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Motor cortex and corticospinal excitability in humans with a history of illicit stimulant use

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Flavel SC, White JM, Todd G. Motor cortex and corticospinal excitability in humans with a history of illicit stimulant use. *J Appl Physiol* 113: 1486–1494, 2012. First published September 6, 2012; doi:10.1152/japplphysiol.00718.2012.—Illicit use of stimulant drugs such as methamphetamine, ecstasy, and cocaine is a current and growing problem throughout the world. The aim of the current study was to investigate the long-term effect of illicit stimulant use on human motor cortical and corticospinal circuitry. We hypothesized that individuals with a history of primarily methamphetamine and ecstasy use would exhibit altered corticospinal excitability and intracortical inhibition within motor cortex. The study involved 52 healthy adults (aged 26 ± 7 yr) comprising 26 abstinent stimulant users, 9 cannabis users, and 17 nondrug users. The experiment involved a routine urine drug screen, drug history questionnaire, neuropsychological assessment, and single- and paired-pulse transcranial magnetic stimulation (TMS) over motor cortex. EMG responses to stimulation [motor evoked potentials (MEPs)] were recorded from the contralateral first dorsal interosseus. At a given stimulus intensity, MEP area was significantly larger in abstinent stimulant users than in nondrug users during both relaxation ($P = 0.045$) and muscle contraction ($P < 0.001$). MEP latency was also significantly longer in abstinent stimulant users ($P < 0.009$), and they exhibited significantly greater muscle activity during performance of a given task ($P = 0.004$). However, resting motor threshold and the response to paired-pulse TMS were unaffected. The results suggest that abstinent stimulant users exhibit long-term changes in the excitability of motor cortical and corticospinal circuitry and muscle activity during movement. These changes may partly underlie anecdotal and objective reports of movement dysfunction in chronic stimulant users.

illicit stimulants; motor cortex; transcranial magnetic stimulation

ILLICIT USE OF STIMULANTS such as amphetamine, methamphetamine, cocaine, and ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] is a current and growing problem throughout the world. The United Nations Office on Drugs and Crime estimates that 0.3–1.2% of the world population aged 15–64 yr have used an illicit stimulant in the last year alone with the prevalence of amphetamines (0.4–1.2%) exceeding that of ecstasy (0.3–0.5%) and cocaine (0.3–0.4%; Ref. 50). The Oceania region (comprising people primarily from Australia and New Zealand) has the highest annual prevalence of illicit stimulant use in the world with 2.4–3.8% of people aged 15–64 yr reporting use of amphetamines or ecstasy in the past year (49).

Illicit stimulants are used to temporarily increase alertness, mood, and euphoria. These effects arise from the drugs' acute mechanism of action on the monoamine neurotransmitters dopamine, norepinephrine, and serotonin. There are important differences in the degree to which the various stimulants affect these three neurotransmitters. For example, ecstasy results in an increase in primarily serotonin and norepinephrine (for review see Ref. 24), whereas amphetamine, methamphetamine, and cocaine cause excess accumulation of mainly dopamine (for review, see Refs. 20, 57).

Studies in rodents suggest that chronic use of stimulants is associated with long-term changes in monoamine neurotransmission. Chronic use of amphetamines is associated with dopamine deficiency and neurotoxicity due to a combination of mechanisms including mitochondrial dysfunction, oxidative stress, excitotoxicity, and neuroinflammation (for review see Ref. 58). Conversely, chronic use of ecstasy is associated with selective neurotoxicity in serotonergic nerve terminals in the rat striatum, cerebral cortex, hypothalamus, and hippocampus (for review see 21).

Investigating the effect of chronic use of illicit stimulants in humans is challenging because of poly-drug use (i.e., use of more than one psychoactive drug; e.g., Refs. 31, 41). For example, in Australia, 70% of amphetamine and methamphetamine users currently use cannabis and 60% had used ecstasy in the past 12 mo (1). Stimulant use is also associated with higher consumption of alcohol and tobacco (2). This aside, long-term changes in monoamine neurotransmission have been observed in abstinent stimulant users with the use of neuroimaging. For example, abstinent methamphetamine users exhibit reduced dopamine reuptake transporter (53) and dopamine (D2) receptor availability (52) in the striatum, whereas abstinent ecstasy users exhibit decreased 5-HT reuptake transporter (32) and changes in 5-HT_2 receptors (38) in several brain regions.

The aim of our study was to investigate if there are long-term changes in cortical excitability in individuals with a history of illicit stimulant use. We chose to investigate motor cortex because transcranial magnetic stimulation (TMS) can be used in conscious humans to investigate motor cortical and corticospinal excitability. Four previous studies have used TMS to investigate excitability in abstinent cocaine users. Two early studies (8, 9) lacked sufficient methodological rigor to draw accurate conclusions, and the latter two studies (19, 46) found that abstinent cocaine users require a higher stimulus intensity to evoke a response (i.e., higher threshold). The studies also revealed increased $GABA_B$-mediated intracortical inhibition (i.e., prolongation of the cortical silent period; Ref. 19) and increased long-interval intracortical facilitation in motor cortex (46). However, the latter studies did not assess excitability during movement and did not quantify lifetime stimulant use. The studies also did not investigate the effect of other illicit drug use, alcohol and tobacco use, or neuropsy-

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chological performance on the results. Thus a secondary aim of our study was to address these limitations. We hypothesized that individuals with a history of illicit stimulant use would exhibit altered motor cortical and corticospinal excitability and that the effects would be related to their poly-stimulant use and not differences in neuropsychological performance or to their use of alcohol, tobacco, or cannabis. Changes in motor cortex and corticospinal circuitry could partly underlie case reports (e.g., Refs. 17, 33) and anecdotal reports (e.g., Ref. 37) of movement dysfunction in stimulant users.

MATERIALS AND METHODS

Ethical approval. The study was performed at the University of South Australia in Adelaide, Australia. All experimental procedures were approved by the Human Research Ethics Committee at the University of South Australia and Drug and Alcohol Services South Australia. Experimental procedures were conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) printed in the *British Medical Journal* (18th July 1964). Written informed consent was obtained. Subjects then underwent a series of screening tests before participation.

Participants. Fifty-two healthy adults aged 18–48 yr were recruited into the study (mean age: 26 ± 7 yr, 32 male, 20 female). Three groups of subjects were investigated: 26 stimulant users, 9 cannabis users, and 17 nondrug users. The cannabis users were included as a drug-use control group because cannabis use is common among stimulant users. The inclusion criterion for the stimulant group was use of stimulants on greater than five occasions. Inclusion criteria for the cannabis group were use of cannabis on greater than five occasions but no history of stimulant use. Inclusion criteria for the control group were cannabis use on <1 occasion and no other history of illicit drug use (alcohol and tobacco use was permitted).

