Published in final edited form as:

Drug Alcohol Depend. 2015 December 1; 157: 28–35. doi:10.1016/j.drugalcdep.2015.07.1196.

A comprehensive study of sensorimotor cortex excitability in chronic cocaine users: Integrating TMS and functional MRI data[☆]

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Abstract

Background—Disruptions in motor control are often overlooked features of chronic cocaine users. During a simple sensorimotor integration task, for example, cocaine users activate a larger area of cortex than controls but have lower functional connectivity between the cortex and dorsal striatum, which is further correlated with poor performance. The purpose of this study was to determine whether abnormal cortical excitability in cocaine users was related to disrupted inhibitory or excitatory mechanisms, as measured by transcranial magnetic stimulation (TMS).

Methods—A battery of TMS measures were acquired from 87 individuals (50 cocaine dependent, 37 controls). Functional MRI data were acquired from a subset of 28 individuals who performed a block-design finger tapping task.

Results—TMS measures revealed that cocaine users had significantly higher resting motor thresholds and higher intracortical cortical facilitation (ICF) than controls. There was no between-group difference in either measure of cortical inhibition. Task-evoked BOLD signal in the motor cortex was significantly correlated with ICF in the cocaine users. There was no significant difference in brain-skull distance between groups.

Conclusion—These data demonstrated that cocaine users have disrupted cortical facilitation (as measured with TMS), which is related to elevated BOLD signal. Cortical inhibition, however, is largely intact. Given the relationship between ICF and glutamatergic agents, this may be a potentially fruitful and treatable target in addiction. Finally, among controls the distance from the scalp to the cortex was correlated with the motor threshold which may be a useful parameter to integrate into therapeutic TMS protocols in the future.

[☆]Supplementary materials for this article can be found by accessing the online version of this paper.

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Authors' contribution

This study was designed by CH and MSG. Initial data collection was done by WD, CH and XL. Analysis was performed by LD, JW, BS, and CH. All authors contributed to the interpretation of the data and composition of the manuscript. All authors have approved the final manuscript.

Conflict of interest

The authors report no biomedical financial interests or potential conflicts of interest.

Keywords

Addiction; Brain stimulation; Electrophysiology; Recruitment curve; Cortex

1. Introduction

Movement disturbances are often overlooked consequences of chronic cocaine abuse. For example, acutely, cocaine causes a hyperkinesia including pronounced dyskinesias, lip-smacking, rapid speech, and punding. Chronic cocaine consumption leads to a decrease in dopamine and norepinephrine binding in the dorsal striatum of non-human primates (Porrino et al, 2004) – a critical motor control hub, which receives input from the premotor cortex and sends information to the motor cortex via the thalamus. Although there are few large studies of motor control in chronic cocaine users, many smaller studies have demonstrated that chronic stimulant use is related to extrapyramidal symptoms – including tics, dystonia, and dyskinesia (Bauer, 1996; Pascual-Leone and Dhuna, 1990; Tanvetyanon et al., 2001; Preller et al, 2013).

Human neuroimaging studies have demonstrated that chronic cocaine users have less functional segregation in their dorsal versus ventral striatum relative to controls (Hanlon et al., 2009), and that low frontal–striatal functional connectivity in these individuals is related to poor motor function. Cocaine users have slower reaction times and make more errors than their non-drug using counterparts, and this is associated with a larger, more diffuse pattern of blood oxygen level dependent (BOLD) signaling in the primary motor cortex (Hanlon et al., 2010). The decrease in functional connectivity between cortical motor control regions (premotor and primary motor cortex) and the striatum (caudate, putamen) when cocaine users are performing a simple movement task is directly correlated with slower reaction times (Hanlon et al, 2011). It is unclear if this aberrant pattern of motor cortex BOLD signal is associated with abnormally elevated cortical facilitation (e.g., through higher glutamatergic tone) or abnormally attenuated cortical inhibition (e.g., through lower GABAergic tone).

