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Human ecstasy (MDMA) polydrug users have altered brain activation during semantic processing

Tristan J. Watkins[1,2], **Vidya Raj**[1,2], **Junghee Lee**[6], **Mary S. Dietrich**[1,2,3], **Aize Cao**[4], **Jennifer U. Blackford**[1,2,5], **Ronald M. Salomon**[1,2], **Sohee Park**[5], **Margaret M. Benningfield**[1,2], **Christina R. Di Iorio**[1,2], and **Ronald L. Cowan**[1,2,5]

[1]Vanderbilt Addiction Center, Vanderbilt University School of Medicine, Nashville, TN 37212, USA

[2]Psychiatric Neuroimaging Program, Vanderbilt University School of Medicine, Nashville, TN 37212, USA

[3]Department of Biostatistics, Vanderbilt University Schools of Medicine and Nursing, Nashville, TN 37212, USA

[4]Vanderbilt University Institute of Imaging Science, Nashville, TN 37232, USA

[5]Department of Psychology, Vanderbilt University, Nashville, TN 37240, USA

[6]Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California 90024-1759, USA

Abstract

Rationale—Ecstasy (MDMA) polydrug users have verbal memory performance that is statistically significantly lower than comparison control subjects. Studies have correlated long-term MDMA use with altered brain activation in regions that play a role in verbal memory.

Objectives—The aim of our study was to examine the association of lifetime ecstasy use with semantic memory performance and brain activation in ecstasy polydrug users.

Methods—23 abstinent ecstasy polydrug users (age=24.57) and 11 controls (age=22.36) performed a two-part fMRI semantic encoding and recognition task. To isolate brain regions activated during each semantic task, we created statistical activation maps in which brain activation was greater for word stimuli than for non-word stimuli (corrected $p<0.05$).

Results—During the encoding phase, ecstasy polydrug users had greater activation during semantic encoding bilaterally in language processing regions, including Brodmann Areas 7, 39, and 40. Of this bilateral activation, signal intensity with a peak *T* in the right superior parietal lobe was correlated with lifetime ecstasy use ($r_s=0.43$, $p=0.042$). Behavioral performance did not differ between groups.

Conclusions—These findings demonstrate that ecstasy polydrug users have increased brain activation during semantic processing. This increase in brain activation in the absence of behavioral deficits suggests that ecstasy polydrug users have reduced cortical efficiency during semantic encoding, possibly secondary to MDMA-induced 5-HT neurotoxicity. Although pre-existing differences cannot be ruled out, this suggests the possibility of a compensatory mechanism allowing ecstasy polydrug users to perform equivalently to controls, providing additional support for an association of altered cerebral neurophysiology with MDMA exposure.

Corresponding author: Tristan Watkins, Tristan. J.Watkins@Vanderbilt.edu, (727) 647 - 0215, Department of Psychiatry, Vanderbilt University School of Medicine, 1601 23rd Avenue South, Suite 3057, Nashville, TN 37212.

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INTRODUCTION

Use of the recreational drug 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) has been increasing in prevalence in the United States since 2007. There was a 23% increase in first-time users between 2008 and 2009, from 894,000 to 1.1 million. Prevalence of current use in children, ages 12 to 17, increased by 0.5% from 2007 to 2009 (Substance Abuse and Mental Health Services Administration, 2010).

Several animal studies show degeneration of presynaptic axon terminals and serotonin (5-HT) depletion after neurotoxic regimens of MDMA (Gibb et al. 1990;Green et al. 2003;Hatzidimitriou et al. 1999;Ricaurte et al. 2000) and an association with MDMA administration and behavioral changes caused by chronic alterations in the 5-HT system (Easton and Marsden 2006). Research in human ecstasy users is complicated by the extensive polydrug use in contemporary ecstasy-using cohorts (Gross et al. 2002;Pedersen and Skrondal 1999;Schifano et al. 1998). Thus, it is important to consider that studies of human recreational ecstasy use are studies of individuals having both ecstasy and polydrug exposure. Research in humans shows MDMA associated alterations on the 5-HT system, including: reduced binding to 5-HT reuptake transporters (5-HTT) (de Win et al. 2004;Kish et al. 2010;McCann et al. 1998;McCann et al. 2005;McCann et al. 2008;Reneman et al. 2001;Semple et al. 1999); reduced levels of the 5-HT breakdown product 5-hydroxyindoleacetic acid (5-HIAA) (McCann et al. 2000); and chronic upregulation of 5-HT2A receptors (Di Iorio et al. 2011;Reneman et al. 2002). The duration of MDMA effects on the 5-HT system remains unclear. Some studies found partial improvement with long-term MDMA abstinence (Semple et al. 1999;Thomasius R et al. 2003), while other data suggest sustained effects (Curran and Verheyden 2003).

The bulk of experiments in MDMA users have found statistically significantly lower neurocognitive function in MDMA users relative to controls, including verbal working memory (Jacobsen et al. 2004), episodic memory (Morgan 2000), and visual working memory (Back-Madruga et al. 2003). Recent reviews found reduced verbal working memory, short-term memory, and long-term memory in subjects with a history of MDMA use (Kalechstein et al. 2007;Laws and Kokkalis 2007) with the greatest effects on verbal memory. Studies show significantly reduced immediate and delayed verbal recognition change scores on the Ray Auditory-Verbal Learning Test in subjects using MDMA compared with non-MDMA polysubstance users (Schilt et al. 2007). Abstinent MDMA users exhibit reduced memory for up to two years after cessation of use, however, the observed reduction diminishes after repeated exposure to the information (Ward et al. 2006).