Subject screening. Subjects were asked to provide a urine sample for routine drug screening (PSCupA-6MBAU; US Diagnostics, Huntsville, AL). Subjects who tested positive for amphetamine, methamphetamine, MDMA (ecstasy), cocaine, opioids, and/or benzodiazepines were excluded from further participation. Subjects who tested positive for cannabis [active ingredient tetrahydrocannabinol (THC)] were allowed to participate if use was >12 h before the experiment. The exemption was due to the metabolite of THC remaining in the body for up to 90 days after last use. Subjects then completed a therapeutic drug history questionnaire to document use of prescription, nonprescription, and complementary medicines within the last month. Subjects were excluded if they reported use of prescription medications that acted on the central nervous system in the last month (e.g., methylphenidate, antipsychotics, and antidepressants). Subjects were then interviewed about past and present alcohol and tobacco use and illicit drug use. The interview consisted of a series of questions of about 20 recreational drugs and any other recreational drugs not listed. Items on the questionnaire included age of first use, age of regular use, duration of use, frequency of use (current and lifetime), number of times used in the last year, average dose (current and lifetime), frequency of high dose use, time since last use, number of drug overdoses, and if they were currently undergoing treatment for drug dependency. Subjects were excluded if they consumed recreational drugs on the day of the experiment (confirmed by positive result on urine drug screen) or if they had a history of recreational opioid use on more than three occasions.

Subjects then completed a brief medical history questionnaire and TMS safety screen (40). Subjects were excluded if they had a history of neurological damage and/or neurological illness before illicit drug use or contraindators for TMS (e.g., metal objects in the skull and cardiac pacemaker). The final screening test involved a neuropsychological assessment of memory and cognition. Four cognitive domains were assessed. New learning was assessed with Logical Memory I and II (56), executive functioning was assessed with Verbal Trails and Verbal Fluency (7, 22), working memory was assessed with Digit Span backwards (55), and attention was assessed with Digit Span forwards (55). Performance in each test was compared with normative data matched for age and years of education. Subjects were excluded if poor performance was observed on three or more of the cognitive domains tested. Poor performance was defined as >2 SD below the mean of the normative data for Digit Span (25), Verbal Fluency (47), and Logical Memory I and II (34) and performance >2 SD above the mean for Verbal Trails (35).

Experimental protocol. The experiment began with preparation and positioning of two surface electromyographic (EMG) electrodes (Ag-AgCl, 10-mm diameter) over the muscle belly and tendon of the first dorsal interosseus on the dominant hand. Hand dominance was confirmed with the use of the Edinburgh Handedness Questionnaire (36). EMG activity was amplified (100 or 1,000×), filtered (20–1,000 Hz), and sampled at 2,000 Hz using a data acquisition system (1902 with Power 1401 Interface and Signal and Spike2 software: Cambridge Electronic Design, Cambridge, UK).

Single- and paired-pulse TMS was then applied to the motor cortex contralateral to the dominant hand with the use of two Magstim 200^2 stimulators (part no. 3010–00), a BiStim^2 UI Controller and Connecting Module (part no. 3021–00 and 3333–00), and a figure-of-eight coil (part no. 3281–00, 90-mm external diameter of wings; Magstim, Whitland, UK). The center of the coil was positioned over the motor area of the first dorsal interosseus. This region is easy to activate with TMS, and the evoked EMG response has been well characterized in the literature. The handle of the stimulating coil pointed posteriorly at ~45° to the midline and tangentially to the skull. This coil position induces a posterior-to-anterior current in the brain and is optimal for stimulating the hand region of the motor cortex. To begin with, single stimuli were applied at a rate of ~0.2 Hz to determine resting motor threshold. The intensity of stimulation was initially set well above threshold and then reduced in steps of 1–3% of stimulator output until it was below threshold. Resting motor threshold was defined as the stimulus intensity that produced a response [termed motor evoked potential (MEP)] of amplitude >50 μV in 5 out of 10 consecutive stimuli. The intensity of stimulation was then increased to 130% of the resting motor threshold to assess resting corticospinal excitability. Fifteen single stimuli were delivered at this intensity. A further 15 stimuli were delivered at the same intensity during weak abduction of the index finger to assess intracortical inhibition and facilitation of corticospinal excitability during movement. The contraction was performed with the wrist supinated and the index finger extended. A 52.7-g weight was positioned at the distal interphalangeal joint, and subjects were instructed to hold the weight using index finger abduction. The weight was then removed, and subjects were instructed to relax. Subjects then received paired-pulse stimulation to investigate short-interval intracortical inhibition and facilitation.

The paired-pulse paradigm was based on that used by Kujairi et al. (26). The intensity of the test pulse was set to produce a resting MEP of ~1 mV in amplitude. The intensity of the conditioning pulse was set at 70% of resting motor threshold. The conditioning pulse preceded the test pulse by 2, 3, 10, or 12 ms. Ten pairs of stimuli were applied at each interstimulus interval, and 20 single test pulses were also applied (~0.2 Hz). The paradigm was then repeated with a higher conditioning stimulus intensity (90% of resting motor threshold).

Subjects then completed three brief (2–3 s) maximal isometric abductions of the index finger to enable normalization of voluntary EMG measured during the TMS protocol. Verbal encouragement and visual feedback of force production were provided to subjects. Maximal isometric abduction force was recorded using a linear strain gauge (LC1205-K020; A&D Mercury, Thebarton, Australia) positioned at the proximal interphalangeal joint. The thumb and middle finger were restrained, and maximal contractions were separated by

~1 min to avoid fatigue. Force was recorded using the above-mentioned data acquisition system. Force signals were amplified (1,000×), filtered (DC to 100 Hz), and sampled at 200 Hz.

Lastly, depression can influence motor cortical excitability (e.g., Refs. 27, 29). Thus symptoms of depression (over the past 2 wk) were assessed with a 21 item self-report rating scale (Beck Depression Inventory-II, 5). The reliability and validity of this questionnaire are well established in adults (43). Speed of information processing was also assessed. Subjects were presented with two parallel lines on a computer screen and asked to indicate which of the two lines was shorter (i.e., "Inspection time test"; Ref. 51). The minimum exposure time required to accurately determine the shorter line was recorded. The test is a measure of speed and efficiency of information processing independent of the motor component of reaction time.

Data analysis. For single-pulse TMS, the latency, area, peak-to-peak amplitude, and duration of resting and contracting MEPs was measured in each trial. Resting MEPs with preceding voluntary EMG were excluded from further analysis. For contracting MEPs, the prestimulus voluntary root mean square EMG (i.e., RMS EMG) was measured (over 100 ms) for each subject and expressed as a percentage of that measured (over 1 s) during brief maximal voluntary abduction of the index finger. The period of EMG silence following contracting MEPs (i.e., silent period) was also measured. A measurement cursor was placed at the stimulus onset and at the resumption of voluntary EMG. Resumption of voluntary EMG was determined by eye with a consistent visual display window (y-axis: ± 0.2 mV). The silent period was defined as the time interval between the stimulus and resumption of voluntary EMG. For paired-pulse TMS, the peak-to-peak amplitude of resting MEPs was measured in each trial. The conditioned MEP was expressed as a percentage of the test MEP.

