = 5.63$, $p = 0.008$, Fig. 3B). In males, resting MEP

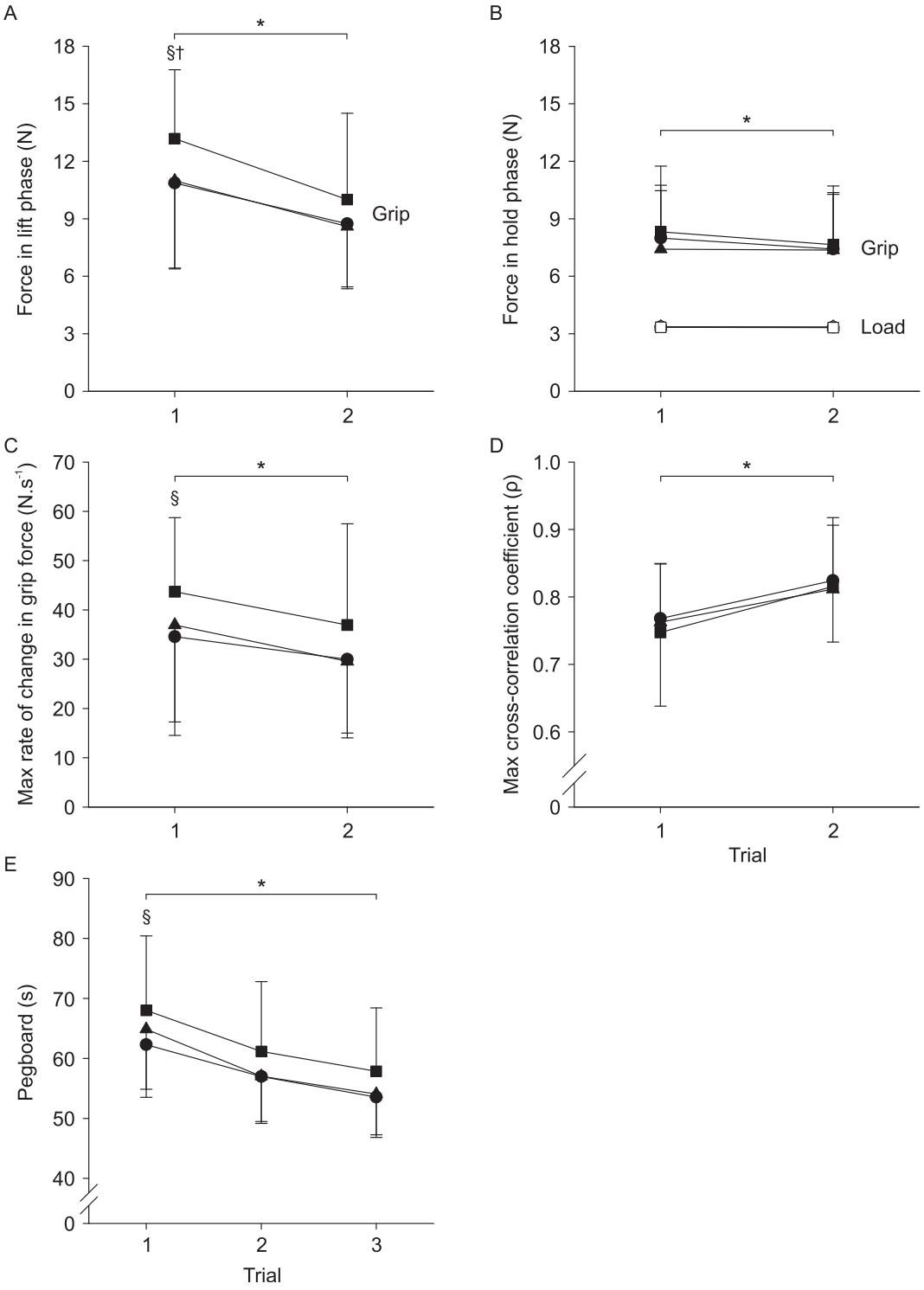

Fig. 2. Group data (mean ± SD) showing parameters measured during the hand function tasks in the non-drug (circles), ecstasy (triangles), and amphetamine (squares) groups. (A) Average grip force during the lift phase of the grip and lift task. (B) Average grip (black symbols) and load (white symbols) force during the hold phase of the grip and lift task. (C) Average maximum rate of change in grip force (i.e. derivative of grip force) during the lift phase of the grip and lift task. (D) Average maximum cross-correlation coefficient during the lift phase of the grip and lift task. The cross-correlation coefficient was derived from cross-correlation of the rate of change (derivative) of grip force and load force. The maximum cross-correlation coefficient is an index of the temporal relationship between changes in grip force and load force. (E) Average time to complete the grooved pegboard test. *Significant difference across trials ($p < 0.019$). §Significant difference between amphetamine and non-drug group ($p < 0.025$). †Significant difference between the amphetamine and ecstasy group ($p = 0.045$).