One of the few techniques available to directly measure cortical excitability in humans is paired-pulse transcranial magnetic stimulation (TMS) (Table 1; reviews see Chen, 2000). Through this technique it is possible to measure intracortical inhibition (ICI) (a surrogate of GABA) and intracortical facilitation (ICF) (a surrogate of glutamate) (Kujirai et al., 1993; Ziemann et al., 1996a). Short inter-stimulus intervals (ISIs = 1–4ms, hereafter SICI) lead to inhibition whereas longer ISIs (8–15 ms, hereafter LICI) lead to facilitation (Kujirai et al., 1993). These tools have now been used to investigate cortical excitability in numerous patients with psychiatric disease (see Barr et al., 2008), and were used in this investigation to measure cortical excitability in cocaine users.

In a series of studies in abstinent cocaine users, Boutros and colleagues have consistently demonstrated that cocaine users have lower baseline cortical excitability (e.g., higher motor thresholds) than non-drug using controls (Boutros et al., 2005, 2001; Gjini et al., 2012; Sundaresan et al., 2007). Specifically, this means that abstinent cocaine users require higher levels of TMS-induced electrical current over the precentral gyrus to achieve a motor evoked

potential (MEP) in their contralateral hand. Although it is theoretically possible that attenuated MEPs in cocaine users are due to peripheral nervous system disruptions or spinal cord transduction abnormalities, this deficit is more likely to be cortical in origin as intracortical circuits are significantly more sensitive to low doses of TMS than corticospinal neurons (Di Lazzaro et al., 2000; Ziemann et al., 1996a). Boutros and colleagues also demonstrated that when the precentral gyrus is primed by a brief subthreshold conditioning pulse, abstinent cocaine dependent individuals have elevated long interval cortical facilitation (LICF) relative to their non-drug using peers (Gjini et al., 2012; Sundaresan et al., 2007). These data suggest that there may be a fundamental disruption in the input/output relationship of the motor cortex in cocaine users, a process which likely depends upon both the balancing influences of glutamate and GABA. To date there have not been any studies that have assessed a full battery of cortical facilitation and inhibition metrics in cocaine users, nor determined whether disruptions in these metrics are associated with changed in motor cortex BOLD signal. Therefore it is difficult to determine if previously observed patterns of elevated motor cortex BOLD signal in cocaine users can be explained by TMS measures of cortical excitability.

The primary goal of this study was to assess motor cortex excitability in a large cohort of current cocaine users. This was achieved by applying a battery of single and paired pulse TMS metrics, including the recruitment curve (an estimate of the cortical excitability dose/response function) to a large group of current cocaine users and age matched controls. A secondary goal was to determine whether elevated BOLD signal in the left and right motor cortex of cocaine users could be replicated and if observed aberrations in these TMS parameters were directly associated BOLD signal in the motor cortex. The potential contribution of cortical atrophy (e.g., a higher brain to scalp distance) to previously observed TMS data (e.g., higher motor threshold in cocaine users) was also assessed.

2. Methods

2.1. Screening

Non-treatment seeking chronic cocaine users and age and gender matched non-drug using controls were recruited from the Charleston, SC metropolitan area via newspaper ads, broadcast messages, and word-of-mouth. Participants provided written informed consent to participate in procedures approved by the Medical University of South Carolina Institutional Review Board (cocaine users: $n = 50$, controls: $n = 37$). They then provided urine samples and were administered the DSM-IV based Mini International Neuropsychiatric Interview, the Beck Depression Inventory (Beck et al., 1996), the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001), the cocaine craving questionnaire (CCQ-brief; Tiffany et al., 1993), and the questionnaire of smoking urges (QSU-brief; Tiffany and Drobes, 1991). The cocaine users had to meet DSM-IV criteria for cocaine dependence, have a positive urine drug screen for cocaine (indicating use within approximately 72 h), and could not meet criteria for dependence on any other class of drugs. Exclusionary criteria for both groups included past-week use of illegal psychoactive drugs (other than cocaine for the cocaine group), present DSM-IV diagnosis for any disorder (other than substance dependence for the

users), current use of prescription medication, AUDIT > 15, >1 pack of cigarettes per day, and lifetime history of head injury with loss of consciousness.