Group data are presented as the means ± SD. Subject characteristics (age, height, weight, education, depression score, and speed of information processing) and use of alcohol and tobacco were analyzed with one-way ANOVA for comparison of group (control, stimulant, cannabis). Nonparametric data were transformed to ranks, and repeated-measure ANOVAs on ranks were performed. Post hoc discrimination between means was made with Student-Newman Keuls procedure (SigmaPlot 11.0; Systat Software, Chicago, IL). Due to widespread poly-drug use in the stimulant group but not in the cannabis group, MEP characteristics were analyzed separately for the stimulant and cannabis groups. Between group (i.e., stimulant vs. control or cannabis vs. control) comparison of MEP area, MEP amplitude, MEP latency, MEP duration, resting motor threshold, silent period duration, and prestimulus voluntary RMS EMG amplitude was made with unpaired Student's t-test. Cohen's d was used to determine effect size (medium effect size: ~0.5; large effect size: >0.8). Group data for paired-pulse stimulation was analyzed with three-way ANOVA for comparison of group (stimulant vs. control or cannabis vs. control; between-subject factor), conditioning stimulus intensity (70 and 90% resting motor threshold; within-subject factor), and interstimulus interval (2, 3, 10, and 12 ms; within-subject factor). Mauchly's test of sphericity was performed and the Greenhouse-Geisser method was used to correct for nonsphericity (IBM SPSS Statistics 20, IBM; Armonk, New York, NY). A Spearman rank order correlation was used to investigate the relationship between the size of contracting MEPs and prestimulus voluntary RMS EMG amplitude and between drug history parameters and TMS parameters (SigmaPlot 11.0, Systat Software).

RESULTS

Subject characteristics. Table 1 shows average subject characteristics for the control, stimulant, and cannabis groups. The average age of the groups was significantly different ($F_{2,49}$ = 3.215; P = 0.049). Subjects in the cannabis group tended to be younger than the stimulant group (P = 0.058), but neither group differed from control. The groups also differed in weight ($F_{2,49}$ = 3.548; P = 0.036) but not height. The groups did not differ in years of education or speed of information processing (i.e., inspection time). All subjects passed neuropsychological screening, but the score on the Beck Depression Inventory-II (BDI-II) significantly differed between groups ($F_{2,49}$ = 8.534; P < 0.001). As expected, symptoms of depression were more evident in the stimulant (P < 0.001) and cannabis (P = 0.013) groups than in the control group. Four subjects in the stimulant group had received a formal diagnosis of depression. The diagnosis was given after commencement of illicit drugs by 2, 8, 14, and 15 yr, respectively, and subjects were not currently being treated with antidepressants. Prior head injuries (involving loss of consciousness) were also more common in the stimulant group.

Drug history. Fourteen subjects had consumed prescribed medication in the month before the experiment, but only three medications had actions on the central nervous system. One subject had consumed one dose of a benzodiazepine (Temazepam; 15 days before the experiment), one subject had consumed steroid and testosterone medications (up until 15 days before the experiment), and another subject had consumed a nicotinic receptor partial agonist (Champix) during the 3 days before the experiment (to aid cessation of smoking). Consumption of over-the-counter medications included pain relief medications (n = 8 subjects, consumed 1–21 days before experiment), antihistamines and other decongestants (n = 6, 0–20 days), heartburn medication (n = 2, 10–21 days), antifungal medication (n = 1, 1 day), and flu vaccination (n = 1, 7 days).

Table 1. *Subject characteristics for the control, stimulant, and cannabis groups*

	Control (n = 17)	Stimulant (n = 26)	Cannabis (n = 9)
Age, yr	25 ± 7	28 ± 7	23 ± 7
Gender	9 male, 8 female	17 male, 9 female	6 male, 3 female
Weight, kg	64 ± 12	77 ± 18*	77 ± 21
Height, cm	171 ± 9	177 ± 11	173 ± 7
Handedness	16 right, 1 left	25 right, 1 left	8 right, 1 left
Education, yr	16 ± 3	15 ± 3	15 ± 2
Depression (score)	3 ± 3	10 ± 7*	11 ± 10*
Diagnosis	0	4	0
Inspection time	682 ± 171	672 ± 175	667 ± 105
Head injuries	0	11	1
Lifetime alcohol (total drinks)	1,285 ± 3,082	6,722 ± 7,273*†	3,165 ± 5,612
Lifetime tobacco (total cigarettes)	1 ± 2	25,052 ± 39,834*†	4,867 ± 8,683*

Data are means ± SD. *Significantly different from control group. †Significant difference between stimulant and cannabis groups.

Consumption of complementary medications included vitamin and mineral preparations ($n = 16$), fish oil ($n = 5$), herbal preparations ($n = 4$), and creatine products ($n = 2$).

Use of alcohol and tobacco was significantly different between the groups (alcohol: $F_{2,41} = 12.056$, $P < 0.001$; tobacco: $F_{2,49} = 35.285$, $P < 0.001$). Lifetime use of alcohol (estimated total drinks) and tobacco (estimated total cigarettes) was significantly greater in the stimulant group than in the control ($P < 0.001$) and cannabis ($P < 0.039$) groups (Table 1).

Table 2 shows single subject data on use of stimulants and cannabis in the stimulant and cannabis groups. Ecstasy was the most commonly used stimulant followed by amphetamine/methamphetamine, cocaine, and recreational use of pharmaceutical stimulants. However, lifetime use (number of occasions) was greater for amphetamine/methamphetamine (318 ± 559) than ecstasy (60 ± 85) and cocaine (8 ± 12). The average duration of abstinence was 4.0 ± 7.1 yr for amphetamines (range: 5 days-30 yr), 3.7 ± 4.6 yr for cocaine (range: 61 days-15 yr), and 2.3 ± 3.8 yr for ecstasy (range: 11 days-17 yr). The duration of abstinence for cannabis was 0.3 ± 0.7 yr in the stimulant group (range: 1 day-3 yr) and 0.7 ± 1.6 yr in the cannabis group (range: 1 day-5 yr).

Table 3 shows the percentage of subjects within each group that had used other types of illicit drugs. This information is rarely reported but is important for interpretation of the results. As expected, poly-drug use was common in the stimulant group. All subjects in the stimulant group had used cannabis, and lifetime use (number of occasions) did not significantly differ between the stimulant and cannabis groups. However, use of other classes of illicit drugs was much more prevalent in the stimulant group than in the cannabis group. The most commonly used hallucinogens were lysergic acid diethylamide (i.e., LSD, 69% of subjects, 53 ± 120 occasions) and "magic" mushrooms (62% of subjects; 14 ± 38 occasions), and the most commonly used inhalant was nitrous oxide (54% of subjects; 31 ± 55 occasions). Due to extensive poly-drug use in the stimulant group, and more frequent drug overdoses, the cannabis group was deemed to be inappropriate as a control group. As a result, further statistical analysis of the stimulant and cannabis groups was performed separately.

