Published in final edited form as:

Drug Alcohol Depend. 2012 January 1; 120(1-3): 41–47. doi:10.1016/j.drugalcdep.2011.06.022.

MDMA (Ecstasy) association with impaired fMRI BOLD thalamic coherence and functional connectivity*

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Abstract

Background—MDMA exposure is associated with chronic serotonergic dysfunction in preclinical and clinical studies. A recent functional magnetic resonance imaging (fMRI) comparison of past MDMA users to non-MDMA-using controls revealed increased spatial extent and amplitude of activation in the supplementary motor area during motor tasks (Karageorgiou et al., 2009). Blood oxygenation level dependent (BOLD) data from that study were reanalyzed for intraregional coherence and for inter-regional temporal correlations between time series, as functional connectivity.

Methods—Fourteen MDMA users and ten controls reporting similar non-MDMA abuse performed finger taps during fMRI. Fourteen motor pathway regions plus a pontine raphe region were examined. Coherence was expressed as percent of voxels positively correlated with an intraregional index voxel. Functional connectivity was determined using wavelet correlations.

Results—Intraregional thalamic coherence was significantly diminished at low frequencies in MDMA users compared to controls ($p=0.009$). Inter-regional functional connectivity was significantly weaker for right thalamo - left caudate ($p=0.002$), right thalamo - left thalamus ($p=0.007$), right caudate - right postcentral ($p=0.007$) and right supplementary motor area - right precentral gyrus ($p=0.011$) region pairs compared to controls. When stratified by lifetime exposure, significant negative associations were observed between cumulative MDMA use and

*Supplementary material providing definitions of index and coherent voxel sets can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

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functional connectivity in seven other region-pairs, while only one region-pair showed a positive association.

Conclusions—Reported prior MDMA use was associated with deficits in BOLD intraregional coherence and inter-regional functional connectivity, even among functionally robust pathways involving motor regions. This suggests that MDMA use is associated with long-lasting effects on brain neurophysiology beyond the cognitive domain.

Keywords

Drug abuse; Neuroimaging; Serotonin; Movement; Toxicity

1. INTRODUCTION

Clear and convincing scientific data are needed to strengthen community health and education efforts targeting the ‘recreational’ abuse of MDMA (3,4-methylenedioxymethamphetamine; Ecstasy). Animal models of MDMA exposure result in chronic, dose-dependent, serotonin-selective toxicity affecting both neural structure and function (Green et al., 2003) that endure long after acute effects on serotonin release (Bankson and Cunningham, 2001) have subsided. However, a causal link to impaired serotonin system function in human populations is weakened because these studies involve repeated, high-doses of highly purified drug. Human studies have produced mixed results (Cowan, 2007; Cowan et al., 2008; Seger, 2010), justifying additional studies with novel approaches.

Ligand-based and magnetic resonance neuroimaging studies have examined changes in ligand binding and activation in human MDMA users and control groups in various regions but have failed to show consistent evidence of serotonin-selective toxicity (Cowan, 2007; Cowan et al., 2006, 2007, 2008; Daumann et al., 2003a,b, 2004; Jacobsen et al., 2004; Jager et al., 2007, 2008; Moeller et al., 2004, 2007; Valdes et al., 2006). Because serotonin innervates motor regions and preclinical studies of MDMA administration in rats produced chronic alterations in motor responses (Balogh et al., 2004; Gyongyosi et al., 2008), a recent study examined motor pathways in a human functional imaging study using an event-related, finger-tapping design (Karageorgiou et al., 2009). Blood oxygenation level dependent (BOLD) imaging showed that historical MDMA use was associated with increased spatial extent and amplitude of motor region activation during a finger tapping task, and that changes were directly proportional to lifetime MDMA use (Karageorgiou et al., 2009). These were interpreted as potential representations of inefficient motor region processing. Visual system studies in MDMA users (Bauernfeind et al., 2011) have also suggested MDMA-related cortical dysfunction.

Since evidence suggests that oscillations in serotonin function may be associated with the coordination of neural network events, we reanalyzed the Karageorgiou et al. (2009) BOLD data set for measures of network function, assessing functional properties of motor regions as an integrated system. Effects of serotonin receptor ligands on oscillatory visual functional tasks have been shown previously (Carter et al., 2005; Frescka et al., 2004). Also, recently, diminished raphé-thalamic functional connectivity observed while serotonin function was low during acute tryptophan depletion suggested serotonergic influences on rostral activities (Salomon et al., 2011). We analyzed intraregional functional efficiency, as coherence. In addition, we determined interregional motor pathway temporal correlations using the entire scan time series, commonly referred to as functional connectivity. Functional connectivity is a measure of BOLD activation synchrony between pairs of regions, and is commonly

interpreted as a potential (albeit possibly indirect) activity relationship between regions without assumptions regarding directionality or the existence of a physical, direct pathway.