The repeated finding of lower verbal memory in association with MDMA use suggests that verbal memory may be among the most sensitive neurocognitive markers for MDMA effects. As such, probing verbal memory in MDMA users may prove to be a useful approach for documenting both the neural basis of MDMA toxicity and the neural basis of MDMA effects on verbal memory. Verbal memory involves at least two cognitive processes: 1) encoding of the stimulus, and 2) subsequent recognition or recall of the encoded stimulus. MDMA might therefore affect verbal memory globally or differentially alter encoding or recognition. We have demonstrated previously that fMRI is sensitive to altered monoamine tone during amphetamine administration and in association with MDMA use (Bauernfeind et al. 2011;Cowan et al. 2006;Cowan et al. 2008b;Karageorgiou et al. 2009;Salomon et al. 2012). Using a semantic memory task that recruits Brodmann Areas (BA) 9, 18, 21/22, and 45 (Lee et al. 2002), we previously reported that lifetime MDMA use was associated with reduced brain activation during semantic recognition, but not semantic encoding, in BA 9, 18, and 21/22 (Raj et al. 2010). However, there were methodological limitations to our initial study because we used an a priori region of interest approach (and the modified task

produced very weak activation in the a priori regions) and we did not isolate semantic memory because the encoding and recall phases were sufficiently close in time as to introduce an element of working memory into the semantic recognition component. These limitations weakened our ability to clearly associate ecstasy use with altered activation during semantic processing. MDMA effects could not be isolated from the effects of cannabis and/or cocaine in that study. Therefore, in the present study we used a task that better isolates semantic processing and chose an exploratory fMRI analysis method to more precisely identify semantically relevant brain regions.

To follow-up on our earlier work, and to further determine if brain function during semantic memory processing is associated with MDMA use, we enrolled a new cohort (having no overlap with the prior study (Raj et al. 2010) of MDMA users and controls to examine behavioral performance and brain activation using the functional magnetic resonance (fMRI) blood-oxygenation-level-dependent (BOLD) method during a task that tapped semantic encoding and semantic recognition.

METHODS

Subjects

34 subjects (11 controls, 23 ecstasy polydrug users) were scanned while they performed a semantic memory task. Detailed demographic information of both samples is provided in Table 1. Subjects were recruited as part of a larger study examining the effects of MDMA on brain structure and function. Subjects were recruited using flyers, advertisements, and email solicitation. Prospective subjects were informed that subjects 18–35 with a history of MDMA use were being recruited for a brain imaging study. The remaining inclusion and exclusion criteria were not disclosed to subjects in an attempt to prevent subjects from falsifying screening information. Subjects were compensated for their participation.

Inclusion/Exclusion Criteria

All subjects were right handed and ages 18–35. This age restriction was set due to the observed findings of diminished BOLD response with an increase in age (D'Esposito et al. 1999;Huettel et al. 2001). Subjects were asked to abstain from MDMA and all other drugs for at least 2 weeks prior to the fMRI study day with the exception of alcohol (48 hours) and nicotine (no restriction). Exclusion criteria included any current or past diagnoses of DSM-IV Axis I psychiatric disorder (except for MDMA-induced disorder or substance abuse) using the Structured Clinical Interview for DSM-IV (SCID-C, First et al. 2007). Current substance dependence, except for ecstasy and nicotine were also exclusions. Ecstasy polydrug users were required to have used > 5 tablets of MDMA. Subjects were excluded for contraindications to MRI, history of unconsciousness > 30 minutes, use of psychoactive medications in the last 6 weeks, any major illnesses, or understanding of the Dutch language (stimuli included both English and Dutch words).

Screening

Subjects completed detailed drug use questionnaires as previously reported (Bauernfeind et al. 2011;Cowan et al. 2006;Cowan et al. 2007;Cowan et al. 2009;Karageorgiou et al. 2009;Raj et al. 2010;Salomon et al. 2012) using a time-line follow back method (Fals-Stewart et al. 2000). The questionnaire examines specific drug use (alcohol, cannabis, stimulants, sedatives, dissociative anesthetics, hallucinogens, steroids, opiates, inhalants, and nicotine), episodes of use over various time periods (previous month, previous 12 months, and lifetime) and quantity. Because we do not have reliable data indicating the quantity of MDMA contained in ecstasy pills in our region, lifetime MDMA exposure was estimated as the quantity of ecstasy consumed. Subjects updated the questionnaire during each visit and

subjects were screened for recent drug use (urine; amphetamines, methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, PCP, and tricyclic antidepressants; Triage Drugs of Abuse Panel, Biosite Diagnostics, San Diego, CA), alcohol use (breath; Alco Sensor III, Intoximeters, St. Louis, MO), and pregnancy (females only [urine; QuPid One Step Pregnancy Test; Stanbio Laboratory, Inc. San Antonio, TX]). Subjects testing positive on any screen were removed from the study. Because anxiety and depression may be increased in ecstasy polydrug users (although not necessarily a direct consequence of MDMA exposure) (Medina and Shear 2007;Parrott et al. 2002) we assessed anxiety and depression using the Hamilton Rating Scale for Depression and the Hamilton Anxiety Rating Scale. Subjects completed the Wechsler Abbreviated Scale of Intelligence and the Edinburgh Handedness Inventory to assess individual intelligence (WASI) and laterality quotient (LQ), respectively. We did not specifically assess socioeconomic status, but assessed subject and maternal education levels as categorical variables consisting of "less than high school graduate", "high school graduate (including equivalency)", "some college or associates degree", or "bachelor's degree or higher". Education levels between groups were compared using Chi-square tests.

Confidentiality and Ethics approval

A Certificate of Confidentiality was obtained from the National Institute of Drug Abuse (NIDA). All subjects were informed of the Certificate protections in the informed consent document.

Research subjects provided written informed consent. The study conformed to the World Medical Association Declaration of Helsinki and was approved by the Vanderbilt University Institutional Review Board.

Semantic Memory Task: Encoding and Recognition

We used a rapid event-related design. During the encoding phase, subjects were asked to memorize 20 words and 20 non-words (pronounceable Dutch words that would have no meaning for the non-Dutch speaking subjects). There were two counterbalanced runs. Each stimulus was randomly presented for 4 seconds with a jittered inter-trial interval of 4–8 seconds. Using words and non-words as our stimuli allowed us to control for the visual and verbal representation of each stimulus. We determined semantic encoding relevant regions of activation by building a word > non-word contrast (Figure 1).