2.2. Transcranial magnetic stimulation (TMS)

The resting motor threshold (RMT) (Borckardt et al., 2006), paired pulse TMS measures (SICI and LICF), cortical silent period (CSP), and the recruitment curve (TMS dose/response relationship) were all measured in a single session which lasted approximately 1 h. For explicit details on the TMS parameters see Supplemental Material.¹ Of the short and long interval paired pulse inhibition and facilitation protocols available LICF (interpulse interval = 15 ms) was chosen based on prior studies that demonstrated cocaine users had abnormal responding on LICF (Gjini et al., 2012; Sundaresan et al., 2007). Those same studies did not find a difference in long interval inhibition, but short interval had not been tested. Consequently we investigated short interval inhibition to sample the parameter space in the literature more completely. The individuals performing the TMS data acquisition and analysis were blind to patient status.

2.3. TMS statistical analysis

As a quality control measure, the data from each individual for each parameter was manually reviewed and checked for missing data. The generalized extreme Studentized deviate (ESD) test (Rosner, 1983) was used to detect outliers in the distribution of data points for each cortical excitability measure that had multiple measurements (SICI, LICF, CSP; all of which had 10 data points per subject). In the event of an outlier in the distribution of values for a single subject on a single parameter, this number was deleted. This occurred 36 times in a data set of 2700 observations [90 participants $\times$ 30 data points for SICI, LICF, CSP per participant]. The data were assessed for normality before commencing subsequent analyses (SPSS 16.0, Statistical Product and Service Solutions Inc., Chicago, IL, USA). Multiple analysis of variance (MANOVA) was used to determine whether there was a main effect or interaction between both group and each of the 5 measures of cortical excitability. Post hoc assessments were performed with independent samples *T*-tests. Results were considered significant at a level of $p < 0.05$. Data are expressed as mean $\pm$ standard deviation. A post hoc analysis was performed using years of education, cigarette usage in the past 2 weeks, current AUDIT score, and BDI score as a covariates in the analysis.

2.4. Structural MRI scan acquisition

T1-weighted structural images were acquired from a subset of these participants after the TMS electrophysiological battery ($n = 28$, 15 cocaine users, 13 controls). Scanning was performed using a 3 T MRI Trio (Siemens Medical, Erlangen, Germany) [MPRAGE, repetition time = 1750 ms, echo time = 4 ms, 1 mm³ voxels]. The brain-to-scalp distance was calculated post hoc for each individual by finding the vector orthogonal to the center of a plane defined by the figure-of-eight coil using theBrainsight coregistration tool. The minimum distance along this vector to the cortical surface was recorded for each individual.

¹Supplementary material can be found by accessing the online version of this paper.

Two-group Students *T*-test was used to determine if there was a difference in brain–scalp distance between the cocaine users and the controls. Pearson’s linear correlation was used to determine if there was a relationship between brain–scalp distance and the electrophysiologic measures (MT, SICI, LICF, CSP).

2.5. Functional MRI task and scan acquisition and analysis

The finger-tapping task was identical to a task used in prior studies by our laboratory (Hanlon et al., 2010). Briefly, participants were required to watch a movie of right hand finger tapping movements on a monitor and mimic the ongoing actions with their own fingers. Their responses to the ongoing visual cues were recorded with an MR compatible response box placed under their right hand. Each participant performed 2,6 min trials in the scanner during which they were required to mimic the ongoing finger-tapping sequences with their dominant, right hand in 30 s blocks interspersed with 30s rest periods. Following each rest block there was also a 9s preparation block in which the participant received a preparation cue which counted down the number of seconds remaining before the motor task began again. This preparation block was modeled separately in the statistical analysis and was used to eliminate the effects of attentional set-shifting to the visuo-motor performance data acquired in the task block.