Diminished synchrony of activities within (coherence) and between motor regions (functional connectivity) was hypothesized for the MDMA group, based on a model associating chronic MDMA use with diminished serotonin function.

2. METHODS

2.1 Overview

Data was reanalyzed from a previously published, Vanderbilt University Institutional Review Board-approved protocol that had examined motor pathways during an event-related analysis (Karageorgiou et al., 2009). Application to the time series analysis was deemed acceptable because: visual cues for finger tapping were identical for each subject during 3T fMRI BOLD data collections from fourteen MDMA users and ten controls; tapping events were completed with similar compliance between groups; individual voxel-wise inspections of BOLD time series records revealed virtually imperceptible changes during tapping events; and similar results were obtained after removing event-related segments from the records. Rationale for region selections, methods for sample characterization, and details of data acquisition were previously reported (Karageorgiou et al., 2009).

Briefly, flyers and other media were used to recruit “Ecstasy or other drug users” for a study of drug effects on the brain. Salient exclusions were for other lifetime Axis I diagnosis, pregnancy, and use of any psychoactive medications for 6 weeks prior to the study. Following phone, clinical and lab screening, participants were to abstain from alcohol and cannabis for 48 hours prior to the scan, and from all other drugs for 14 days. On the scan day, positive urine drug screens (amphetamines, methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, PCP, and tricyclic antidepressants) or alcohol breathalyzer were also cause for exclusion, but MDMA itself was not assayed (Karageorgiou et al., 2009). Other than their MDMA use, the MDMA users differed significantly from the non-MDMA counterparts only in having had greater cocaine exposure (3 of 10 control non-MDMA users reported 3.9 ± 9.7 (as mean $\pm$ SD, throughout) episodes for lifetime, using about 1.0 ± 2.8 g, and cocaine abstinence of 399.7 ± 345.0 days prior to study; 9 of 14 MDMA users reported 26.7 ± 33.2 episodes for lifetime, using about 15.4 ± 26.7 g and cocaine abstinence for 676.5 ± 980.1 days; Mann-Whitney test $p = 0.022$), with no other detected difference in historical abuse. Percent regional signal change during tapping showed no statistically significant correlations with lifetime use of alcohol, cannabis, cocaine, or methamphetamine. Only lifetime alcohol use correlated with changes in percent activated voxels in a subset of regions (left postcentral and left precentral cortex), in addition to the observed changes correlated with MDMA use.

For the present report, the same fourteen motor network regions were defined in Montreal Neurological Institute (MNI) space (Collins et al., 1994). We added a dorsal raphe region because it gives rise to the bulk of serotonergic fibers susceptible to MDMA toxicity (Wilson et al., 1989). Its fibers project to the motor system and have a major role in its function (Jacobs and Fornal, 1997; DeVito et al., 1980; Lavoie and Parent, 1990; McQuade and Sharp, 1997; Wilson and Molliver, 1991). The pontine raphe region was identified using a manual, anatomically-guided boundary selection (Salomon et al., 2011).

The intraregional coherence, and inter-regional functional connectivity analyses used wavelet (Daubechies 1992) correlations detailed below (Salomon et al., 2011; Eryilmaz et al., 2011), with comparisons to finite impulse response (FIR) filtered and unfiltered signals

processed in parallel fashion. Regional coherence and inter-regional functional connectivity were examined for group differences and for a dose-response relationship.

2.2 Participants

The recruitment drew a group of moderate to heavy users of MDMA by exclusion of subjects who self-reported less than 5 tablets of lifetime MDMA use. A Certificate of Confidentiality was obtained from the National Institute on Drug Abuse (NIDA) and participants were informed of the Certificate protections in the informed consent document. Twenty-seven right-handed participants [16 MDMA polydrug users (4 females) and 11 non-MDMA polydrug-using controls (5 females), from 18 to 35 years old (mean 25.2, SD=5.6)] met entry criteria. Twenty-four analyzable motor function studies were completed. Fourteen polydrug MDMA users (four females) reported a minimum of 8 and maximum of 80 episodes of MDMA use (median=24.5), and abstinence for a median of 505 (min=20, max=1938) days. Similar historical use of, and abstinence from, alcohol, methamphetamine, and cannabis were reported, leaving only one potential confound in a differential, although currently inactive, past use of cocaine (MDMA users: median=6 grams, min=0, max=100; non-MDMA users: median=0, min=0, max=9 grams, see Karageorgiou et al. 2009 for additional demographic details). Exclusions were for low accuracy on the behavioral tasks (two participants) and for excessive motion (one participant). All reported abstaining from alcohol and cannabis use for at least 48 h prior to the study day and from all other drugs for at least 14 days.