An approximately 20 minute delay was interposed between the encoding and recognition tasks by having subjects take part in other non-semantic fMRI tasks, including a flanker task, Stroop task, and a finger tapping motor task. For the recognition phase of the task, subjects were randomly presented with 20 pairs of words and 20 pairs of non-words. These pairs consisted of a word presented during the encoding phases and a new homophone stimulus (e.g. course versus coarse). Each homophone pair had similar phonological properties but different spelling. Subjects were to identify which stimulus they had seen during the encoding run by pressing a button. This recognition phase had an inter-trial interval of 2–6 seconds, with a mean interval of 4 seconds. The word pairs were presented for 4 seconds independent of subject response.

fMRI acquisition

Imaging was performed using a Philips 3T Intera Achieva MRI scanner (Philips Medical Systems, Andover, MA, USA). In each 244 second functional run, 28 field echo EPI (122 dynamics, 4.50 mm slice thickness with 0.40 mm gap, 2x2x2 voxel size, 2s TR, 35 ms TE, 79° flip angle, FOV=240, matrix=128X128) scans were acquired.

fMRI preprocessing

Data were analyzed using SPM5 (Wellcome Department of Cognitive Neuroscience, London, UK) utilizing the General Linear Model (GLM). The functional data were slice-time corrected using the first slice as the reference slice. Subject functional data were spatially aligned to their mean functional image for motion correction without the inclusion of motion parameters. Functional images were stereotactically normalized using SPM's EPI template (Montreal Neurological Institute). Normalized functional images were smoothed with a full-width half maximum (FWHM) 8 mm Gaussian Kernel.

Statistical analyses

Subject demographic characteristics were summarized using frequency distributions (gender) and means (standard deviations) for age. Because distributions for the drug history and use data were heavily skewed, those data were summarized using the median, minimum and maximum values, and ranges. Between groups analysis of drug use was examined using the Mann-Whitney U test because of the non-parametric distribution of the data.

fMRI data analysis

Because we were interested primarily in assessing MDMA effects on cortical semantic processing and in order to reduce the effects of multiple comparisons and increase statistical power, we applied a cortical mask during 2nd level processing in SPM5. The cortical mask was created in WFUpickatlas by combining the frontal, limbic, occipital, parietal, and temporal lobe masks. We used the AFNI based Alphasim program to run a Monte Carlo simulation to determine the extent threshold voxel cluster sizes (276 voxels) and uncorrected p value ($p \leq 0.01$) to generate a family wise error (FWE) corrected $p \leq 0.05$.

Between groups analysis

We conducted a between-groups analysis of the fMRI data comparing ecstasy polydrug users to controls using a random effects two-sample t-test in SPM5 ($p \leq 0.05$, corrected). To isolate semantically relevant activation for the encoding and recognition tasks, we created the contrast of word > non-word.

Within group analysis

Since the amount of past MDMA use has been shown to be associated with altered regional brain activation (Bauernfeind et al. 2011;Cowan et al. 2006;Cowan et al. 2008a;Karageorgiou et al. 2009), we examined the association of lifetime MDMA use with BOLD signal intensity change during task performance. Within ecstasy polydrug group analysis of the associations of signal intensity with past MDMA use were conducted using SPSS software version 18.0. We calculated signal intensity using an in-house script and MarsBar toolbox (Brett M et al. 2002). We extracted signal intensity in activated regions as determined by the between groups semantic (word>non-word) analysis (as described above) from SPM. The associations of signal intensity with past MDMA use, as well as possible confounding associations with other drug use were tested using Spearman's Rho correlations due to the non-parametric nature of our data.

Behavioral data analysis

Reaction time and accuracy of recognition were recorded for the recognition portion of the task. There were three indices of accuracy: % correct, % errors of omission and % errors of commission. A data coding error led to loss of half of the response data for approximately half of the subjects in each group. Since the missing data affected ecstasy polydrug users and non-users equally, and since the missing responses were dispersed throughout each experiment (making it unlikely that any effects caused by fatigue or trial order would be

confounded) we excluded the effects of missing data by modeling each instance a term of no-interest in the general linear model.

Since prior evidence suggests that MDMA exposure is associated with altered verbal memory performance (Kalechstein et al. 2007;Laws and Kokkalis 2007), we also examined the associations of lifetime MDMA use with indices of accuracy during the semantic recognition task. Data distributions for the groups were summarized using median and min, max values; between groups comparisons were conducted using Mann-Whitney tests. Spearman's Rho correlations assessed the degree of possible associations of the total amount of lifetime MDMA use with semantic recognition accuracy within the ecstasy polydrug group.

RESULTS

Demographics and drug use

The cohort included data from 34 subjects (11 controls; 5 males, 6 females, 9 white, 1 Asian, 1 African American), 23 ecstasy polydrug users (17 males, 6 females, 22 white, 1 Hispanic with mixed race). Although there were more males in the ecstasy group than in the control group, the difference was not significant (χ^2=2.64; p=0.138). The control group had a mean±SD age of 22.4±3.7 and the ecstasy group had a mean±SD age of 24.6±4.6. There was no statistically significant between-group difference for age (two-sample t-test, p=0.17). The control group had a mean±SD WASI of 66.70±9.63 and a mean±SD LQ of 46.09±4.42. The ecstasy group had a mean±SD WASI of 62.64±5.65 and a mean±SD LQ of 46.13±3.91.There were no statistically significant between-group differences for WASI or LQ (two-sample t-test, p=0.238, p=0.979, respectively). Regarding subject education level, 3 control and 2 ecstasy users were high school graduates; 4 control and 14 ecstasy users had some college education; 4 control and 7 ecstasy users had a bachelor's degree or higher. For maternal education, no control mothers and 1 ecstasy user mother had some high school education, 5 control mothers and 7 ecstasy user mothers were high school graduates, 4 control mothers and 7 ecstasy user mothers had some college education, and 2 control mothers and 8 ecstasy user mothers had a bachelor's degree of higher. There were no statistically significant between group differences for subject education level (χ^2=2.67; p=0.263) or subject mother's education level (χ^2=1.73; p=0.630, respectively). Control subjects had previous polydrug use with no exposure to ecstasy. Lifetime drug use (cannabis, methamphetamine, cocaine, sedatives/hypnotics, ketamine, LSD, psilocybin, opium) was higher (p<0.05) in the ecstasy group. No statistically significant correlations were found (all r_s < 0.33, p>0.188) with any of these drugs and BOLD activation (p>0.05). To determine the degree of correlation of lifetime ecstasy exposure and other drug exposure, we next examined the degree of correlation between lifetime quantity of ecstasy use and episodes to quantity and episodes of other drug use only in the ecstasy cohort for all drugs listed in Table 1. For lifetime quantity of ecstasy use, there was a significant positive correlation with lifetime quantity of codeine (r_s=0.439; p<0.036). Lifetime episodes of ecstasy were also significantly associated with lifetime quantity (r_s=0.714; p<0.001) and episodes (r_s =0.714; p<0.001) of ketamine and with lifetime quantity (r_s=0.482; p=0.023) and lifetime episodes (r_s=0.556; p=0.006) of methamphetamine use. Lifetime quantity of ecstasy use also correlated significantly with lifetime episodes of ecstasy use (r_s=0.583; p=0.003). Current nicotine use was reported as a "yes" or "no" response. There was no statistically significant between-group difference in nicotine use χ^2, p=0.255. One subject in the ecstasy polydrug group reported ecstasy-induced bulimia and body dysmorphic disorder.