amplitude was significantly larger in the amphetamine group than in the non-drug (coefficient ± standard error; 1.19 ± 0.30, $p = 0.001$) and ecstasy groups (1.02 ± 0.34, $p = 0.005$) but, there was no difference between the non-drug and ecstasy groups. In females, resting MEP amplitude was significantly smaller in the amphetamine group than in the non-drug using group (−1.59 ± 0.48, $p = 0.002$), but there was no difference between the two female ecstasy participants and the non-drug or

amphetamine groups. No significant main effect of group or group-by-sex interaction was observed for resting motor threshold (non-drug: 47 ± 8%, ecstasy: 43 ± 7%, amphetamine: 46 ± 5% of stimulator output), or other MEP parameters measured during relaxation or muscle contraction. In the amphetamine group, there was no correlation between TMS parameters and (i) amphetamine drug-use parameters or (ii) object manipulation parameters.

4. Discussion

History of illicit stimulant use is associated with abnormal manipulation of novel objects (Pearson-Dennett et al., 2014) and elevated excitability of the motor cortex and descending pathway from the motor cortex to hand muscles (Flavel et al., 2012b). The results of the current study demonstrate that these abnormalities are associated with use of illicit amphetamines, primarily methamphetamine, and not use of ecstasy.

When gripping and lifting a novel object (in trial 1), abstinent amphetamine users utilized a grip force that was 20% larger than non-drug users and ecstasy users. This suggests that individuals with a history of illicit amphetamine use overestimate the grip force that is required to lift a novel object and as a result, manipulate new objects in a manner that is less efficient. Estimation of the grip force required to lift a novel object begins prior to touching the object and is thought to engage an internal model that incorporates the objects' physical properties (Westling and Johansson, 1984), prior experience gripping and lifting similarly shaped objects (Augurelle et al., 2003), sensory feedback (Jenmalm and Johansson, 1997), and the individual's safety margin to prevent slip (for review see Johansson, 1998, Flanagan et al., 2006). The results of the current study suggest that this internal model may be altered in individuals with a history of illicit amphetamine use. Such alterations in movement planning may contribute to the poor initial performance of the grooved pegboard test in the amphetamine group relative to the non-drug group. Interestingly, the deficits in movement planning can be overcome with practice. Improved performance of the grip and lift task and grooved pegboard task occurred across trials in the amphetamine group, and performance in the subsequent trial/s did not differ between the groups.

The motor cortices (primary motor cortex, supplementary motor area, and premotor cortex) provide descending input to spinal motoneurons that innervate muscles in the arm and hand (for review see Matelli et al., 2004). The amplitude of the MEP evoked by TMS provides an index of excitability in this pathway (Hess et al., 1987, Baker et al., 1995). Resting MEP amplitude differed between the groups in males and females. Resting MEP amplitude was significantly larger in male amphetamine users than in the male non-drug users and ecstasy users. This suggests that the net basal excitability of the motor cortices, corticospinal tract, and/or spinal motoneurones is abnormally high in males with a history of illicit amphetamine use. Increased excitability in this pathway could theoretically arise from one, or a combination of, the following mechanisms: (i) increased depolarization of