Table 2. *Summary of lifetime use of stimulants and cannabis in the stimulant and cannabis groups*

			Stimulants			
Subject	Cannabis Total	Stimulants Total	Amphetamine	Cocaine	Ecstasy	Pharmac.
Stimulant (S)						
S1	28	2,241	2,070	2	169	—
S2	15	1,694	1,512	42	50	90
S3	8,212	1,396	1,024	10	362	—
S4	13	833	832	—	1	—
S5	1,140	670	520	—	150	—
S6	4,380	367	206	5	156	—
S7	1,251	332	227	1	104	—
S8	7,365	247	240	4	3	—
S9	6,570	209	208	—	1	—
S10	23	199	65	28	106	—
S11	1,529	156	1	—	153	2
S12	212	97	—	—	5	92
S13	128	78	11	2	73	—
S14	4,380	57	—	5	52	—
S15	5,616	38	26	—	12	—
S16	474	36	4	—	26	6
S17	270	27	26	—	1	—
S18	1,456	22	1	1	20	—
S19	6	19	—	8	11	—
S20	15	19	—	1	18	—
S21	2,763	17	3	1	13	—
S22	72	12	1	—	9	2
S23	4,384	7	6	1	—	—
S24	183	7	1	—	6	—
S25	60	6	1	—	5	—
S26	450	6	1	—	5	—
Means (SD)	1,961 (2,604)	338 (581)	318 (559)	8 (12)	60 (85)	38 (48)
Cannabis (C)						
C1	8,395	—	—	—	—	—
C2	364	—	—	—	—	—
C3	154	—	—	—	—	—
C4	104	—	—	—	—	—
C5	92	—	—	—	—	—
C6	80	—	—	—	—	—
C7	64	—	—	—	—	—
C8	39	—	—	—	—	—
C9	9	—	—	—	—	—
Means (SD)	1,033 (2,763)					

Single subject data are presented (number of times used). The term "amphetamine" describes methamphetamine and khat (1 subject only). The term "ecstasy" describes ecstasy, MDA (3,4-methylenedioxyamphetamine, 2 subjects), and MCAT (mephedrone; 1 subject only). Pharmac, pharmaceutical stimulants (Ritalin and dexamphetamine).

Table 3. *Percentage of subjects in the stimulant and cannabis groups that had consumed other types of illicit drugs in their lifetime*

	Stimulant Group	Cannabis Group
Stimulants	100%	0%
Ecstasy	96%	—
Methamphetamine	85%	—
Cocaine	54%	—
Pharmaceutical	19%	—
Cannabis	100%	100%
Hallucinogens	88%	22%
Opiates	27%	0%
Inhalants	62%	22%
Sedatives	31%	11%
Overdoses (occasions)	10	1 (alcohol)

The term "hallucinogen" describes LSD (lysergic acid diethylamide), LSA (D-lysergic acid amide), "magic" mushrooms, DOI (2,5-dimethoxy-4-iodoamphetamine), mescaline, salvia divinorum, and/or ketamine. The term "opiate" describes heroin, methadone, opium, and recreational use of codeine, oxycodeine, and/or morphine (total use <3 occasions per subject). The term "inhalant" describes amyl nitrate, ethyl choride, and/or nitrous oxide. The term "sedative" describes GHB (or "fantasy," γ-hydroxybutyric acid) and recreational use of benzodiazapine, antihistamine, and/or antidepressants.

Stimulant group. There was no significant difference in resting motor threshold between the stimulant (45.5 ± 7.5%) and control (48.6 ± 7.2%) groups. MEP characteristics were measured during relaxation and weak contraction at a given stimulus intensity (130% of resting motor threshold). Figure 1 shows averaged EMG data for one control subject and one stimulant subject. Resting MEPs tended to be larger in the stimulant subject than in the control.

MEPs were significantly larger in the stimulant group than in the control group during relaxation (area: $P = 0.045$, Cohen's $d = 0.62$; amplitude: $P = 0.089$, Cohen's $d = 0.53$; Fig. 2, *A* and *B*) and contraction (area: $P < 0.001$, Cohen's $d = 1.05$; amplitude: $P = 0.002$, Cohen's $d = 0.93$; Fig. 3, *A* and *B*). Prestimulus voluntary RMS EMG amplitude was calculated to determine if the larger MEPs observed during contraction were due to differences in task performance. Prestimulus voluntary RMS EMG was expressed as a percentage of that measured during maximal voluntary abduction of the index finger. Surprisingly, prestimulus voluntary RMS EMG amplitude was significantly larger in the stimulant group (9.4 ± 5.1%) than in the control group (5.4 ± 2.1%; $P = 0.004$, Cohen's $d = 0.87$), suggesting greater muscle activation while holding a 52.7-g weight. The greater muscle activation occurred even though maximal isometric force was significantly higher in the stimulant group (42.7 ± 14.6 N) than in the control group (30.8 ± 10.1 N; $P = 0.005$, Cohen's $d = 0.84$). However, the greater muscle activity appeared to have a minimal effect on the size of contracting MEPs because there was no significant correlation between contracting MEP size and prestimulus voluntary RMS EMG amplitude across subjects (MEP area: correlation coefficient=0.18; $P = 0.25$; MEP amplitude: correlation coefficient = 0.16; $P = 0.31$). Variability of MEP area and amplitude did not significantly differ between groups during relaxation but was significantly less in the stimulant group during contraction (stimulant MEP area: 14.1 ± 7.6%; stimulant MEP amplitude: 15.3 ± 7.8%; control MEP area: 21.5 ± 10.2%; control MEP amplitude: 21.3 ± 11.1%; $P < 0.043$).

The duration of resting and contracting MEPs did not significantly differ between groups, but the latency of MEPs was significantly longer in the stimulant group than in the control group (Figs. 2*C* and 3*C*; $P < 0.009$, Cohen's $d = 0.80$). The duration of the silent period following contracting MEPs tended to be longer in the stimulant group than in the control group but did not reach statistical significance ($P = 0.060$, Cohen's $d = 0.58$; Fig. 3*D*).

As expected, paired-pulse stimulation induced inhibition at interstimulus intervals of 2 and 3 ms and facilitation at interstimulus intervals of 10 and 12 ms (main effect of interstimulus interval: $F_{3,336} = 98.705$; $P < 0.001$) and differed between the two conditioning stimulus intensities (main effect of intensity: $F_{1,336} = 18.848$; $P < 0.001$; stimulus intensity-by-interstimulus interval interaction: $F_{3,336} = 6.758$; $P < 0.001$). However,