Global semantic effects

To determine which regions were activated during the semantic encoding task, we examined global effects of the task across all subjects (ecstasy and controls). Regions found to have greater activation during the semantic encoding task (word > non-word) included the right supramarginal gyrus, left middle occipital cortex, left precuneus, right superior frontal cortex, right Brodmann Area (BA) 40, and left BA 19 (corrected FWE $p < 0.05$; Table 2; Figure 2). Activation during the semantic recognition task (word > non-word) included left precuneus, left middle temporal gyrus, left superior medial frontal gyrus, and BA 6 (Table 3; Figure 2).

There were no statistically significant associations of age or gender with BOLD signal intensity in the global semantic activated regions ($p>0.05$). Furthermore, there were no statistically significant differences between groups on the Hamilton Rating Scale for Depression or Hamilton Anxiety Scale ($p > 0.05$, Mann-Whitney test). Therefore, these factors were not included in subsequent analyses.

Comparison of MDMA users to controls

Ecstasy polydrug users had greater activation than controls in bilateral posterior parietal cortex during semantic encoding (word > non-word) (Figure 3). Peak activations occurred in right superior parietal lobule and left precuneus. Activated subregions within the main clusters, including BA 7, 39, and 40, are shown in Table 4. There were no statistically significant differences in activation between ecstasy polydrug users and controls during the semantic recognition task.

MDMA dose-response effects on brain activation

Within the ecstasy polydrug group, lifetime ecstasy use was correlated with activation identified in the between groups analysis with a peak *T* in right superior parietal and left precuneus regions for semantic encoding (regions and subregions shown in Table 4). Within the right parietal region, increasing lifetime ecstasy use statistically significantly associated with increasing BOLD signal intensity (Spearmans' Rho, $r_s = 0.43$, $p = 0.042$) (Figure 4). There was no such statistically significant correlation observed within the left precuneus (Spearmans' Rho, $r_s = 0.12$, $p = 0.583$). No statistically significant ($p > 0.05$, Spearmans' Rho, r_s) associations were observed for lifetime MDMA use (as ecstasy mg or episodes) with signal intensity for any individual encoding contrast conditions (word > fixation, non-word > fixation, word < fixation, non-word < fixation) nor were any other associations of ecstasy use with activation during semantic recognition or individual contrasts statistically significant ($p > 0.05$, Spearman's Rho). There was no effect of sex on brain activation in the right superior parietal ($p=0.609$) and left precuneus ($p=0.759$) regions during semantic encoding (Mann-Whitney test).

Since the majority of subjects had some level of other drug exposure (see Table 1), we explored possible correlations between activation in the right superior parietal and left precuneus regions and lifetime use of other drugs to determine if these other drugs were associated with BOLD activation. There were no statistically significant correlations between lifetime use of any drug and activation in the right superior parietal lobule or left precuneus ($p>0.05$).

Behavioral results

Both ecstasy polydrug users and controls demonstrated high levels of accuracy on the semantic recognition task (Table 5) and there were no statistically significant differences between those groups ($p > 0.05$, Mann-Whitney test). There was no statistically significant

associations of any of the indices of performance with lifetime ecstasy use (mg) (see Table 5).

DISCUSSION

Ecstasy polydrug users had greater activation than controls in bilateral posterior parietal regions (Table 4) during semantic encoding and greater lifetime ecstasy exposure was associated with greater activation in the region with peak *T* in the right superior parietal region during semantic encoding as well. In contrast, there were no regions of activation that differed between groups during semantic recognition. Behavioral performance for semantic recognition did not differ in ecstasy polydrug users and controls. The association of lifetime ecstasy exposure with greater activation was found in the right hemisphere, whereas no significant associations were observed with lifetime ecstasy exposure and activation found in the left hemisphere. We have previously reported stronger MDMA-associated effects observed in the right hemisphere as compared to the left hemisphere (Di Iorio et al. 2011), suggesting that if MDMA is responsible for lasting neurophysiological effects, the right hemisphere may be more susceptible. The current results are consistent with our earlier cross-sectional findings that lifetime ecstasy use is associated with greater task-evoked activation during simple motor (Karageorgiou et al. 2009) and visual tasks (Bauernfeind et al. 2011;Cowan et al. 2006), and with altered functional connectivity (Salomon et al. 2012). However, given the cross-sectional nature of the current study, the potential for both pre-existing differences in the control and ecstasy polydrug user groups, and the unknown effects of higher polydrug use levels in the ecstasy cohort, considerations of the potential links between our findings and altered 5-HT function are speculative. Notably, given the presence of polydrug use and the fact that our current cohort differed from controls in terms of polydrug exposure and possibly in terms of unidentified factors, such as genetic differences, socioeconomic status, and environmental exposures, many factors other than ecstasy exposure may contribute to the observed findings.

The current findings are somewhat at odds with our earlier study of semantic processing in ecstasy users (Raj et al. 2010), where we found that lifetime ecstasy use was negatively associated with brain activation. This may be due in part to the fact that we used an *a priori* region of interest approach during our first study and resultant task-relevant activations were very small; in addition, both cannabis and cocaine had statistical associations overlapping those of ecstasy, so we could not isolate the statistical association of ecstasy effects from those of other drugs in the original study. If a portion of the current results are related to MDMA effects on 5-HT function, these differences could be attributable to the role of 5-HT in regulating cortical gain--therefore loss of 5-HT may have very different effects in regions weakly activated by a task, versus those more strongly activated by a task when synaptic drive is greater (Higgs et al. 2006). If the current results are not related to MDMA exposure but to some other unmeasured or uncontrolled variable, the differences in outcomes between the two studies could be related to cohort differences. Extrapolating from complex cognitive paradigms is also not as straightforward as interpreting simple sensory or motor paradigms because complex cognitive contrasts compare task-induced activation to another cognitive task while the analysis of simple sensory and motor paradigms requires only the comparison of task-induced activation to a low level baseline. By using a task that effectively probes semantic processing, conducting a whole-brain exploratory analysis of the fMRI data, and enrolling a novel cohort, we found between group differences in brain activation and a positive correlation of lifetime ecstasy use with brain activation in one brain region. This approach strengthened the relevance of the current study with regard to assessment of semantic function in ecstasy polydrug users, in comparison to our initial report.