A total of 236 co-planar functional images were acquired using a gradient echoplanar sequence (TR = 3000ms, TE = 40ms, voxel dimensions 3.0 mm × 3.0 mm × 3.0 mm, imaging matrix 64 × 64 voxels). Preprocessing and whole brain image analysis was conducted with SPM8 (Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab 7.14 (MathWorks, Natick, MA). Preprocessing steps included: realignment to the mean, coregistration of the T1-weighted structural scan and the mean realigned image, normalization to standard space (Montreal Neurological Institute template), and 8 mm Gaussian smoothing. Time series analyses were performed individually using a boxcar model convolved with the canonical hemodynamic response function. Statistical contrast maps were made for each individual comparing brain activity in movement blocks to rest blocks. These data were modeled across all subjects in order to obtain a voxel-based representation of brain areas being used to perform the task for each group.

Group level differences between movement and rest were calculated using second-level, random-effects analyses of the first-level contrasts for the entire sample (FWE corrected cluster $p < 0.05$). Random-effects analyses of were then performed with the RMT and LICF TMS parameters as regressors. (Note: given that this was a secondary aim of the study, only the parameters which were significantly different between the cocaine users and controls in the primary TMS analysis were included as regressors in the general linear model). Regressions were performed separately for the controls and for the cocaine users given the difference in the motor cortex BOLD signal between groups. All reported results for the regressions had to be in clusters that met significance at $p < 0.05$ corrected for multiple comparisons (determined by Monte Carlo simulation; voxel-level threshold of $p < 0.005$ for at least 26 contiguous voxels; Alphasim in REST toolbox). As with the TMS data, the individuals performing the fMRI acquisition and data analysis were blind to patient status.

3. Results

3.1. Participants

There was no significant difference in age or gender between the groups [cocaine users: 36.1 ± 8.2 years old, 44% female; controls: 33.0 ± 9.0 years old, 52% female]. All individuals stated that they were right hand dominant and used their right hand to complete the study assessments. There was a significant difference in years of education [users: 13.7 ± 2.6 ; controls: 15.8 ± 2.0], cigarette usage in the past 2 weeks [users: 90%; controls: 10%], alcohol use (AUDIT) [users: 7.14 ± 4.03 , controls: 4.15 ± 2.41] and Beck Depression Score (BDI) [users: 7.84 ± 8.22 , controls: 1.34 ± 4.81]. Among the cocaine users, crack-cocaine was the drug of choice for all participants. The age of first use of cocaine was 19.6 ± 4.5 years old, average length of use at the current level was 14 ± 6.2 years and they currently spent an average of $\$326 \pm 85$ /week on crack cocaine. The average cocaine craving score was 4.3 ± 2.2 which corresponds to low craving on the CCQ-brief. The average smoking urge score was 29.7 ± 17.3 which corresponds to relatively low smoking urges. Individuals in the imaging substudy were demographically and psychiatrically similar to the larger population [cocaine users: 36.53 ± 8.70 years old, 13.0 ± 2.6 years of education, 85% cigarette smokers, AUDIT: 7.00 ± 4.68 ; BDI: 6.92 ± 6.49 ; controls: 34.92 ± 7.83 years old, 16.4 ± 1.6 years of education, 0% cigarette smokers, AUDIT: 3.445 ± 2.62 ; BDI: 2.0 ± 2.79].

3.2. Cortical excitability

Overall, there was a significant interaction between group (users, controls) and measures of cortical excitation (RMT, SICI (% change in MEP amplitude), LICF (% change in MEP amplitude, CSP (length of the silent period)) ($F(4,71) = 3.2583.211$, $p < 0.001$). Specifically, the cocaine users had significantly higher motor thresholds (RMT) (44 ± 6.4) than did the controls (39.7 ± 5.4 ; $t = 2.17$, $p = 0.033$) as expressed by percent of Magstim Bistim machine output (Fig. 1A). They also had significantly higher long interval cortical facilitation (LICF) ($77\% \pm 35$) than controls ($32\% \pm 15$; $p = 0.006$) as expressed by percent increase in the amplitude of the MEP following an unconditioned pulse (Fig. 1B). These differences between the groups were not significantly correlated with education, smoking, AUDIT, CCQ-brief, QSU-brief, or BDI scores.