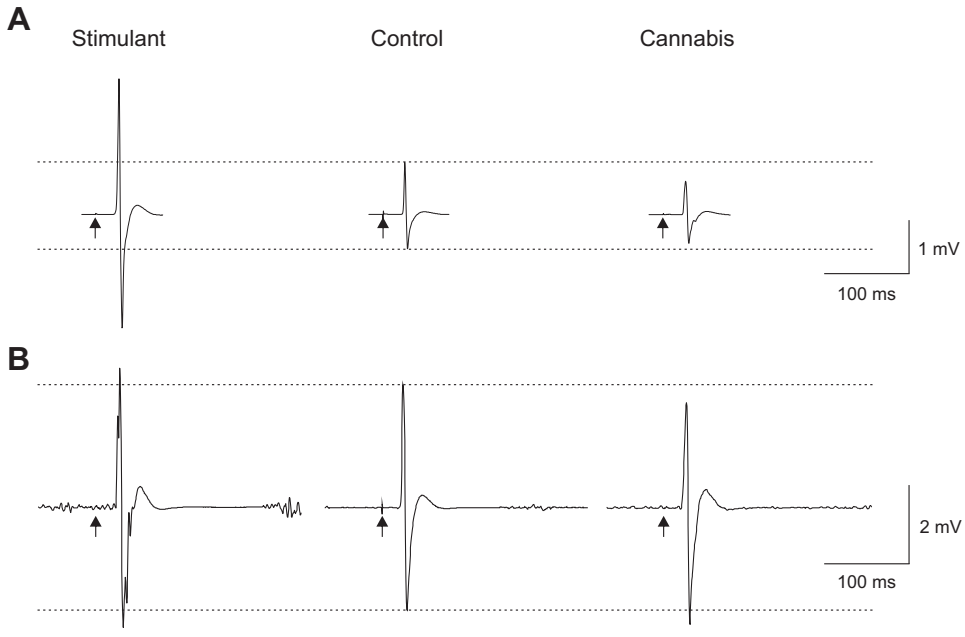

Fig. 1. Single subject data showing the amplitude of the motor evoked potential (MEP) in the first dorsal interosseus muscle during relaxation (*A*) and contraction (weak abduction of the index finger; *B*). Average EMG traces from one stimulant subject (*left*), one control subject (*middle*), and one cannabis subject (*right*) are shown. Each trace is the average of 15 individual trials. Single ended arrows indicate the timing of single transcranial magnetic stimuli (TMS).

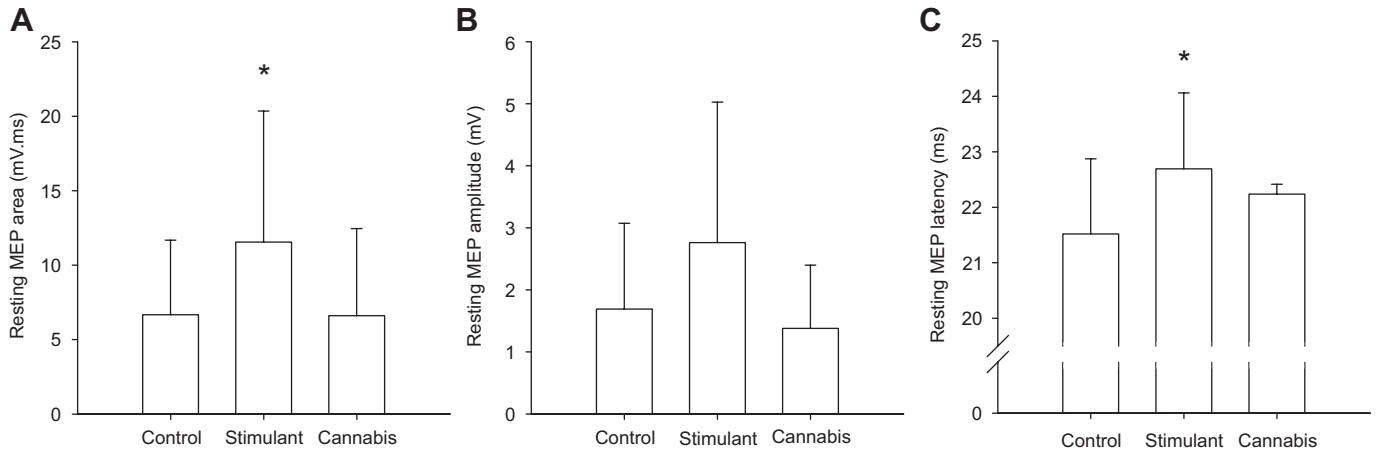

Fig. 2. Group data (means ± SD) showing the characteristics of resting MEPs in the control, stimulant, and cannabis groups. *A*: average MEP area. *B*: average MEP amplitude. *C*: average MEP latency. *Significantly different from control ($P < 0.05$).

there was no significant main effect of group and there were no significant interactions with group.

There was no significant correlation between TMS parameters and total stimulant use (number of occasions) or duration of abstinence. However, short-interval intracortical inhibition (2-ms interstimulus interval) tended to increase with increasing duration of abstinence (correlation coefficient = −0.343; $P = 0.085$) but only for the higher conditioning intensity (90% resting motor threshold).

Cannabis group. There was no significant difference in resting motor threshold between the cannabis (45.1 ± 6.8%) and control groups. Resting MEPs did not significantly differ between the cannabis and control groups, but contracting MEPs tended to be larger in the cannabis group than in the

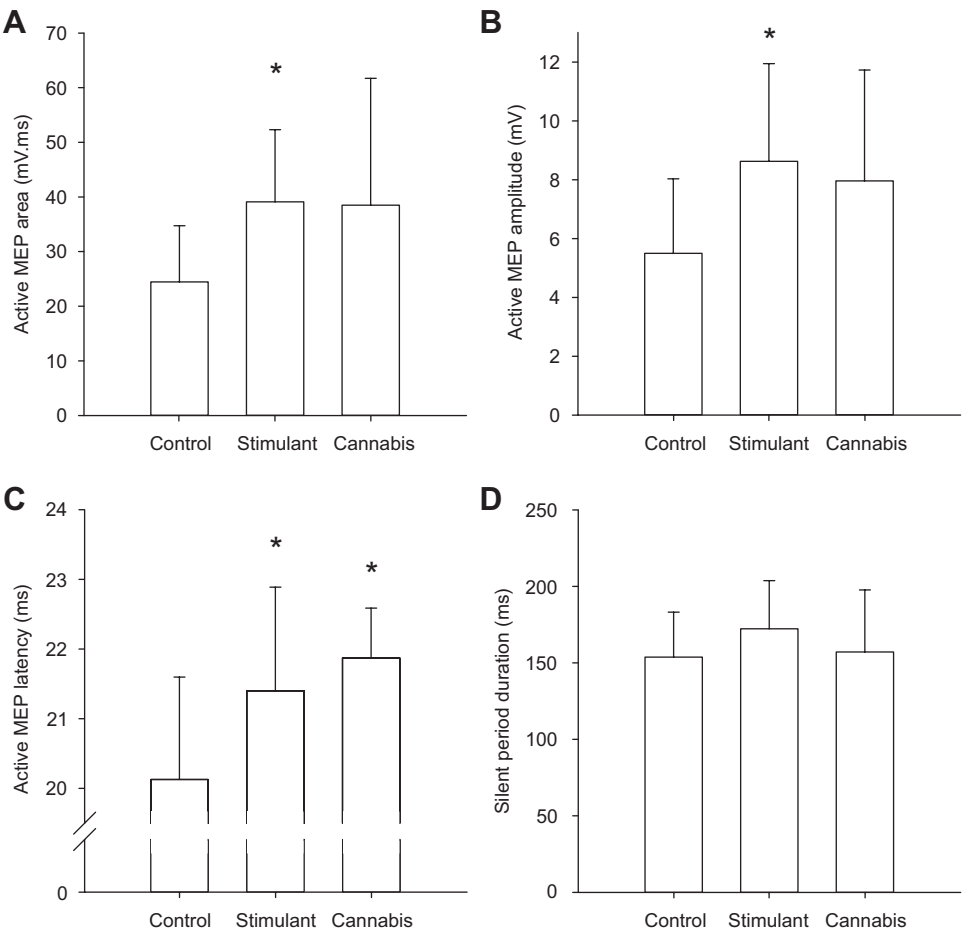

Fig. 3. Group data (means ± SD) showing the characteristics of contracting MEPs in the control, stimulant, and cannabis groups. *A*: average MEP area. *B*: average MEP amplitude. *C*: average MEP latency. *D*: average duration of the silent period. *Significantly different from control ($P < 0.05$).