The semantic task that we employed here, while it is useful for isolating low-level semantic processing and for producing activation in brain regions related to semantic encoding and recognition, may not have isolated the components of verbal memory that have been previously been shown to be lower in ecstasy users than controls. Alternatively, a group of heavier ecstasy users than included here might show performance reductions in simple encoding and recognition. It is possible that a task eliciting greater cognitive demand would produce quantifiable behavioral deficits in ecstasy polydrug users. In a report by Ward (2006) and colleagues, ecstasy users were shown to have memory reductions relative to controls during initial task performance, but showed improvement with repeated task exposure, eventually matching control performance, suggesting a possible effect at the level of memory encoding (Ward et al. 2006). Therefore, it is possible that the repeated encoding period that we used might account for the lack of performance differences in our study. A meta-analysis of ecstasy effects found that among neurocognitive effects, those on verbal learning and memory appeared greatest but the studies included in the meta-analysis explored varying aspects of verbal learning and memory (Kalechstein et al. 2007). A separate meta-analysis found a large association of ecstasy use and lower verbal memory (Laws and Kokkalis 2007). Furthermore, a prospective cohort study found that individuals who use even a first low cumulative dose of ecstasy had significantly lower change scores on immediate and delayed verbal recognition and verbal recall tasks as compared to non-users (Schilt et al. 2007). A separate prospective study by Wagner (2012) and colleagues found that individuals using a minimum of 10 ecstasy pills in one year had significantly reduced change scores on immediate and delayed recall of a visual paired associated learning task when compared to ecstasy-abstinent individuals (Wagner et al. 2012). Similar to our findings, a recent report found preserved performance on verbal memory in association with altered neurophysiology as measured by event related potentials that were linked to verbal recall (Burgess et al. 2011). In a recent well-controlled study, Halpern and colleagues did not find significant associations of ecstasy use and verbal memory (Halpern et al. 2011); however, for example, others have found that lifetime ecstasy is associated inversely with verbal memory performance (Bedi and Redman 2008), semantic word fluency (de Sola et al. 2008); broad verbal memory performance (Quednow et al. 2006); and delayed verbal recall (Schilt et al. 2008).

Posterior parietal regions, including superior parietal lobule and precuneus, had bilaterally greater activation in the ecstasy polydrug users during semantic encoding (word > non-word). While we cannot isolate the precise role of the brain regions that showed increased activation in association with ecstasy use in semantic processing; BA 7, 39, and 40 have roles in cognitive and language functions and thus task activation in these brain regions may be relevant to semantic processing. The fact that these regions were activated during our specific semantic tasks also highlights their relevance to semantic processing. BA 7 has several higher order visual functions including: extracting object affordances, basic categorization of objects into living or non-living categories, and pairing specific actions to a viewed stimulus (Canessa et al. 2008;Cousin et al. 2007). Phonological properties such as rhyme detection of pair words generate a stronger BOLD response than a control visual detection task in BA 7 (Cousin et al. 2007). BA 39 is associated with processing noun characterization during a semantic decision task (Kim et al. 2011). BA 39 is also associated with rhyme detection and distinguishing between living and non-living stimuli (Cousin et al. 2007). Lee, et al. (2001) used PET to show an association with BA39 and semantic memory retrieval (Lee et al. 2002). BA 40 has some functional overlap with BA 7 for detecting pair word associations, rhyming, similarities, and assessing categories of stimuli (Binder et al. 1997;Cousin et al. 2007;Price et al. 1999;Pugh et al. 1996). Additionally, BA 40 is responsible for concrete versus abstract word judgments and covert word generation for semantically ambiguous versus semantically precise words (Chan et al. 2004;Chee et al.

1999). During semantic priming tasks, BA 40 shows an increased BOLD response (Sachs et al. 2008).

Irrespective of the origins of the increased semantic activation in ecstasy polydrug users, the implications of increased activation are unclear in the current cohort. First, given the preserved performance on the semantic task, there is no evidence to suggest that the greater activation is related to a gain of function in semantic processing ability in the ecstasy users. Second, the meaning of increased activation, in terms of brain function, is also unclear, since as discussed below, lower activation can correlate with improved functional efficiency. Third, we found that ecstasy polydrug users had increased activation in both right and left hemispheres in comparison to control subjects. Given the general localization of language process in the left hemisphere in right handed individuals, this suggests the possibility that ecstasy users more strongly recruited contralateral brain regions during semantic performance. Similar findings have been shown in Alzheimer's disease during semantic object naming tasks, where there are both areas of increased activation in the same areas activated in controls, but also changes in the patterns and regions activated during task performance (Wierenga et al. 2011). In aging, task performance during a digit symbol verification task at younger ages is linked to lower prefrontal activation while task performance at older ages is linked to higher activation (Motes et al. 2011). Individuals trained in meditation, a practice potentially increasing attentional efficiency, had lower activation (interpreted by the investigators as increased efficiency) during the Stroop task when compared to non-meditators (Kozasa et al. 2012). Others have interpreted preserved behavioral performance in the presence of increased brain activation as consistent with reduced brain efficiency and a requirement to more strongly recruit additional brain volume to preserve performance (Bondi et al. 2005). If neuronal function is indeed rendered less efficient, then additional brain regions or additional neuron numbers may be needed to ensure task completion. This is one reasonable interpretation of the current observations. Alternatively, pre-existing factors associated with brain activation and with ecstasy polydrug use may non-specifically lead to increased task-evoked brain activation that is unrelated to semantic performance. In addition, ecstasy or polydrug effects on brain vasculature, which influences the BOLD signal, might produce brain activation differences unrelated to altered neural function.