2.3 fMRI acquisition

A Philips 3T Intera Achieva MRI scanner equipped with a SENSE coil (Philips Medical Systems, Andover, MA, USA) acquired 266-second functional volumes with field echo EPI (BOLD, 130 dynamics, 4.50 mm slice thickness with 0.40 or 0.45 mm gap, 2 s TR, 35 ms TE, 79° flip angle, FOV=240, matrix=128×128). The functional data were coregistered with whole-brain 3-D anatomical T1-weighted/TFE images for each subject (4.6 s TE, 8° flip angle, FOV=256, matrix=256×256, voxel size=1×1×1 mm).

2.4 fMRI preprocessing

The first four volumes were discarded to minimize T1 incursion effects. Using the next volume as a reference in the sequence, BOLD functional data were spatially realigned for motion correction and then coregistered with the anatomical data. Images were normalized to the SPM 152-average MNI T1 template and then smoothed with a full-width half maximum (FWHM) 8 mm Gaussian kernel. For the pontine raphé region, BrainVoyager QX (BV; Brain Innovation, Maastricht, The Netherlands) was used to assess motion with exclusions where movement exceeded 1 mm translation or 1 degree rotation. No smoothing or low pass filter (prior to wavelet filtering) was used in preprocessing the raphé region data. For all regions, the wavelet transform outputs are essentially detrended, except the lowest frequency residual, which was detrended with an effective high pass cutoff of 0.0026 s^{-1} .

2.5 Regions of interest

Fourteen motor-associated regions were identified in MNI space as previously published (Karageorgiou et al., 2009) using an explicit mask (in MarsBaR; Brett et al., 2002), to reduce the number of statistical comparisons with an *a priori* selection of target regions. Selection of motor-relevant regions was based on basal ganglia–thalamo-cortical circuits (Alexander et al., 1990). Seven selected bilateral motor regions in the Statistical Parametric Mapping (SPM) AAL (automated anatomical labeling) toolbox (Tzourio-Mazoyer et al., 2002) included: supplementary motor area (SMA), precentral gyrus (primary motor cortex; MC), caudate, putamen, pallidum, thalamus, and postcentral gyrus (primary sensory cortex).

The pontomesencephalic pontine raphé region, approximating dorsal portions, was manually selected (Salomon et al., 2011) using coregistration with 3D anatomical scans within the first transverse slice where both cerebral peduncles were well-defined immediately superior to the pons, one transverse anatomical slice (1 mm) superior to the isthmus and immediately anterior to the fourth ventricle. Lateral boundaries were defined so that the region width was one third the midbrain width at that level. Height was 3 (mm) anatomical voxels. The inferior border was defined 2 mm anterior to the fourth ventricle (see Baker et al., 1990).

Voxel-wise time series tables for the selected regions were imported into MATLAB (ver. R2009b, Mathworks, Natick, MA) for wavelet-based and other frequency filtering and subsequent analyses.

2.6 Filtering procedures and metric calculations

Custom programmed, high resolution Daubechies 2 orthogonal level 3 wavelet (with 2 vanishing moments) filtering isolated signal power in ultralow ($<0.03 \text{ s}^{-1}$), low (0.03 to 0.06 s^{-1}), medium (0.06 to 0.12 s^{-1}), and high (0.12 to 0.25 s^{-1}) frequency bands (Daubechies, 1992). The discrete wavelet transform (DWT) provides orthogonal sequences that reflect brain activity in octave-scaled frequency bands and can be used as a filtering method. Orthogonal properties of the sequences may decrease risks of exaggerated correlations between sequences. Wavelet methods have been used in several published fMRI reports, each with variations in application of wavelet properties (Bullmore et al., 2004 (review), Salomon et al., 2011, Eryilmaz et al., 2011, Achard et al., 2006, Richiardi et al., 2011). Briefly, as a filter bank, the discrete wavelet transform provides a spectrally filtered time series with natural, softly-defined frequency bands, and with minimal artifact. Application to time series correlations in fMRI is recently gaining attention (see Discussion). Lowpass finite impulse response filtering at 0.08 s^{-1} and raw signal analyses were compared to the wavelet results to confirm and assess generalizability to broader frequency bands.