control group (area: $P = 0.059$, Cohen's $d = 0.83$; amplitude: $P = 0.087$, Cohen's $d = 0.76$; Fig. 3, *A* and *B*). Prestimulus voluntary RMS EMG amplitude in the cannabis group (7.6 ± 1.3%) was not significantly different from the control group. The variability of contracting MEPs did not differ between groups, but resting MEP area and amplitude were more variable in the cannabis group (coefficient of variation; area: 73.6 ± 27.6%; amplitude: 76.5 ± 38.5%; $P < 0.011$) than in the control group. The silent period duration (Fig. 3*D*) and MEP duration (resting: 42.7 ± 11.8 ms; contracting: 47.1 ± 4.4 ms) in the cannabis group did not significantly differ to controls, but the latency of contracting MEPs was longer in the cannabis group than in the control group ($P = 0.041$, Cohen's $d = 1.16$; Fig. 3*C*). The paired-pulse paradigm did not reveal any differences between the cannabis and control groups.

DISCUSSION

We investigated motor cortex and corticospinal excitability in individuals with a history of illicit stimulant use. The novel features of our study were investigation of individuals with predominant use of methamphetamine and ecstasy, assessment of excitability during movement, assessment of recent and lifetime drug history, and inclusion of several control measures to aid interpretation of the results. Our results show for the first time that individuals with a history of primarily methamphetamine and ecstasy use exhibit significantly larger MEPs during relaxation and contraction, increased muscle activity during a given task, a prolonged MEP latency, and a tendency for a prolonged cortical silent period.

MEP size is sensitive to the level of cortical excitability and reflects activity in intracortical circuits and projections to the spinal cord. At a given stimulus intensity, resting MEPs were significantly larger in the stimulant group than in the control group. This suggests that individuals with a history of stimulant use exhibit increased resting motor cortical and/or corticospinal excitability. Identifying the underlying mechanism for the increased excitability is difficult in humans. We can conclude that the effect is not associated with the acute mechanism of action of stimulants because the average duration of abstinence was >2 yr and all subjects had a negative urine screen for stimulants, opiates, and benzodiazepines. However, beyond that one can only speculate due to poly-drug use and the potential for interaction between different classes of drugs.

It is conceivable that use of methamphetamine and ecstasy had a greater effect on resting excitability than symptoms of depression or use of cocaine and/or cannabis. Several pieces of evidence support this view. First, resting motor threshold was normal in the current cohort of stimulant users but is significantly higher in abstinent cocaine-dependent individuals (19, 46) and unmedicated patients with depression (29). Second, resting MEP size was larger in the current cohort of stimulant users but is normal in abstinent cocaine-dependent individuals (19, 46) and cannabis users (current study; see also Ref. 18). Third, half of the subjects in the current cohort of stimulant users had tried cocaine but only on a small number of occasions. Other neuropsychological factors such as altered memory, cognition, and speed of information processing are also unlikely to have contributed to the result because inspection time was normal in stimulant users and all subjects passed neuropsychological screening.

MEPs measured during weak abduction of the index finger were also significantly larger in the stimulant group than in the control group. This is the first time that contracting MEPs have been investigated in illicit stimulant users. The increased MEP size suggests that individuals with a history of stimulant use also exhibit increased motor cortical and/or corticospinal excitability during movement. The increased MEP size could partly be due to cannabis use because contracting MEPs also tended to be larger in cannabis users ($P = 0.059$). It could also be due to greater voluntary muscle activity during the movement in individuals with a history of stimulant use. Voluntary muscle activity was quantified by normalization of the prestimulus voluntary RMS EMG amplitude to the voluntary RMS EMG amplitude recorded during brief maximal voluntary contractions to enable comparison between subjects. The contribution of greater muscle activity to contracting MEP size is likely to be minimal given that there was no correlation between contracting MEP size and prestimulus voluntary RMS EMG amplitude across subjects. Nonetheless, the greater muscle activation is still surprising given that subjects in the stimulant group were stronger (i.e., higher maximal abduction force) than subjects in the control group. Further investigation of muscle activity patterns during other types of movement is necessary to determine if planning and performance of movement is altered by illicit drug use.

Variability in MEP size did not underlie the increase in MEP size observed in the stimulant group. The coefficient of variation for MEP area and amplitude was equal to or less than that observed in the control group. However, the way in which TMS activates cells within the motor cortex may differ in people with a history of stimulant use. Recordings from the corticospinal tract of anesthetized primates (3) and humans (10, 14) show that a single TMS pulse normally produces multiple descending volleys in corticospinal axons. The initial volley, known as a D wave, is short in latency and is produced by direct stimulation of corticospinal axons at or near the first node of Ranvier (3, 4, 16). The later volleys, termed I waves, occur at intervals of ~1.5 ms and are thought to reflect indirect activation of corticospinal neurons (for review, see Ref. 61). The latency of the resting and contracting MEPs was significantly longer in the stimulant group (by ~1–2 ms) than in the control group. This could be due to altered generation of D and I waves in stimulant users or changes in axonal conduction velocity given that height did not significantly differ between the groups.

The duration of EMG silence that follows a contracting MEP reflects the strength of $GABA_B$-mediated intracortical inhibition within motor cortex if it exceeds 100 ms in duration (for review, see Ref. 59). Although not significant, individuals with a history of stimulant use tended to exhibit a longer cortical silent period ($P = 0.06$) than subjects in the control group. This is consistent with dopaminergic agonists (pergolide mesylate and L-DOPA) producing acute prolongation of the cortical silent period in healthy nondrug using adults (60) and patients with Parkinson's disease (39). The cortical silent period is also prolonged in abstinent cocaine-dependent individuals and the duration appears to increase with increasing severity of behavioral symptoms experienced during cocaine use (19).

The results of paired-pulse stimulation did not significantly differ in adults with a history of stimulant use. This suggests that short-interval intracortical inhibition (mediated by $GABA_A$

receptors) and facilitation were unaffected. Similar results have also been observed in abstinent cocaine-dependent individuals (19), but reduced short-interval intracortical inhibition has been observed in heavy cannabis users (18).