While we cannot assert that MDMA caused the observed findings, we have previously outlined a model to predict changes in cortical activation that would result from reduced cortical 5-HT signaling (Cowan et al. 2008a) and we have recently reviewed human imaging studies which indicate a very strong concordance between the predicted effects of MDMA-induced 5-HT neurotoxicity and findings in human recreational ecstasy users (Benningfield and Cowan, 2012). Since the net effect of 5-HT in cortex is inhibitory, especially influencing cortical gain, we had hypothesized that if the current cohort suffered from the effects of MDMA toxicity, that ecstasy users would have increased activation relative to control subjects. This effect would be present irrespective of whether lower 5-HT resulted from frank loss of axons or due to chronic reductions of 5-HT signaling with preserved axons and would be consistent with increases in cortical excitability in ecstasy users as previously reported by others (Oliveri and Calvo 2003). While altered activation can arise via many mechanisms, these alterations in cortical physiology are consistent with MDMA-induced reductions in 5-HT in cortical and subcortical regions (Salomon et al. 2011). When we compared the relationship of lifetime quantity of drug use to brain activation in brain regions showing greater activation in ecstasy users during semantic processing, we found that of all commonly used drugs (Table 1), only lifetime quantity of ecstasy use showed a statistically significant association with brain activation and this association was confined to the brain region showing increased activation in the ecstasy users during semantic processing in the right parietal region only. The lack of association of other drug use with

brain activation measures may reflect either a lack of effect of these drugs on brain activation or an inability to detect an association because of the complex interaction of polydrug effects, and the small sample size. Drugs of abuse could theoretically influence activation via a number of routes, including altered neuroplasticity, neurotransmitter changes, or neuron loss or damage. And, pre-existing factors associated with increased brain activation could predispose to polydrug use, so that the increased activation is not caused by drug use.

Limitations

Due to the cross-sectional nature of the current study and the presence of between-group differences in polydrug use and perhaps other variables that were not assessed or controlled for, we cannot conclude that MDMA exposure caused the observed effects. Ecstasy-use was collected using self-report, allowing for recall-bias or intentional deception artifacts that could correlate with other factors such as performance variables. However, research shows that individual self-reports on illicit drug use tends to be valid when compared to biochemical assays (Elman et al. 2000). Drug impurities make it impossible to know the exact amount of MDMA consumed per episode, if any. Ecstasy polydrug users typically have broad exposure to drugs other than MDMA; however, the association of MDMA with brain activation in the current cohort did not appear to be due to the contributions of other drugs because we found no evidence for an association of other drug exposure with brain activation in the regions showing greater activation in ecstasy users. Our cohorts differed in size (fewer numbers in the control group) and overall drug use and there were more males in the ecstasy group. While we did not see an association of sex with brain activation, the failure to detect such an association could be limited by the small sample size. As noted above, it is possible that pre-existing brain differences led to the observed findings, or that some combination of pre-existing differences and aggregate effects of ecstasy polydrug exposure account for the observed higher levels of activation in the ecstasy polydrug group.

Clinical Implications

We found that ecstasy use was associated with increased brain activation in the presence of preserved behavioral performance. While this permits us to conclude that between-group performance differences or ecstasy-associated effects on performance are not responsible for the observed effects, we cannot conclude that the observed differences in brain activation are related to the previously reported association of MDMA use with lower verbal memory. However, while the observed findings are consistent with reduced efficiency, it remains unknown whether the greater activation is solely a consequence of increased cortical excitability due to loss of serotonergic inhibitory effects, whether the increase in activation is unrelated to 5-HT physiology, or whether some combination of explanations accounts for this observation. It is also possible that the observed increase in activation is unrelated to the performed cognitive task. We have previously speculated that MDMA-associated increases in task activation reflect a fundamental shift in cortical excitability (Bauernfeind et al. 2011). MDMA administration in animal models can produce a reduction in seizure threshold, and a single report using transcranial magnetic stimulation in human visual cortex is consistent with a reduced cortical excitatory threshold (Giorgi et al. 2005;Oliveri and Calvo 2003). Additional studies are necessary to confirm the presence of altered cortical excitability in ecstasy polydrug users. If further studies link ecstasy exposure with increased cortical excitability, additional prospective studies of cognition and brain function would seem warranted to determine whether there are clinical consequences, e.g. further declines in memory or increased seizures, of the lower excitability threshold and whether incident ecstasy use influences excitability and brain activation.

Conclusions

Ecstasy polydrug users had greater activation in semantic processing regions during a semantic task in the presence of preserved behavioral performance. The increased activation in ecstasy polydrug users paired with equivalent behavioral performance to controls suggests that there may be a compensatory mechanism whereby greater neuronal activity is necessary in ecstasy polydrug users to preserve the same level of performance. Alternatively, the increased task-evoked activation may reflect pre-existing or drug-related effects that broadly affect brain function and that are not related directly to semantic processing. Additional studies using a semantic task that is sufficiently challenging to produce group differences might help resolve this question. While the observed findings are consistent with the predicted consequences of MDMA-induced reductions in 5-HT signaling, pre-existing group differences, sex differences, polydrug use, or other unknown factors might account for the between group difference in activation and we therefore cannot ascribe these effects to MDMA-induced toxicity.

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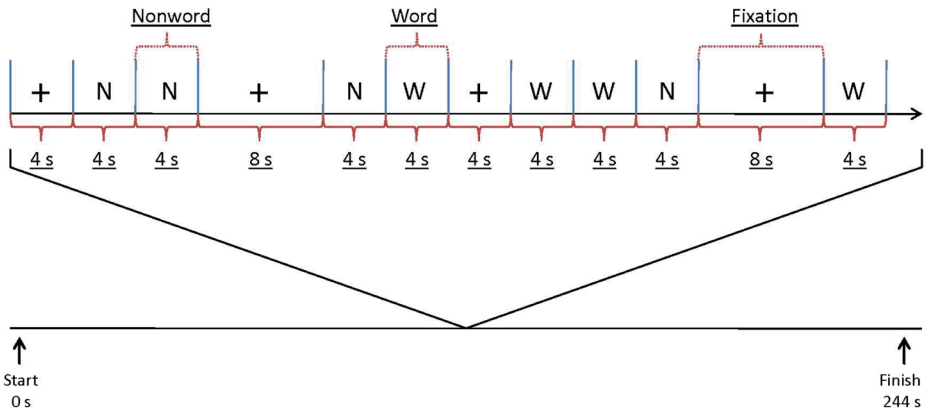

Fig. 1.
Task design showing stimulus presentation and onsets.