Details of frequency filtering procedure and analyses of the filtered data matrices have been published previously (Salomon et al., 2011). Stated briefly, functional coherence was determined within each region in order to determine dominant regional activation sequences. The procedure was run separately for each filtered time series. Regional signals were the average time series from the coherent voxels within each region at each frequency band. For functional connectivity, correlations of regional signals from each of 105 possible pairs using the 15 regions were tested, all for each of the four wavelet-derived frequency bands, and also for FIR-filtered and unfiltered signals.¹

2.7 Statistical methods

Statistical analyses were performed in MATLAB (Mathworks, Natick, MA) with packaged functions. Statistical summaries are presented as mean and standard deviation. No singleton outlier values were observed. Tests were considered statistically significant on 2-tailed analysis if $p \leq 0.05$ after Bonferroni correction for multiple comparisons due to testing the data set for four frequency bands, giving a revised p value cutoff of 0.0125 for significance. The non-parametric Wilcoxon Rank Sum test was used for between group comparisons for intraregional coherence and for functional connectivity.

For the within Group Stratification by Lifetime MDMA use, functional connectivity r values for each pairing of the 15 regions were correlated with lifetime MDMA use across the subjects in the MDMA group only. No r -to- z conversion was performed. Statistical

¹Definitions of index and coherent voxel sets can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

significance was based on correlation tables, again with a Bonferroni correction for the four frequency bands.

3. RESULTS

3.1 Recap of published findings

Characterizations of the sample and of fMRI data were previously analyzed and published (Karageorgiou et al., 2009). As noted above, fourteen MDMA polydrug users (4 females) were well-matched for a case-control design with 10 non-MDMA polydrug users (5 females) except that MDMA users had overall greater exposure to cocaine than their non-MDMA counterparts (Mann–Whitney test; $p=0.022$). This presents a possible limitation of these analyses, however, the cocaine use was not active and was not associated with changes in activation spatial extent or amplitude. For the right supplementary motor area, the initial event-related analyses of tapping compared to fixation found greater magnitude ($p=0.035$) and spatial extent ($p=0.026$) of activation in MDMA users than controls. When MDMA group data were stratified by lifetime use, significant increases in event-related signal magnitude were observed in the right putamen ($p=0.044$) and pallidum ($p=0.015$, all without correction for multiple comparisons). Spatial extent of activation was most strongly positively correlated with lifetime MDMA use in the right precentral ($p=0.030$) and post-central ($p=0.013$) gyri and the thalamus bilaterally (left $p=0.032$; right $p=0.009$). The findings were controlled for other drug use, with a suggestion that alcohol use episodes may be correlated with left precentral ($p=0.035$) and post-central ($p=0.045$) spatial extent of activation (Karageorgiou et al., 2009).

3.2 Intra-regional Coherence (Table 1)

Thalamic coherence at low frequencies (range: 0.06 to 0.03 s^{-1}) was significantly weaker in the MDMA group than controls (Wilcoxon Rank Sum, left: MDMA users 71.5%, controls 86.2%, $p=0.010$; right: MDMA users 71.3%, controls 89.3%, $p=0.009$), as confirmed using unfiltered signals (left: MDMA 59.2%, control 78.7%, $p=0.001$, right: MDMA 58.0%, control 80.5%, $p=0.002$). These were consistent with findings using low pass FIR-filtered data (frequencies: $<0.08 s^{-1}$), for the right thalamus (MDMA 72.3%, control 88.0%, $p=0.0123$) but were not supported for the left thalamus. At medium frequencies (range: 0.13 to 0.06 s^{-1}), only right thalamus differences in coherence were significant (MDMA 62.3%, control 80.6%, $p=0.010$). No group differences in coherence for other motor pathway regions, or within the small pontine raphe region, were observed.

The high coherence measures suggest that the index voxel selection method successfully provided a highly representative voxel. Overall, relatively strong mean (across all subjects and regions) regional coherence measures were observed by frequency band (mean of 15 regions from all subjects in each group and standard deviations) across regions: ultralow (control $76.0\% \pm 6.4\%$, MDMA $69.0\% \pm 7.3\%$); low (control $82.9\% \pm 6.7\%$, MDMA $74.6\% \pm 7.5\%$); and medium (control $77.2\% \pm 7.9\%$, MDMA $69.7\% \pm 8.3\%$). The high frequency band (frequency range: 0.25 to 0.13 s^{-1}) showed more modest correlations within the regions (control $50.6\% \pm 10.4\%$, MDMA $44.2\% \pm 12.4\%$), suggesting that noise may be a significant factor in this frequency band, and may account for the paucity of findings in this frequency band.