There were no significant group differences on either measure of cortical inhibitory tone (SICI, CSP). Specifically, the average cortical silent period was 174 ms (± 47) in the cocaine users and 162 ms (± 42) in the controls ($t = 1.2$, $p = 0.2$) (Fig. 1C). Short interval cortical inhibition was -25% (± 31) in the cocaine users and -34% (± 25) in the controls ($t = 0.9$, $p = 0.3$) (Fig. 1D). Including years of education, smoking, AUDIT, and BDI scores in the model did not reveal any group differences for either CSP or short interval cortical facilitation.

3.3. TMS dose/response relationship

Additionally, slope of the recruitment curve, a measure of the relationship of cortical input (via TMS) to MEP output, was steeper in cocaine users ($0.17\text{mV} \pm 0.11$) than controls ($0.12\text{mV} \pm 0.09$; Fig. 2).

3.4. Relationship of TMS parameters to brain–scalp distance

Of the subset of participants that also received an MRI ($n = 28$; cocaine users: $n = 15$; 10 males, 5 females; controls: $n = 13$; 5 males, 8 females), the average motor threshold in these subgroups was 47.13 ± 7.81 for the cocaine users and 41.46 ± 6.25 for the controls. There was no significant difference in brain to scalp distance between the cocaine users (7.87 ± 1.90) and the controls (6.91 ± 1.31 ; Fig. 3A).

There was a significant correlation between motor threshold and brain–scalp distance for the controls ($r = 0.66$, $p = 0.014$). There was no significant relationship, however, within the cocaine users ($r = 0.24$, $p = 0.389$) or for the entire population as a whole ($r = 0.29$, $p = 0.134$; Fig. 3B). A linear regression with age and audit scores as control variables and brain to scalp distance as a predictive variable failed to find a significant relationship with motor threshold, SICI, LICF, or CSP.

3.5. Task-evoked BOLD signal in cocaine users and controls

During the finger tapping task controls had significant clusters of activity in the left primary visual cortex [T -value: 9.58, x, y, z : -46, -76, 0, cluster size: 1113], right primary visual cortex [T -value: 9.37, x, y, z : 46, -70, -2, cluster size: 439, and the left primary motor cortex (the brain region hypothesized to be most active) [T -value: 9.25, x, y, z : -56, 4, 34, cluster size: 715]. A similar group of regions were activated for the cocaine users including the left primary visual cortex [T -value: 9.42, x, y, z : -44, -76, 10, cluster size: 498], right primary visual cortex [T -value: 9.79, x, y, z : 46, -70, 0, cluster size: 1116, and the left primary motor cortex (the brain region hypothesized to be most active) [T -value: 9.12, x, y, z : -54, 4, 34, cluster size: 2132]. Additionally, cocaine users also had significant BOLD signal in the right primary motor cortex [T -value: 9.78, x, y, z : 50, 8, 26, cluster size: 1268]. Relative to the controls, cocaine users had significantly higher activity in the right and left primary motor cortex, consistent with prior studies that have used this task (Hanlon et al., 2010, 2011).

3.6. Relationship between TMS parameters and BOLD signal in the motor cortex

Second level random effects analysis revealed that within the controls, neither RMT nor LICF were positively nor negatively correlated with BOLD signal anywhere in the brain. This may be due to low within-group variability in RMT and LICF parameters in this healthy group. Within the cocaine users there was not a significant relationship between RMT and task-evoked BOLD signal, but there was a significant positive correlation between LICF and task-evoked BOLD signal in the left and right motor cortex. Specifically, individuals with the highest LICF values also had the highest BOLD signal associated with the motor task (Fig. 4).

