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Dysbalance of cortical inhibition and excitation in abstinent cocaine-dependent patients☆

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ABSTRACT

The effects of chronic cocaine dependence on cortical inhibitory/excitatory processes are not well characterized. Employing transcranial magnetic stimulation measures of motor cortical excitability, we have previously reported an elevation of motor threshold (MT) suggesting reduced excitability and an increased long-interval intracortical facilitation (LICF) suggesting increased excitability. In the current study, we used an expanded battery of TMS cortical excitability measures to further examine motor cortex excitability in a larger sample of well-characterized and closely monitored for drug use, abstinent cocaine-dependent subjects ($N = 52$) and healthy controls ($N = 42$). Furthermore, coil-to-cortex distance was assessed in a subsample of both groups. We verified that long-interval intracortical facilitation (LICF), possibly representing glutamatergic cortical neurotransmission, was significantly increased in cocaine-dependent patients. Significantly longer cortical silent periods (CSP) and elevated MT were also observed while there was no significant abnormality in long-interval intracortical inhibition (LICI). Increased LICF and CSP duration suggest increased cortical excitability and increased inhibition, respectively, of different neurotransmitter systems in cocaine-dependent patients. Increased MT might reflect an adaptation to those effects of cocaine abuse that enhance cortical excitability. Overall, the data point to the complex nature of chronic cocaine dependence on the balance of cortical inhibitory/excitatory mechanisms.

1. Introduction

The effects of chronic cocaine use on cortical excitability in humans are not well characterized. Understanding of the chronic effects of cocaine dependence on cortical inhibitory and excitatory mechanisms is likely to be important not only for understanding the disorder itself, but also for the development of treatment and rehabilitation programs. Transcranial magnetic stimulation (TMS) provides a noninvasive and safe method to examine cortical excitation and inhibition in humans (Barr et al., 2008; Ziemann and Hallett, 2007). The current study optimized TMS assessments to shed new light on paucities in the literature.

When a TMS pulse of sufficient strength is delivered to the motor cortex, the corticospinal pathway is activated and the muscles represented by the stimulated region twitch. The threshold intensity of the magnetic pulse necessary to induce a motor response (motor threshold or MT) is thought to reflect voltage-gated sodium channel conductivity and hence membrane excitability in cortical pyramidal neurons (Ziemann et al., 1996a). Drugs that block voltage-gated ion channels, but lack significant action on neurotransmitter function, increase MT (Ziemann et al., 1996a). Glutamatergic facilitation and GABA(B) receptor-mediated inhibition can be studied in human motor cortex by long-interval paired-pulse TMS protocols (McDonnell et al., 2006; Nakamura et al., 1997). Long-interval intracortical facilitation (LICF) at an interstimulus interval of 25–30 ms most likely reflects glutamatergic mechanisms (Nakamura et al., 1997), similar to paired-pulse facilitation of excitatory postsynaptic currents mediated by glutamatergic receptors in animal preparations (Clark et al., 1994). Long-interval intracortical inhibition (LICI) at an interstimulus interval of 50–150 ms is enhanced by baclofen, a specific GABA(B) receptor agonist, and therefore reflects GABA(B) receptor-mediated cortical inhibition (McDonnell et al., 2006).

Another widely used TMS-based cortical excitability measure is the cortical silent period (CSP). This silent period represents a transient absence or significant decrement of EMG activity during

☆ Data were collected at the Clinical Electrophysiology Laboratory, Wayne State University, Detroit, MI, USA.

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sustained voluntary muscle contraction and can be induced by TMS over the motor cortex area. Evidence suggests that the CSP duration reflects motor cortical inhibition possibly mediated by GABA(B) receptors (Siebner et al., 1998). A significant correlation between the P50 suppression and CSP has been shown in healthy individuals (Möller et al., 2007).

Using single-pulse TMS, we have previously observed that MT is significantly elevated in abstinent cocaine-dependent subjects as compared to age and gender matched healthy controls (Boutros et al., 2001, 2005). This finding does not appear to concur with evidence for increased excitability (Lason, 2001) and decreased inhibition (Fein et al., 1996) in cocaine-abusing individuals. Subsequently, using a paired-stimulus protocol, we demonstrated exaggerated motor cortical excitability in a relatively small sample of abstinent chronic cocaine users (Sundaresan et al., 2007). The enhanced long-interval intracortical facilitation (LICF) most likely reflects increased glutamatergic neurotransmission.

In the current study, we used an expanded battery of TMS cortical excitability measures in a relatively large sample of well-characterized and closely monitored for drug-use abstinent cocaine-dependent subjects. We hypothesized that either increased LICF and/or decreased LICI, as markers of enhanced cortical excitability, will be detected. An important new feature of the current study was the assessment of coil-to-cortex distance (CCD) in a subsample of both subject groups.