3.3 Functional Connectivity (Tables 2, 3)

Group-wise comparisons of the 105 functional connectivity pairs showed four region-pairs with significant (after correction for multiple tests) differences between MDMA users and controls. Ultralow ($<0.03 s^{-1}$) frequencies showed only one significant pairing: left caudate – right thalamus (MDMA: 0.11; control: 0.86; $p=.0015$). Likewise, only one significant

pairing was observed at low (0.06 to 0.03 s^{-1}) frequencies: right caudate – right postcentral gyrus (MDMA: 0.38; control: 0.64; $p=.0073$). Two significant pairings were observed at medium ($0.013 - 0.03\text{ s}^{-1}$) frequencies: right supplementary motor area – right precentral gyrus (MDMA: 0.70; control: 0.84; $p=.0107$) and the bilateral thalamic pair (MDMA: 0.65; control: 0.93; $p=.0073$). Functional connectivity was stronger among controls than MDMA users in all four of these pairs (Table 2), confirming a consistent direction of change despite the small number of significant findings compared to the many analyses.

In the within-group analysis stratifying by lifetime use of MDMA, significantly altered functional connectivity was observed in eight region pairs with a negative relationship in seven of the eight pairs, again suggesting losses of functional connectivity associated with MDMA use (Table 3). Only ultralow frequencies (range: $<0.03\text{ s}^{-1}$) showed a positive correlation for right postcentral – pallidum functional connectivity ($r = 0.64$, $p = 0.0128$). Functional connectivity was significantly negatively correlated with lifetime MDMA use for four region pairs at medium frequencies (0.13 to 0.06 s^{-1}): left precentral – postcentral ($r = -0.65$, $p = 0.0121$); interhemispheric putamina ($r = -0.73$, $p=0.003$); left putamen – postcentral ($r = -0.68$, $p = 0.008$); and right putamen – left pallidum ($r = -0.72$, $p = 0.004$). At high frequencies (0.25 to 0.13 s^{-1}), three other functional connectivity pairings were significantly negatively correlated with lifetime use: left precentral – postcentral gyri ($r = -0.71$, $p=0.004$); left thalamus – putamen ($r = -0.65$, $p=0.011$); and right thalamus – postcentral gyrus ($r = -0.82$, $p=0.0003$).

4. DISCUSSION

This re-analysis of an fMRI data set suggests impaired communications within and among brain regions in motor pathways in MDMA users compared to controls, and also among the MDMA users when stratified by lifetime exposure. Findings with these analyses were strikingly more robust than the event-related regional activation amplitudes and geographic spreads from the same data set. Disruptions were represented within and among all three domains of the thalamo-cortico-striatal behavioral control triangle. To our knowledge, this is the first data analysis to show altered functional connectivity in groups of MDMA users. This advances a growing body of literature regarding risks of MDMA use and provides an example of a developing, robust, analytic methodology using wavelet correlations for functional connectivity studies in motor regions.

Thalamic communications were consistently and markedly diminished in MDMA users in comparison to controls and also in the historical MDMA use stratification. Changes in putamen connectivities were also very frequently found. These are consistent with previous blood volume, ligand structural, and functional imaging results that have suggested thalamic, pallidum and putamen changes with MDMA use (Reneman et al., 2000; Obrocki et al., 2002; McCann et al., 2008; de Win et al., 2008a; Karageorgiou et al., 2009; Bauernfeind et al., 2010). Deficits observed here are also consistent with animal models showing MDMA-induced alterations in basal ganglia–thalamo-cortical circuit neurophysiology and with an overall model of diminished 5-HT signaling in the presence of MDMA neurotoxic effects (Colussi-Mas et al., 2008). In considering mechanisms of MDMA use effects on thalamic, striatal, and cortical connectivity, the nature of the putative serotonin dysfunction may reflect quantity or qualities of the signal. Coherence and functional connectivity measures are based on oscillatory activity, and oscillatory serotonin activity has been shown to influence motor pathways (Jacobs and Fornal, 1991, 1995). Losses of thalamic functional connectivity were also observed in remitted (previously depressed) patients during an acute dietary depletion of tryptophan, which transiently but markedly diminishes serotonin availability (Salomon et al., 2011). Losses of pulsatile

patterning may be a stronger marker of diminished serotonin function than the loss of serotonin itself.