4. Discussion

The data from this multimodal investigation of motor cortex excitability and task-evoked BOLD signal in cocaine users largely replicates data from prior TMS studies and functional MRI investigations of sensorimotor cortex excitability in smaller cohorts of cocaine users. More importantly, this investigation unites these two bodies of research, demonstrating that

the elevated bilateral motor cortex BOLD signal observed in cocaine users during a simple motor task is directly related to amplified cortical facilitation in these individuals. Consistent with studies in abstinent cocaine users (Boutros et al., 2005; Gjini et al., 2012; Sundaresan et al., 2007), these non-treatment seeking cocaine users had lower resting motor thresholds and higher TMS-primed cortical excitability (LICF) than controls. There was, however, no significant difference in cortical inhibitory tone. The results of this investigation suggest that non-invasive TMS measures of LICF are a valid surrogate of motor cortical BOLD signal. Given that ICF can be manipulated by glutamate-sensitive pharmacotherapeutics – an active area of preclinical pharmaceutical development in addiction – these data made provide a foundation for future translational research efforts in this area.

The role of glutamate in initiating, maintaining, and reinstating cocaine use after a period of withdrawal is a very active area of basic science research in addition. There have been a number of recent reviews detailing many of the changes in this system in animal models of addiction (Kalivas and Volkow, 2011; Wolf, 2010). Preclinical studies in rodents that have chronically self-administered cocaine have demonstrated that electrical stimulation to the prefrontal cortex can induce psychomotor slowing, a decrease in subcortical glutamate, and a selective decrease in cocaine choice behavior (Levy et al., 2007). Additionally, alterations in GABA following acute and chronic cocaine exposure are also well-known. Basic science studies have demonstrated that cocaine produces an inhibitory effect on GABAergic neurons and decreases GABA release in the ventral tegmental area of the thalamus and the striatum (Cameron and Williams, 1994; Centonze et al., 2002). From a therapeutic perspective multiple GABAergic drugs have been investigated including Gamma-vinyl GABA (Vigabatrin®), gabapentin, topiramate, and baclofen (see Xi and Gardner, 2008). Whether GABAergic agents or glutamatergic agents show more promise as therapeutic agents for cocaine dependence is not clear.

Although we did not give the cocaine users any pharmacotherapeutics in this study, prior studies have demonstrated a causal relationship between TMS electrophysiological metrics and pharmacotherapeutics (see Bunse et al., 2014). Long interval cortical facilitation appears to be an indirect measure of glutamate and pyramidal cell activity in the cortex and changes in LICF over time are considered a surrogate of cortical plasticity (Chen et al., 1998). Resting motor threshold (RMT), however, likely reflects the excitability of neuronal membranes since voltage-gated sodium-or calcium-channel blockers increase motor threshold (Boroojerdi, 2002; Li et al., 2004; Tergau et al., 2003; Ziemann, 2004; Ziemann et al., 1996b), and it can be manipulated with ion-channel blockers, such as lamotrigine (Li et al., 2009, 2004; Manganotti et al., 1999; Ziemann et al., 1996b). Of the measures of cortical inhibitory tone, CSP is sensitive to GABAB agents (e.g., Baclofen) (Hattemer et al., 2006; Reis et al., 2006), whereas SICI is sensitive to increased GABA_A function (e.g., benzodiazapines) (Reis et al., 2008).

From a cortical excitability perspective, cocaine users had consistent differences in both measures of cortical excitability that have been related to glutamate but no differences in cortical excitability measures that have been related to GABA. These data are largely consistent with results from other studies that have addressed each of these tests independently (Boutros et al., 2005; Gjini et al., 2012; Sundaresan et al., 2007). The

presence of higher TMS-primed cortical excitability (LICF) than controls, but intact cortical inhibitory tone suggests that the pathology may be related more directly to glutamate (cortical facilitation) than to GABA (lack of inhibition). Given the evidence that GABAergic therapeutics may be helpful to cocaine users, it was surprising that we did not observe any differences in the cortical silent period or the paired pulse inhibition. Furthermore, Gjini and colleagues have observed both longer paired pulse facilitation (consistent with our study) and longer cortical silent periods (different from our study) in abstinent cocaine users. While the divergence of our results with regards to the cortical silent period are not clear, this may be related to the participant selection, wherein they observed longer inhibition in individuals that have been abstinent from cocaine for at least 3 weeks, which is a very unique subset of formally cocaine dependent individuals. These data suggest that there may either be (1) unique cortical features of individuals that are able to achieve longer term abstinence or (2) that the abstinence process itself is a dynamic period for cortical inhibitory mechanisms.