A limitation of the current study is that the response to TMS was only recorded in one muscle, the first dorsal interosseus. This muscle was selected because it has a large representation within motor cortex, it has an important role in precision grip and manipulation of objects, and the EMG response evoked by TMS has been well characterized in the literature. Further work is required to determine if the effect of stimulant use on motor cortical excitability is consistent across muscle groups.

How might stimulant use affect motor cortical and/or corticospinal excitability? Long-term changes in monoamine neurotransmission could underlie the altered excitability of motor circuitry observed in the current cohort of abstinent methamphetamine and ecstasy users and in the cohorts of previous studies involving abstinent cocaine-dependent individuals. Human neuroimaging studies show that abstinent methamphetamine users exhibit reduced dopamine reuptake transporter (53) and dopamine (D2) receptor availability (52) in the striatum whereas abstinent ecstasy users exhibit decreased 5-HT reuptake transporter (32) and changes in 5-HT_2 receptors (38) in several brain regions and decreased 5-hydroxyindoleacetic acid, the main metabolite of serotonin, in cerebrospinal fluid (31).

On the basis of their mechanisms of action, amphetamine, methamphetamine, and cocaine are most likely to alter brain regions involved in movement. These drugs cause excess accumulation of primarily dopamine. Animal and in vitro studies show that amphetamine and methamphetamine disrupt synaptic vesicles, block and/or reverse vesicular monoamine transporters (VMAT-2) and dopamine reuptake transporters (DAT; Ref. 23, 44), and inhibit monoamine oxidase (30, 42) (for review, see Refs. 45, 57), whereas cocaine mainly affects dopamine reuptake (for review, see Refs. 6, 20). Very few studies have examined the association between use of these drugs and movement. However, new cases of dystonia and tic disorders have been attributed to cocaine use (for review, see Ref. 12) and choreiform syndrome has been associated with amphetamine use (15, 28). Exacerbation of symptoms of preexisting movement disorders such as Tourette syndrome, essential tremor, tardive dystonia, and idiopathic dystonia has been noted with cocaine use (for review, see Refs. 12, 13), and epidemiological data suggest that methamphetamine use is associated with increased risk (hazard ratio = 2.65) of developing Parkinson's disease later in life (11). The few studies that utilized objective quantification of movement also indicate that abstinent methamphetamine users exhibit poorer motor performance on timed gait and grooved pegboard tasks (48, 54). However, the potential for other types of drugs to alter brain regions involved in movement should not be ignored given that poly-drug use is common among stimulant users.

In summary, individuals with a history of primarily methamphetamine and ecstasy use exhibit long-term changes in excitability of motor cortical and corticospinal circuitry and muscle activity during movement. Further studies are necessary to *1*) determine if the effect is present in other muscles, *2*) identify the functional consequence of these changes, and *3*) determine if stimulant use is a risk factor for developing a movement disorder later in life.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: S.C.F. and G.T. performed experiments; S.C.F. and G.T. analyzed data; S.C.F., J.M.W., and G.T. interpreted results of experiments; S.C.F. and G.T. prepared figures; S.C.F., J.M.W., and G.T. edited and revised manuscript; S.C.F., J.M.W., and G.T. approved final version of manuscript; J.M.W. and G.T. conception and design of research; G.T. drafted manuscript.

REFERENCES

1. **AIHW.** *2010 National Drug Strategy Household Survey Report*. Canberra, Australia: Australian Institute of Health and Welfare, 2011.
2. **AIHW.** *Statistics on Drug Use in Australia 2004*. Canberra, Australia: Australian Institute of Health and Welfare, 2005.
3. **Amassian VE, Quirk GJ, Stewart M.** A comparison of corticospinal activation by magnetic coil and electrical stimulation of monkey motor cortex. *Electroencephalogr Clin Neurophysiol* 77: 390–401, 1990.
4. **Baker SN, Olivier E, Lemon RN.** Task-related variation in corticospinal output evoked by transcranial magnetic stimulation in the macaque monkey. *J Physiol* 488: 795–801, 1995.
5. **Beck AT, Steer RA, Brown GK.** *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corp., 1996.
6. **Benowitz NL.** Clinical pharmacology and toxicology of cocaine. *Pharmacol Toxicol* 72: 3–12, 1993.
7. **Benton AL, Hamsher K.** *Multilingual Aphasia Examination*. Iowa City: AJA Associates, 1983.
8. **Boutros NN, Lisanby SH, McClain-Furmanski D, Oliwa G, Gooding D, Kosten TR.** Cortical excitability in cocaine-dependent patients: a replication and extension of TMS findings. *J Psychiatr Res* 39: 295–302, 2005.
9. **Boutros NN, Lisanby SH, Tokuno H, Torello MW, Campbell D, Berman R, Malison R, Krystal JH, Kosten T.** Elevated motor threshold in drug-free, cocaine-dependent patients assessed with transcranial magnetic stimulation. *Biol Psychiatry* 49: 369–373, 2001.
10. **Burke D, Hicks R, Gandevia SC, Stephen J, Woodforth I, Crawford M.** Direct comparison of corticospinal volleys in human subjects to transcranial magnetic and electrical stimulation. *J Physiol* 470: 383–393. 1993.
11. **Callaghan RC, Cunningham JK, Sajeev G, Kish SJ.** Incidence of Parkinson's disease among hospital patients with methamphetamine-use disorders. *Mov Disord* 25: 2333–2339, 2010.
12. **Cardoso F, Jankovic J.** Movement disorders. *Neurol Clin* 11: 625–638, 1993.
13. **Cardoso FE, Jankovic J.** Cocaine-related movement disorders. *Mov Disord* 8: 175–178, 1993.
14. **Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Meglio M, Cioni B, Colosimo C, Tonali PA, Rothwell JC.** Direct recording of the output of the motor cortex produced by transcranial magnetic stimulation in a patient with cerebral cortex atrophy. *Clin Neurophysiol* 115: 112–115, 2004.
15. **Downes MA, Whyte IM.** Amphetamine-induced movement disorder. *Emerg Med Australas* 17: 277–280, 2005.
16. **Edgley SA, Eyre JA, Lemon RN, Miller S.** Excitation of the corticospinal tract by electromagnetic and electrical stimulation of the scalp in the macaque monkey. *J Physiol* 425: 301–320, 1990.
17. **Farrell PE, Diehl AK.** Acute dystonic reaction to crack cocaine. *Ann Emerg Med* 20: 322, 1991.
18. **Fitzgerald PB, Williams S, Daskalakis ZJ.** A transcranial magnetic stimulation study of the effects of cannabis use on motor cortical inhibition and excitability. *Neuropsychopharmacology* 34: 2368–2375, 2009.
19. **Gjini K, Ziemann U, Napier TC, Boutros N.** Dysbalance of cortical inhibition and excitation in abstinent cocaine-dependent patients. *J Psychiatr Res* 46: 248–255, 2012.