Wavelet correlations have been used to study fMRI activation in several studies (Bullmore et al., 2004 (review); Salomon et al., 2011; Eryilmaz et al., 2011; Achard et al., 2006; Richiardi et al., *in press*). Acute tryptophan depletion was analyzed using wavelet filtered BOLD activation time series and showed significantly diminished functional connectivity between the raphe and four cerebral regions, most specifically at low frequencies (0.06 – 0.03 Hz): anterior thalamus, caudate head, anterior cingulate, and habenula (Salomon et al., 2011). Cubic B-spline wavelet correlations were used to analyze data after subjects viewed emotional movies as stimuli (Eryilmaz et al., 2011), showing enhanced resting activity and functional connectivity in the anterior cingulate cortex and insula and diminished functional connectivity (also using wavelet correlations) between ventral-medial prefrontal cortex and amygdala. Cubic Battle–Lemarié wavelets were used recently in a study of functional connectivity for identifying global brain states (Richiardi, *in press*). Comparisons of Daubechies wavelet with finite impulse response (FIR) and other routine filter processing methods, using noisy simulated data sets, suggest favorable signal extraction from noise, with a broader range correlation values contrasting with potentially exaggerated values due to artifacts of other filter methods (Salomon et al., 2008 unpublished).

Caveats in this small study are several, including many that were addressed previously (Karageorgiou et al., 2009): the retrospective, historical basis for estimating MDMA use, mixed substance use histories, and the small sample size. Although subjects were not currently using cocaine, the MDMA group did have greater historical use than the controls. Acutely, cocaine use is known to affect thalamic activation and functional connectivity (Tomasi et al., 2010; Gu et al., 2010). The greater historical use of cocaine among the MDMA group should be considered a potential confound in this work since even distant use could conceivably have chronic, long-lasting effects. Globally, any interpretations of the findings must be cautious due to mixed substance exposures ubiquitous in clinical populations, while noting that the analytic strategy stratifying by MDMA use provides some assurance that non-MDMA-related population differences, between controls and target subjects, are not likely to explain all of demonstrated differences in thalamic functional connectivity with other regions. Additionally, the work here is entirely from post-hoc analyses, so that a confirmation in an independent data set would add credibility.

Diminished thalamic connectivity could be viewed as representing enhanced independence of diverse intrathalamic nuclei included in the region. However, this argument is limited by the spatial and temporal resolutions of these scans. The voxels used here (each with a volume of approximately 35 mm³) each include hundreds of thousands of neurons (estimate based on Kreczmanski et al., 2007). The temporal resolution even for high frequency filtered data is at best about five seconds. It appears unlikely that diminished coherence, measured with these tools, could detect enhanced independence of individual nuclei.

Overall, the decreased proportion of coherent voxels in the thalamus and losses of connectivity with other regions suggests that the coincident increase in amplitude associated with tapping may be due to inefficient and incomplete regional function. This reinforces the argument that additional brain resources are necessary to achieve the same outcome in dysfunctional states (Bondi et al., 2005; Vannini et al., 2007). With increasing MDMA use, there appears to be a chronic and enduring increase in thalamic region activity with less to show for it in global functional connectivity.

Motor system deficits, in contrast to deficits found in frontal cognitive and emotional processing, would not be expected to predispose to judgment defects that might reinforce

substance abuse. Here, the comparison with non-MDMA substance users, the findings on stratification of the MDMA participants by use history, and the use of the motor pathway regions as a focus of study all suggest that differences in MDMA vs. non-MDMA users are not due to *a priori* individual variations in judgment or substance abuse propensity. Although cognitive measures were not obtained, there is no indication that the observed motor pathway changes can be attributed to a pre-MDMA use deficit. Indeed, one prospective study (de Win et al., 2008a) examining individuals before and after MDMA exposure found structural (pallidum, thalamus and frontoparietal white matter) and brain perfusion (pallidum and putamen) changes in novel low-dose ecstasy users.

Known losses of serotonin function related to MDMA in preclinical studies favors a specific effect of MDMA on fine-diameter dorsal raphé fibers (Cowan et al, 2006), but our measures did not show effects on dorsal raphé coherence or functional connectivity. The absence of dorsal raphé findings for coherence and functional connectivity in our analysis of a single, small pontine slice is not surprising given the small size of the region, and the limited number of subjects, and warrants further consideration. Hopefully, MDMA does not cause raphé function effects as severe as those observed during acute tryptophan depletion in remitted depressive patients (Salomon et al., 2011).