Beyond the cross-sectional markers of disrupted cortical facilitation we have, for the first time, demonstrated that the TMS recruitment or dose/response curve (a causal relationship between TMS induced input and evoked motor output) is steeper and “shifted to the right” in cocaine users. That is, it takes a larger dose of TMS to evoke a consistent motor output in the cocaine users, but once that critical dose is achieved (aka motor threshold) the cocaine users have an amplified behavioral response relative to controls. The specific contributions neurotransmitters to the shape of the recruitment curve are not well understood. However, it likely requires a complex orchestration of both cortical excitatory and inhibitory mechanisms (including ionotropic and metabotropic receptor transmission). Prior studies have demonstrated that the slope of the recruitment curve is related to the input–output properties of motor neurons (Devanne et al., 1997) and can be altered by active motor training (Lotze et al., 2003).

While the last two decades have seen TMS advance significantly as a tool to probe the function of the healthy brain as well as patients with various brain disorders, it has limited potential as a stand-alone technique. Hence, there are a growing number of TMS studies which incorporate other modalities for investigating brain function (including EEG, PET, NIRS, and MRS; Ziemann, 2011). Two other investigations of TMS and BOLD signal have found relationships between TMS measurements and BOLD signal. Talelli et al. (2008) for example, demonstrated that interhemispheric inhibition was directly related to evoked BOLD signal among 27 healthy controls when there was a 40 ms delay between the priming pulse and the test pulse. Sarfeld et al. (2012) demonstrated that evoked BOLD signal in the motor cortex was related to resting motor threshold among 17 healthy controls. The present manuscript demonstrates that paired pulse cortical facilitation (a measure of cortical excitability) is correlated with task-evoked BOLD signal (an indirect measurement of cortical activity related to oxygen consumption) in cocaine users. We did not however observe a significant linear nor non-linear correlation between these parameters within our subset of 13 healthy controls that received both modalities. This may be due to low variance in LICF values within this healthy population. In the cocaine users however, the range was larger for both LICF and for BOLD signal, thereby enable a higher likelihood of detecting a true positive. With respect to resting motor threshold, we did not find a relationship with BOLD signal as Sarfeld et al. (2012) found in healthy controls, but this may be related to

differences in the task and the careful calibration they performed for force (whereas our task was one that required less attention to force and more attention to visuo-motor integration). A sample of 13 individuals however is likely not sufficient to make definitive conclusions about this lack of an observed effect. Consequently, these data should be interpreted with caution.

Finally, another very important observation from this study is that there was a correlation between resting motor threshold and the scalp to cortex distance. While this is not the first time this relationship has been observed (Kozel et al., 2000), nor is it surprising given the basic relationship between the power of an induced magnetic field and distance (Maxwell, 1865), it is a parameter which is often ignored in both human laboratory studies of TMS as well as therapeutic TMS studies (including depression, pain, and addiction). As the field of therapeutic brain stimulation moves forward and continues to refine its technology and sophistication, parameters such as scalp to cortex distance will be integral to developing a maximally effective therapy.

The primary limitations of this study are that it is a cross-sectional investigation of cocaine users relative to controls that were matched based on age and gender but not concurrent nicotine and alcohol use. Although none of the cocaine users were dependent upon any substance other than cocaine, as with most human laboratory studies, the cocaine users smoked tobacco and drank alcohol more often than the controls. Although the post hoc analyses did not demonstrate that differences in these variables were responsible for the observed group effects, it is possible that other non-specific effects that occur with using multiple substances (both central nervous system stimulants and depressants) may contribute to the differences in cortical excitability observed at both baseline and in the cortically primed state. Future investigations with more extensive control groups, and those that quantify the measure of urine or serum cocaine metabolites are necessary in order to probe this question further.