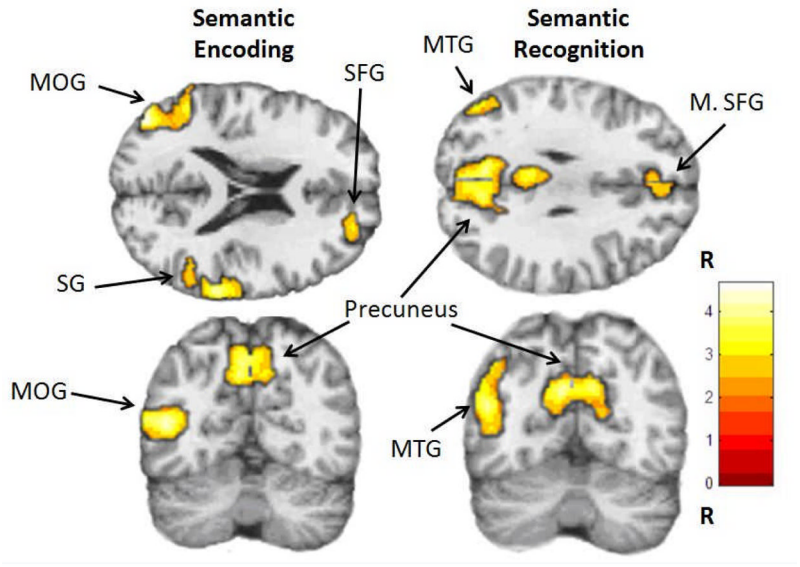

Fig. 2.

Semantic activation of all subjects during tasks.

Note: All regions labeled according to peak *T.* Column a: semantic (word > non-word) activation across all subjects (user and controls) during encoding phase. Column b: semantic activation across all subjects during recognition phase. Color bar represents *T* values for activated voxel group at statistical threshold of $p < 0.01$ and extent threshold = 276 voxels for corrected FWE $p < 0.05$. MOG – Middle Occipital Gyrus; SG – Supramarginal Gyrus; SFG – Superior Frontal Gyrus; MTG – Middle Temporal Gyrus; M.SFG – Medial Superior Frontal Gyrus

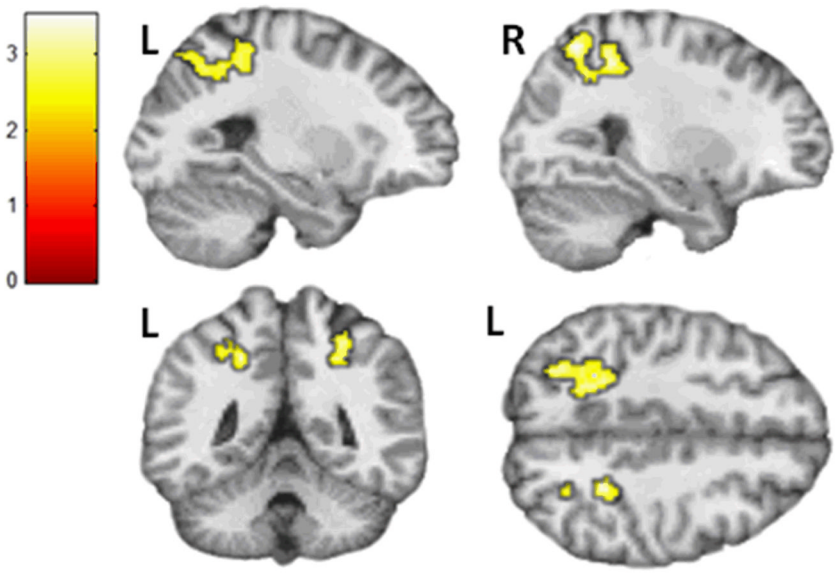

Fig. 3.

Regions with greater semantic encoding activation in ecstasy polydrug users

Note: Regions (labeled according to peak *T*) with greater semantic encoding activation in ecstasy polydrug users. Top row: Unilateral activation of left precuneus and right parietal lobule, respectively. Bottom row: Bilateral activation of coronal and axial slice of both left precuneus and right superior parietal lobule, respectively. Color bar represents *T* values for activated voxel group at statistical threshold of $p < 0.01$ and extent threshold = 276 voxels for corrected FWE $p < 0.05$. MNI coordinates of peak *T*: left precuneus(−20, −50, 44), right parietal lobules(30, −62, 54).

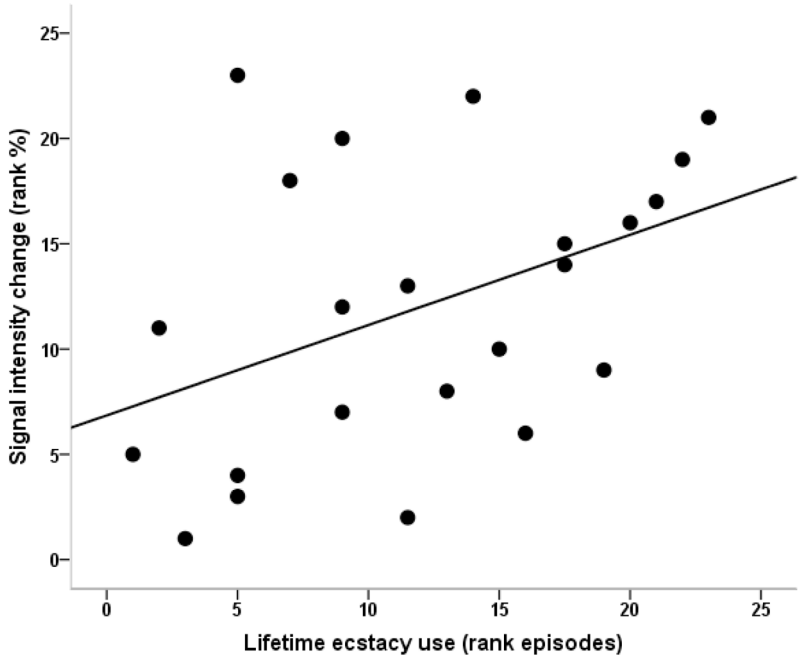

Fig. 4.
Correlation of right superior parietal lobule activation with lifetime ecstasy use during semantic encoding