In summary, these analyses confirm and extend concerns that MDMA use impedes even robust motor pathway functions. Because previous preclinical and clinical data suggest that MDMA adversely affects serotonergic function, our data offers evidence that motor pathways are in some way coordinated by serotonergic input with specific frequencies most likely to contribute to this processing. MDMA's effects on interregional functional connectivity, not previously shown, raise an implication that previously shown effects on individual motor regions appear now to also alter interregional communications important to brain function. The motor system was validated here as sensitive to toxic effects on 5-HT function. Our findings of MDMA effects on coherence and functional connectivity in motor regions suggest a need for similar studies of regions supporting mood and higher cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1
Intraregional Coherence (percent of voxels) MDMA (mean, n=14), Control (n=10) by frequency and region name*

Coherence among regional voxels during 260 s BOLD scan with TR 2 s, given as percent of voxels correlated to an intraregional index voxel with $r > 0.5$. Frequency bands from wavelet filtering are: ULow ($< 0.03 \text{ s}^{-1}$), Low ($0.03\text{--}0.06 \text{ s}^{-1}$), Med ($0.06\text{--}0.12 \text{ s}^{-1}$), and High ($0.12\text{--}0.25 \text{ s}^{-1}$).

	ULow		Low		Med		High		Raw(ALL)		FIR $< .08 \text{ s}^{-1}$	
	Ctrl	MDMA	Ctrl	MDMA	Ctrl	MDMA	Ctrl	MDMA	Ctrl	MDMA	Ctrl	MDMA
Supp_Motor_Area_L	82.7%	78.0%	87.6%	76.4%	80.7%	74.6%	47.7%	42.8%	78.2%	71.4%	84.5%	78.6%
Supp_Motor_Area_R	80.5%	73.1%	76.9%	69.1%	69.6%	61.9%	40.9%	32.9%	69.5%	60.7%	79.3%	74.6%
Precentral_L	71.0%	63.2%	77.4%	69.0%	71.6%	64.5%	43.0%	36.7%	65.4%	56.5%	73.8%	66.2%
Precentral_R	68.4%	55.0%	73.9%	62.1%	71.6%	60.3%	41.8%	31.8%	65.3%	49.7%	68.5%	55.6%
Caudate_L	64.6%	66.3%	73.9%	73.1%	61.9%	64.6%	42.2%	41.9%	58.3%	60.0%	65.0%	67.5%
Caudate_R	70.0%	59.9%	77.0%	72.8%	70.1%	67.1%	44.5%	36.8%	64.8%	54.4%	70.4%	61.7%
Putamen_L	73.4%	71.8%	90.0%	86.5%	86.1%	82.7%	53.2%	50.4%	78.7%	70.8%	83.2%	75.7%
Putamen_R	76.1%	72.3%	83.7%	80.0%	86.6%	74.0%	55.5%	43.7%	78.5%	67.5%	82.3%	74.5%
Pallidum_L	75.3%	71.9%	92.4%	87.3%	84.9%	77.4%	59.9%	62.3%	78.3%	72.4%	82.4%	76.6%
Pallidum_R	83.7%	80.0%	91.3%	84.3%	87.5%	86.5%	75.8%	64.3%	87.6%	80.8%	90.1%	84.9%
Thalamus_L	<u>84.6%</u>	<u>70.5%</u>	<u>86.2%</u>	<u>71.5%</u>	<u>77.3%</u>	<u>61.6%</u>	46.7%	36.3%	<u>78.7%</u>	<u>59.2%</u>	<u>87.0%</u>	<u>72.2%</u>
Thalamus_R	86.1%	70.7%	<u>89.3%</u>	<u>71.3%</u>	<u>80.6%</u>	<u>62.3%</u>	50.5%	37.9%	<u>80.5%</u>	<u>58.0%</u>	<u>88.0%</u>	<u>72.3%</u>
Postcentral_L	73.0%	68.2%	<u>88.3%</u>	<u>75.6%</u>	<u>84.7%</u>	<u>74.5%</u>	49.2%	46.5%	<u>78.1%</u>	<u>66.1%</u>	79.6%	72.5%
Postcentral_R	73.7%	57.7%	<u>79.8%</u>	<u>64.5%</u>	72.9%	62.5%	40.4%	29.7%	<u>70.0%</u>	<u>50.8%</u>	75.4%	62.2%
Raphé	76.7%	76.2%	76.3%	76.2%	71.3%	70.2%	67.5%	69.6%	74.2%	70.2%	71.7%	72.6%
MEAN	76.0%	69.0%	82.9%	74.6%	77.2%	69.7%	50.6%	44.2%	73.7%	63.2%	78.7%	71.2%
StdDev	6.4%	7.3%	6.7%	7.5%	7.9%	8.3%	10.4%	12.4%	7.8%	8.9%	7.6%	7.4%

* Underlined bold significant after Bonferroni correction for multiple frequency band analyses $p < 0.0125$; underlined italic $p < 0.05$.