The results of this study provide a foundation for future studies which may use these data to address the effect of a pharmaceutical agent on cortical facilitation, the shape of the TMS dose/response relationship, and the inferred changes in BOLD signal in the cortex. However, until we can robustly cross-validate the results of these TMS excitability studies with a measure of cortical chemistry, it is prudent to realize that these are surrogates of cortical excitability rather than direct measurements. Although several studies have used TMS to address cortical excitability in rodents (see Vahabzadeh-Hagh et al., 2012), with current technology it is difficult to make a coil small enough to activate a localized region of cortex reliably without the coil overheating. With the ongoing technical developments in magnetic resonance spectroscopy however, it may be possible to determine whether there is a direct link between TMS excitability measures, task-evoked BOLD signal, and cortical chemistry. This would enhance our understanding of cortical plasticity that occurs following chronic cocaine use, as well as the cortical plasticity that occurs following a stroke (wherein loss of laterality and altered frontal–striatal connectivity is also an active area of research (Cramer, 1999; Cicinelli et al., 1997; Hanlon et al., 2005).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to acknowledge Melanie Canterbury, Daniel Tagge, and Spencer Bell for assisting in the preparation of this manuscript.

Funding

Funding was provided by NIDA K01DA027756 (Hanlon), R01DA036617, and MUSC's CTSA UL1 RR029882 from the National Center for Research Resources. The funding source had no further role in study design, collection, analysis, interpretation or in the decision to submit the paper for publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.drugalcdep.2015.07.1196>.

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Fig. 1.

Cortical excitability in cocaine dependent individuals and non-drug using controls. The average value and standard error are plotted for measures of cortical excitatory tone {resting motor threshold (A), long interval cortical facilitation (B)}, and cortical inhibitory tone {cortical silent period (C), short interval cortical inhibition (D)} for cocaine users (black bars) and controls (gray bars).

Fig. 2.

TMS dose/response curve. The relationship between TMS intensity (percentage of that individual's resting motor threshold (RMT)) over the left primary motor cortex and the average motor evoked potential in the right anterior pollicus brevis muscle. The average and standard error for the mean is plotted for each interval (90–130%) for cocaine users (black line) and controls (gray line).

Fig. 3.

Relationship between brain to scalp distance and motor threshold. The distance from the cortical surface (mm) to the position of the TMS coil over the left primary motor cortex was compiled for cocaine users (black triangles) and controls (gray circles) (A). There was no significant difference between the groups. The relationship between this distance and resting motor threshold is also displayed (B) along with linear trendlines plotted for the cocaine users and the controls. Although there was a trend toward significance in the controls there was no significant relationship within the cocaine users or across the entire sample of participants.

Fig. 4.

Relationship motor cortex facilitation and task-evoked BOLD response in cocaine users. Among the cocaine users there was a significant positive correlation between left primary motor cortex long interval cortical facilitation (LICF, as measured by TMS) and task-evoked BOLD signal in the left and right primary motor cortex during a basic finger tapping task with the right hand. Coronal slices are shown which demonstrate the 2 clusters significantly correlated with LICF in the cocaine users (SPM8, random effects analysis, corrected clusters at $p < 0.005$, T -values displayed on colorbar, L = left).

Table 1

A brief summary of TMS measures of cortical excitability and their relationship to neurotransmitters.

TMS measure	Motor evoked potential (MEP) (right anterior pollicus brevis following TMS to the left motor cortex)	Pharmacology involved	Select references
Resting motor threshold (the amplitude of TMS input required to evoke an MEP 50% of the trials)		Ion channels (voltage gated Na+, AMPA glutamate)	Di Lazzarro et al. (2008) and Ziemann and Rothwell (2000)
Paired pulse facilitation (long interval facilitation, 15 ms)		Glutamate (AMPA, NMDA)	Reis et al. (2008)
Paired pulse inhibition (short interval inhibition, 3 ms)		GABAa	Ziemann et al. (1996a), Di Lazzaro et al. (2000) and Korchounov et al. (2005)
Cortical silent period		GABA _B , dopamine	Ziemann (2004)

Note: this is a sample of studies that have found a relationship and not an exhaustive list of studies that have sought a correlation (some of which have not found a direct relationship between these parameters and neurotransmitter levels).