Table 1

Subject demographics & drug use

	Group		
	Control (n=11)	**Ecstasy (n=23)**	**Significance**
	Mean ± S.D.	**Mean ± S.D.**	
Male [N(%)]	5 (45.6)	17 (73.9)	p=0.138
Age	22.4 ± 3.7	24.6 ± 4.6	p=0.170
WASI	66.70 ± 9.63	62.64 ± 5.65	p=0.238
LQ	46.09 ± 4.42	46.13 ± 3.91	p=0.979
MDMA Use	Median (Min, Max)	Median (Min, Max)	
Lifetime Units (mg)	-	1250.0 (300, 12,500)	
Lifetime Episodes	-	16.0 (3, 125)	
Days since last dose	-	476.0 (14, 1938)	
Other Drugs Lifetime Units			
Alcohol	n=11	n=23	
Lifetime Units (drinks)	404.0 (63, 3948)	1736.0 (24, 100300)	
Lifetime Episodes	158.0 (26, 1370)	584.0 (12, 12600)	
Days since last dose	16.0 (14, 41)	17.0 (6, 75)	
Cannabis	n=11	n=21	
Lifetime Units (joints) *	25.0 (1, 759)	139.3 (0, 402000)	
Lifetime Episodes *	25.0 (2, 1516)	250.0 (0, 101000)	
Days since last dose	51.0 (15, 524)	26.0 (14, 6212)	
Methamphetamines	n=0	n=8	
Lifetime Units (mg)	-	0.0 (0, 8000)	
Lifetime Episodes	-	0.0 (0, 2000)	
Days since last dose	-	1723.5 (37, 4056)	
Cocaine	n=2	n=17	
Lifetime Units (g) *	0.0 (0, 1)	3.0 (0, 800)	
Lifetime Episodes *	0.0 (0, 5)	7.0 (0, 600)	
Days since last dose	562.5 (368, 757)	358.0 (34, 3288)	
Sedative/Hypnotics	n=1	n=12	
Lifetime Units (mg) *	0.0 (0, 100)	30.0 (0, 1000)	
Lifetime Episodes *	0.0 (0, 10)	45.0 (0, 100)	
Days since last dose	917.0 (917, 917)	640.5 (61, 2242)	
Ketamine	n=0	n=10	
Lifetime Units (mg)	-	0.0 (0, 1800)	
Lifetime Episodes	-	0.00 (0, 30)	
Days since last dose	-	1790.5 (481, 3653)	
LSD	n=1	n=20	
Lifetime Units (μg) *	0.0 (0, 1800)	720.0 (0, 265800)	
Lifetime Episodes *	0.0 (0, 15)	5.0 (0, 900)	

	Group		
	Control (n=11) **Mean ± S.D.**	**Ecstasy (n=23)** **Mean ± S.D.**	**Significance**
Days since last dose	3173.0 (3173, 3173)	905.5 (37, 2933)	
Psilocybin	n=4	n=20	
Lifetime Units (g) *	0.0 (0, 9)	14.0 (0, 1000)	
Lifetime Episodes *	0.0 (0, 4)	7.0 (0, 500)	
Days since last dose	775.0 (412, 3599)	395.0 (37, 4018)	
Codeine	n=2	n=11	
Lifetime Units (mg)	0.0 (0, 950)	0.0 (0, 1225)	
Lifetime Episodes	0.0 (0, 30)	0.0 (0, 35)	
Days since last dose	1263.0 (666, 1860)	463.0 (34, 1833)	
Opium	n=1	n=15	
Lifetime Units (mg) *	0.0 (0, 35)	72.0 (0, 1006)	
Lifetime Episodes *	0.0 (0, 1)	5.0 (0, 106)	
Days since last dose	109.0 (109, 109)	310.0 (39, 3658	

Note:

* = Statistically significant between group differences for drug use ($p < 0.05$, Mann-Whitney tests). All group differences in other drug use were statistically significant except for alcohol and codeine use. Nicotine use was not statistically different χ^2, p=0.255.

Table 2

Activated regions during semantic encoding across all subjects (users & controls)

Global Semantic Activation (N = 34)				
		MNI		
Region (BA)	Peak *T*	Coordinates		
		x	y	z
Right Supramarginal Gyrus (40)	4.68	62	−32	26
Left Middle Occipital Cortex	4.50	−42	−78	20
Left Precuneus (19)	4.16	−6	−70	44
Right Superior Frontal Cortex	3.55	26	52	14

Note: Peak *T* is for activated voxel group at statistical threshold of $p < 0.01$ and extent threshold = 276 voxels for corrected FWE $p < 0.05$. MNI coordinates are for peak *T* value.

Table 3

Activated regions during semantic recognition across all subjects (users & controls)

Global Semantic Activation (N = 34)				
Region (BA)	Peak T	MNI Coordinates		
		x	y	z
Left Precuneus	4.88	−10	−54	14
Left Middle Temporal Gyrus	4.49	−46	−68	20
Left Superior Medial Frontal Lobule (6)	3.66	−4	36	40
Left Middle Temporal Gyrus	3.59	−54	−38	−8

Note: Peak *T* is for activated voxel group at statistical threshold of $p < 0.01$ and extent threshold = 276 voxels for corrected FWE $p < 0.05$. MNI coordinates are for peak *T* value.

Table 4

Regions and subregions with greater semantic encoding activation in ecstasy polydrug users.

Greater Semantic Encoding Activation in Ecstasy vs. Control			
Left Precuneus (3488 mm^3)		**Right Superior Parietal Lobule (3320 mm^3)**	
Subregion	**Volume (mm^3)**	**Subregion**	**Volume (mm^3)**
Inferior Parietal Lobule	1000	Inferior Parietal Lobule	280
Superior Parietal Lobule	912	Superior Parietal Lobule	1624
Postcentral Gyrus	592	Postcentral Gyrus	440
Precuneus	544	Precuneus	232
Brodmann Area 40	448	Brodmann Area 40	816
Brodmann Area 7	96	Brodmann Area 7	104
		Brodmann Area 39	288

Table 5

Subject performance data for semantic recognition task

	Control (n=11) Median (Min, Max)	Ecstasy (n=23) Median (Min, Max)	Association with Ecstasy Use (mg) r_s (*p*-value)
Correct (%)	88.2 (47, 100)	85.3 (50, 100)	.10 (.659)
Errors			
Omission (%)	5.9 (0, 41)	7.4 (0, 27)	−.17 (.457)
Commission (%)	5.9 (0, 15)	7.2 (0, 29)	.01 (.985)

Note: No statistically significant differences between the groups ($p > 0.05$, Mann-Whitney test).