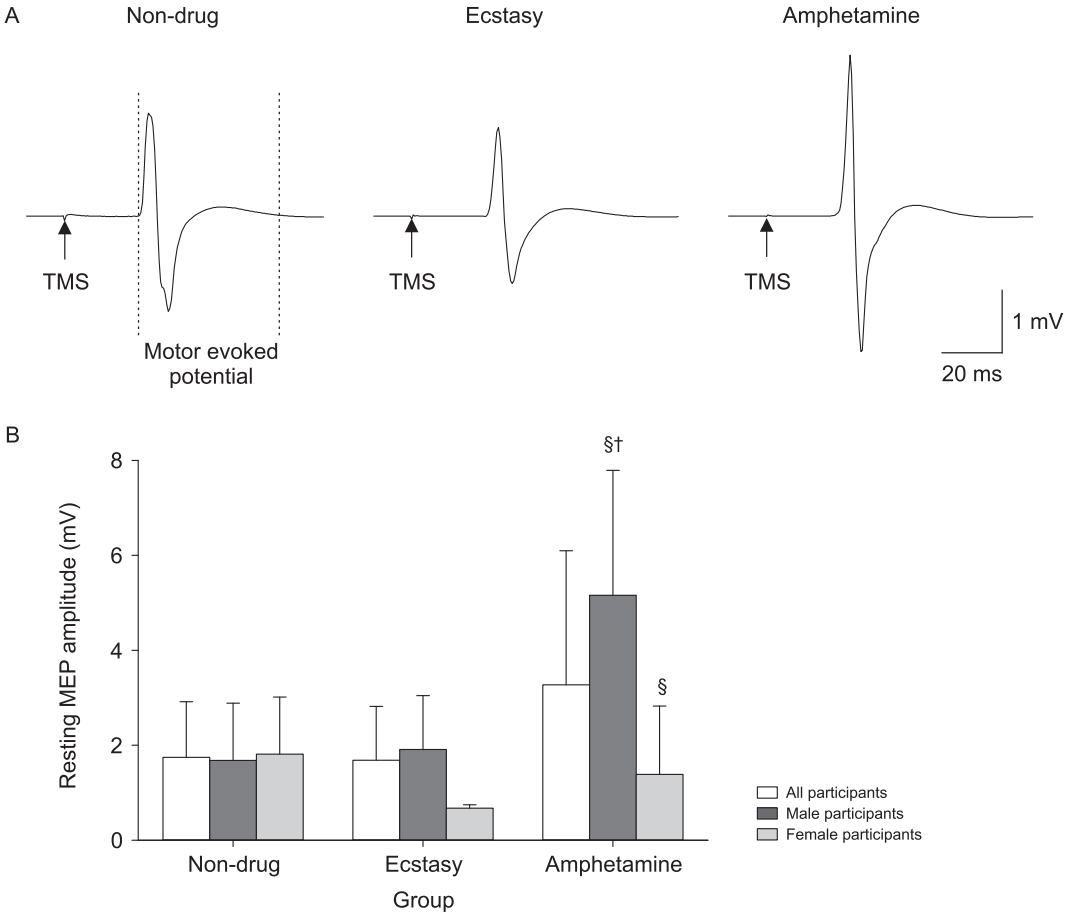

Fig. 3. Single participant and group data (mean ± SD) showing the amplitude of the resting motor evoked potential (MEP) following single-pulse TMS delivered at an intensity of 130% of resting motor threshold. (A) Averaged EMG traces from one representative participant in each group showing the amplitude of the resting motor evoked potential. Arrows indicate the timing of the TMS pulse. Vertical dashed lines show the start and end of the motor evoked potential in the non-drug-using participant. (B) Group data showing the average resting MEP amplitude. White bars, all participants in the group. Dark grey bars, male participants in the group. Light grey bars, female participants in the group. § Significant difference between amphetamine and non-drug group ($p < 0.005$). †Significant difference between the amphetamine and ecstasy group ($p = 0.021$).

excitatory interneurons in the motor cortex, (ii) decreased depolarization of inhibitory interneurons in the motor cortex, (iii) increased depolarization of pyramidal neurons that descend from the motor cortex to the spinal cord, and/or (iv) changes in the excitability of spinal interneurons and motoneurons. Two lines of evidence suggest that reduced intracortical inhibition is unlikely. First, the duration of the silent period did not differ between groups in the current study, suggesting that $GABA_B$-mediated intracortical inhibition within the motor cortex is unaltered (Ziemann, 2004). Second, $GABA_A$-mediated intracortical inhibition, measured with paired-pulse TMS, is also unaltered in individuals with a history of mixed stimulant use (Flavel et al., 2012b). In females, resting MEP amplitude was significantly lower in amphetamine users than in non-drug users. However, the magnitude of reduction was small and there was no difference observed between the ecstasy group and the amphetamine or non-drug groups.

There was no association between elevated basal excitability in the motor cortex and/or corticomotoneuronal pathway and overestimation of grip force during manipulation of novel objects in the amphetamine group. The relationship between abnormal excitability and motor planning may be better explored with application of TMS over the premotor or supplementary motor cortices immediately prior to gripping and lifting a novel object (e.g. Dafotakis et al., 2008, White et al., 2013). There was also no association between the number of occasions of amphetamine use and hand function and TMS parameters. This suggests that dose, which is difficult to quantify retrospectively in humans, may be a more important factor than occasions of use. This view is supported by a significant dose-dependent relationship between amphetamine use and neurotoxicity in rodents, primates, and humans (Yamamoto et al., 2010).