20. **Greco PG, Garris PA.** In vivo interaction of cocaine with the dopamine transporter as measured by voltammetry. *Eur J Pharmacol* 479: 117–125, 2003.
21. **Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI.** The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Rev* 55: 463–508, 2003.
22. **Grigsby J, Kaye K.** Alphanumeric sequencing and cognitive impairment among elderly persons. *Percept Mot Skills* 80: 732–734, 1995.
23. **Jones SR, Gainetdinov RR, Wightman RM, Caron MG.** Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. *J Neurosci* 18: 1979–1986, 1998.
24. **Kalant H.** The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *CMAJ* 165: 917–928, 2001.
25. **Kear-Colwell JJ, Heller M.** A normative study of the Wechsler Memory Scale. *J Clin Psychol* 34: 437–442, 1978.
26. **Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferber A, Wroe S, Asselman P, Marsden CD.** Corticocortical inhibition in human motor cortex. *J Physiol* 471: 501–519, 1993.
27. **Loo CK, Sachdev P, Mitchell PB, Gandevia SC, Malhi GS, Todd G, Taylor JL.** A study using transcranial magnetic stimulation to investigate motor mechanisms in psychomotor retardation in depression. *Int J Neuropsychopharmacol* 1–12, 2008.
28. **Lundh H, Tunving K.** An extrapyramidal choreiform syndrome caused by amphetamine addiction. *J Neurol Neurosurg Psychiatry* 44: 728–730, 1981.
29. **Maeda F, Keenan JP, Pascual-Leone A.** Interhemispheric asymmetry of motor cortical excitability in major depression as measured by transcranial magnetic stimulation. *Br J Psychiatry* 177: 169–173, 2000.
30. **Mantle TJ, Tipton KF, Garrett NJ.** Inhibition of monoamine oxidase by amphetamine and related compounds. *Biochem Pharmacol* 25: 2073–2077, 1976.
31. **McCann UD, Ridenour A, Shaham Y, Ricaurte GA.** Serotonin neurotoxicity after (+/−)3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"): a controlled study in humans. *Neuropsychopharmacology* 10: 129–138, 1994.
32. **McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA.** Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 352: 1433–1437, 1998.
33. **Merab J.** Acute dystonic reaction to cocaine. *Am J Med* 84: 564, 1988.
34. **Mittenberg W, Burton DB, Darrow E, Thompson GB.** Normative data for the Wechsler Memory Scale-Revised: 25- to 34-year-olds. *Psychol Assess* 4: 363–368, 1992.
35. **Mrazik M, Millis S, Drane DL.** The oral trail making test: effects of age and concurrent validity. *Arch Clin Neuropsychol* 25: 236–243, 2010.
36. **Oldfield RC.** The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9: 97–113, 1971.
37. **Parrott AC, Buchanan T, Scholey AB, Heffernan T, Ling J, Rodgers J.** Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. *Hum Psychopharmacol* 17: 309–312, 2002.
38. **Reneman L, Habraken JB, Majoie CB, Booij J, den Heeten GJ.** MDMA ("ecstasy") and its association with cerebrovascular accidents: preliminary findings. *AJNR Am J Neuroradiol* 21: 1001–1007, 2000.
39. **Ridding MC, Inzelberg R, Rothwell JC.** Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. *Ann Neurol* 37: 181–188, 1995.
40. **Rossi S, Hallett M, Rossini PM, Pascual-Leone A.** Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 120: 2008–2039, 2009.
41. **Scholey AB, Parrott AC, Buchanan T, Heffernan TM, Ling J, Rodgers J.** Increased intensity of Ecstasy and polydrug usage in the more experienced recreational Ecstasy/MDMA users: a WWW study. *Addict Behav* 29: 743–752, 2004.
42. **Scorza MC, Carrau C, Silveira R, Zapata-Torres G, Cassels BK, Reyes-Parada M.** Monoamine oxidase inhibitory properties of some methoxylated and alkylthio amphetamine derivatives: structure-activity relationships. *Biochem Pharmacol* 54: 1361–1369, 1997.
43. **Segal DL, Coolidge FL, Cahill BS, O'Riley AA.** Psychometric properties of the Beck Depression Inventory II (BDI-II) among community-dwelling older adults. *Behav Modif* 32: 3–20, 2008.
44. **Sulzer D, Chen TK, Lau YY, Kristensen H, Rayport S, Ewing A.** Amphetamine redistributes dopamine from synaptic vesicles to the cytosol and promotes reverse transport. *J Neurosci* 15: 4102–4108, 1995.
45. **Sulzer D, Sonders MS, Poulsen NW, Galli A.** Mechanisms of neurotransmitter release by amphetamines: a review. *Prog Neurobiol* 75: 406–433, 2005.
46. **Sundaresan K, Ziemann U, Stanley J, Boutros N.** Cortical inhibition and excitation in abstinent cocaine-dependent patients: a transcranial magnetic stimulation study. *Neuroreport* 18: 289–292, 2007.
47. **Tombaugh TN, Kozak J, Rees L.** Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol* 14: 167–177, 1999.
48. **Toomey R, Lyons MJ, Eisen SA, Xian H, Chantarujikapong S, Seidman LJ, Faraone SV, Tsuang MT.** A twin study of the neuropsychological consequences of stimulant abuse. *Arch Gen Psychiatry* 60: 303–310, 2003.
49. **NODC.** *Amphetamines and Ecstasy: 2011 Global ATS Assessment*. Viena, Austria: United Nations Office on Drugs and Crime, 2011.
50. **UNODC.** *World Drug Report*. New York: United Nations Office on Drugs and Crime, 2009.
51. **Vickers D, Nettelbeck T, Willson RJ.** Perceptual indices of performance: the measurement of "inspection time" and "noise" in the visual system. *Perception* 1: 263–295, 1972.
52. **Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, Logan J, Franceschi D, Gatley J, Hitzemann R, Gifford A, Wong C, Pappas N.** Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry* 158: 2015–2021, 2001.
53. **Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, Gatley SJ, Miller E, Hitzemann R, Ding YS, Logan J.** Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *J Neurosci* 21: 9414–9418, 2001.
54. **Volkow ND, Chang L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi D, Sedler MJ, Gatley SJ, Hitzemann R, Ding YS, Logan J, Wong C, Miller EN.** Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry* 158: 377–382, 2001.
55. **Wechsler D.** *Wechsler Adult Intelligence Scale* (revised). New York: Psychological Corp., 1981.
56. **Wechsler D.** *Wechsler Memory Scale* (revised). New York: Psychological Corp., 1987.
57. **Yamamoto BK, Bankson MG.** Amphetamine neurotoxicity: cause and consequence of oxidative stress. *Crit Rev Neurobiol* 17: 87–117, 2005.
58. **Yamamoto BK, Moszczynska A, Gudelsky GA.** Amphetamine toxicities: classical and emerging mechanisms. *Ann NY Acad Sci* 1187: 101–121, 2010.
59. **Ziemann U.** TMS and drugs. *Clin Neurophysiol* 115: 1717–1729, 2004.
60. **Ziemann U, Bruns D, Paulus W.** Enhancement of human motor cortex inhibition by the dopamine receptor agonist pergolide: evidence from transcranial magnetic stimulation. *Neurosci Lett* 208: 187–190, 1996.
61. **Ziemann U, Rothwell JC.** I-waves in motor cortex. *J Clin Neurophysiol* 17: 397–405, 2000.