2. Materials and methods

52 cocaine-dependent individuals (48 men; mean age: 42 years, range 21–57 years) and 42 healthy controls (34 men; mean age: 41 years, range 23–57 years) were examined. The study was approved by Wayne State University Human Investigations Committee. Based on a Structured Clinical Interview for DSM-IV all cocaine-dependent subjects met criteria for dependence on cocaine but without meeting criteria for dependence on other substances. Subjects were excluded if they had a history of non-cocaine related Axis-I psychiatric disorders. Additionally, subjects with known Axis-II diagnoses were excluded based on available medical records. None of the subjects were receiving any CNS-active medications. All cocaine-dependent subjects were free of cocaine use for at least three weeks (mean abstinence duration: 4.13 ± 2.64 months). None of the subjects had a history of any neurological disorders. All cocaine-dependent subjects were recruited from treatment and/or long-term rehabilitation programs which routinely employ random urine drug screens and were able to verify the duration of abstinence obtained as self-report from the subjects. A urine screen was obtained from all subjects in the morning of the study. None of the subjects exhibited outward evidence of stress (i.e., perspiring or agitation), as stress could have a possible effect on laboratory measurements (White et al., 2005). All subjects completed the procedure without complaints or side effects.

The Cocaine Experience Questionnaire (CEQ)(Satel and Edell, 1991) was administered by trained raters in order to determine whether a subject had experienced paranoid symptoms during cocaine use. An analog scale (range 0–6) assessed the psychotic experience itself ranging from minimally distressing to intolerable and terrifying. Scores of 5 or 6 on this sub-scale indicate a frankly psychotic experience. Insight, behavioral severity and behavioral response to CIP were assessed using CEQ.

TMS testing was divided over two sessions, one session in each of two separate days, being not more than one week apart. One hemisphere was measured in one session, and the other hemisphere in the other session, with the order of hemispheres randomized. Motor responses were recorded from the right and left first dorsal interosseus (FDI) muscles, using surface electromyogram (EMG) electrodes (bandpass filter 1 Hz–2 kHz, sampling rate 5 kHz). Motor evoked potential (MEP) amplitudes were measured peak-to-peak. A figure-of-8, hand-held coil was used to deliver monophasic magnetic pulses generated by a Magstim magnetic stimulator. TMS was applied to the left and right motor cortex as guided by the ten/twenty EEG placement position of C3 and C4, respectively; the optimal site for stimulation of the FDI was determined using a search procedure (Rossini et al., 1999).

2.1. Motor thresholds

Starting at a stimulus intensity that was below the MT, single pulses were delivered. The strength of the stimulus was incremented by 5% until a motor response was obtained. Subsequently, 1% increments/decrements were used for the final determination of resting motor threshold (RMT), which was defined as the lowest stimulus intensity (in % of maximum stimulator output) that elicited at least five small MEPs (greater than 50 μV) out of ten consecutive stimulations and is given as a percentage of the maximum output of the magnetic stimulator.

Active motor thresholds (AMT) were obtained after RMTs were determined. Subjects were asked to use their index finger and thumb to press a lever of a dynamometer to achieve a level of tension 10% of maximum voluntary contraction. Stimulus intensity was then lowered from RMT by 1% increments until the AMT was determined in a similar fashion to RMT. AMT was defined as the lowest stimulus intensity that generated a MEP > 200 μV in at least five out of ten trials.

2.2. Cortical silent period

Subjects were instructed to exert a steady voluntary isometric muscle contraction of the target muscle at 10% maximum effort and to maintain the contraction until told to relax. Ten pulses each at six different intensities (100,110,120,130,140,150% of AMT) were delivered and the conditional averages of the single-trial peak-to-peak MEP amplitudes were used for analysis. The CSP duration was measured in milliseconds in the EMG trace from the onset of the MEP to the end of this period defined as the first point when background EMG was restored to 50% of pre-stimulus EMG amplitude. We followed an automated procedure for CSP determination (Daskalakis et al., 2003), which included squaring of the EMG signal (for enhancement and rectification) and a modified threshold criterion for the CSP offset of 50% of the pre-stimulus EMG level (instead of 25% used in Daskalakis et al., 2003). The EMG pre-stimulus analysis period contained 200 samples (40 ms).

The steadiness of baseline EMG preceding the motor evoked potential (MEP) was assessed by calculating the coefficient of variation of consecutive EMG data points (SD/mean $\times$ 100). The mean MEP amplitude at each intensity was calculated from the responses to ten stimuli.

2.3. Paired-pulse measures

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were tested in the relaxed FDI. The intensity of the conditioning stimulus was 80% of RMT (subthreshold) followed by a suprathreshold test stimulus with intensity of 120% of RMT. Three conditions (10 repeats each) were randomly presented. In the control condition, the test stimulus was given alone. In the other two conditions, the conditioning stimulus was given prior to the test stimulus at ISIs of 3 and 10 ms. SICI and ICF were expressed as the percentage of the mean conditioned MEP amplitude to the