Identifying the mechanisms that underlie the elevated corticomotoneuronal excitability and altered manipulation of novel objects in the amphetamine group is challenging. The abnormal excitability and manipulation of novel objects is unlikely to reflect a generalised change in cortical function as the groups did not differ in neuropsychological performance. An acute effect of amphetamines is not possible because all participants returned a negative urine screen for amphetamines. Use of cannabis, ecstasy, alcohol, and tobacco is also unlikely to play a major role because resting MEP amplitude is unchanged in a small sample of alcohol-dependent patients with uncertain history of illicit drug use (Conte et al., 2008), and participants in the ecstasy group had a history of both ecstasy and cannabis use and resting excitability did not differ between the ecstasy and non-drug using groups.

The drug most likely to be associated with the elevated corticomotoneuronal excitability and altered manipulation of novel objects is methamphetamine. Methamphetamine was the main amphetamine drug consumed by participants in the amphetamine group. Methamphetamine is toxic to primarily dopaminergic neurones and induces long-lasting changes in dopaminergic neurotransmission (Yamamoto et al., 2010). There is rich dopaminergic innervation of the motor cortex in rodents (Awenowicz and Porter, 2002) and primates (Goldman-Rakic et al., 1989), and spontaneous discharge of pyramidal tract neurones decreases with local application of dopamine (Awenowicz and Porter, 2002). Thus, methamphetamine-induced changes in dopaminergic neurotransmission could alter basal excitability of the motor cortex and/or corticomotoneuronal pathway. The long-lasting effects of methamphetamine on dopaminergic neurotransmission could also partly explain why excitability and manipulation of novel objects is abnormal in individuals who had abstained from amphetamines for an average of 1.8 years.

The elevated corticomotoneuronal excitability in male amphetamine users but not female amphetamine users could be related to levels of gonadal steroid hormones. Testosterone is toxic to dopaminergic neurons experiencing oxidative stress in cell culture (Holmes et al., 2016), and oxidative stress is present in dopaminergic neurons that have been exposed to amphetamine and/or methamphetamine (Yamamoto and Bankson, 2005). Conversely, estrogen can protect nigrostriatal dopaminergic neurons against neurotoxicity induced by methamphetamine or MPTP (Dluzen et al., 1996, Miller et al., 1996). Healthy adult females also have a higher density of dopamine transporters in the striatum than males (e.g. rodents: Rivest et al., 1995, e.g. humans: Lavalaye et al., 2000) and thus methamphetamine-induced loss of dopamine transporters (McCann et al., 1998, Volkow et al., 2001) could lead to greater alterations in neural circuitry and motor function in males compared to females.

This study has three limitations. First, lifetime use of alcohol and tobacco was higher in the amphetamine group than in the ecstasy and non-drug groups. The number of participants in the amphetamine group who had a history of heavy drinking, according to the 2015-2020 Dietary Guidelines for Americans, was 37% compared to 21% for the ecstasy group (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015). While the acute effects of alcohol on excitability have been investigated, along with the efficacy of repetitive TMS in treating alcohol and tobacco addiction (Barr et al., 2011, Loheswaran et al., 2016a, Loheswaran et al., 2016b), the long-lasting effects of alcohol and/or tobacco use on resting MEP amplitude are unknown. Second, it is not possible to determine in humans if methamphetamine alone is responsible for the long-lasting elevation in excitability or whether use of methamphetamine and other drugs is important. Individuals who use methamphetamine have a history of other drug use (e.g. Table 1; McCann et al., 1994, Scholey et al., 2004) and it is not possible to differentiate the effects of methamphetamine alone from the combined effects of methamphetamine and other drugs. The latter may be important given that ingredients in alcohol and cigarettes inhibit monoamine oxidase (Tabakoff et al., 1985, Lewis et al., 2012) which may further impair monoamine neurotransmission in methamphetamine users by decreasing the rate of dopamine degradation in the cytosol. Third, interpretation of TMS data for female ecstasy users is limited due to difficultly in recruiting female participants with a history of ecstasy use but minimal amphetamine use (n = 2 females in the ecstasy group).

4.1. Conclusions

The results of the current study suggest that use of illicit amphetamines (in particular methamphetamine), but not ecstasy, is associated with abnormal manipulation of novel objects in abstinent young adults. Elevated excitability in the hand representation of the motor cortex and the corticomotoneuronal pathway to hand muscles is also present in abstinent male amphetamine users but not in abstinent female amphetamine users. The abnormalities are long-lasting and provide further insight into the consequences of methamphetamine use on the human brain and movement. Further research is required to determine if these abnormalities are clinically significant and if these abnormalities could be used as an objective index of methamphetamine-induced damage and recovery in addiction and rehabilitation settings. The results may also guide exploration of the potential therapeutic use of rTMS for treatment of methamphetamine addiction (Makani et al., 2017).

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Contributors

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

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.02.005.

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