TABLE 2
Controls vs MDMA Group comparison for Functional Connectivity*

Functional connectivity for control subjects (n=10) and MDMA users (n=14), Wilcoxon rank sum. Frequency bands from wavelet filtering are: ULow ($< 0.03 \text{ s}^{-1}$), Low ($0.03\text{--}0.06 \text{ s}^{-1}$), Med ($0.06\text{--}0.12 \text{ s}^{-1}$), and High ($0.12\text{--}0.25 \text{ s}^{-1}$).

Paired Regions		P value	Frequency Band	Control Connectivity	MDMA Connectivity
Caudate_L	Thalamus_R	0.0015	ULow	0.86	0.11
Caudate_R	Postcentral_R	0.0073	Low	0.64	0.38
Supp_Motor_Area_R	Precentral_R	0.0107	Med	0.84	0.70
Thalamus_L	Thalamus_R	0.0073	Med	0.93	0.65

* Data shown only for region pairs significant after Bonferroni correction ($p=0.0125$) for four frequency bands studied. Fifteen regions gave 105 analyzed pairs.

Table 3
Functional Connectivity by Lifetime Use *

Twenty nine pairs of regions with functional connectivity and lifetime MDMA exposure correlation ($p < 0.05$) across 14 MDMA users. Only one pair (L Caudate – R Thalamus) was also significantly different between groups (controls vs. MDMA users, Table 2.) Frequency bands from wavelet filtering are: ULow ($< 0.03 \text{ s}^{-1}$), Low ($0.03\text{--}0.06 \text{ s}^{-1}$), Med ($0.06\text{--}0.12 \text{ s}^{-1}$), and High ($0.12\text{--}0.25 \text{ s}^{-1}$). Region abbreviations: supplementary motor area (Supp_Motor_Area).

Paired Regions		Freq band	r value	P value
Supp_Motor_Area_L	Pallidum_L	ULow	0.61	0.022
Putamen_L	Postcentral_R	ULow	0.55	0.043
Putamen_R	Postcentral_R	ULow	0.57	0.034
Pallidum_L	Postcentral_R	ULow	0.59	0.025
Pallidum_R	Postcentral_R	ULow	0.64	0.012
Supp_Motor_Area_R	Putamen_L	Low	−0.57	0.033
Precentral_R	Putamen_L	Low	−0.56	0.036
Putamen_L	Thalamus_R	Low	−0.55	0.043
Supp_Motor_Area_L	Putamen_R	Medium	−0.55	0.043
Supp_Motor_Area_L	Pallidum_L	Medium	−0.63	0.017
Supp_Motor_Area_R	Putamen_R	Medium	−0.57	0.032
Precentral_L	Postcentral_L	Medium	−0.65	0.012
Precentral_R	Putamen_L	Medium	−0.56	0.038
Caudate_L	Thalamus_R	Medium	−0.61	0.021
Caudate_L	Postcentral_L	Medium	−0.53	0.050
Caudate_L	Postcentral_R	Medium	−0.59	0.028
Putamen_L	Putamen_R	Medium	−0.73	0.003
Putamen_L	Postcentral_L	Medium	−0.68	0.008
Putamen_L	Postcentral_R	Medium	−0.62	0.019
Putamen_R	Pallidum_L	Medium	−0.72	0.004
Pallidum_L	Thalamus_R	Medium	−0.56	0.038
Pallidum_L	Postcentral_L	Medium	−0.61	0.020
Supp_Motor_Area_L	Thalamus_R	High	−0.55	0.040
Precentral_L	Postcentral_L	High	−0.71	0.004
Precentral_R	Putamen_L	High	−0.54	0.047
Precentral_R	Putamen_R	High	−0.55	0.043
Putamen_L	Thalamus_L	High	−0.65	0.011
Pallidum_L	Thalamus_L	High	−0.56	0.037
Thalamus_R	Postcentral_R	High	−0.82	0.0003

* Bold significant after Bonferroni correction $p < 0.0125$.