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Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: Contributions of polydrug use

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Abstract

Background: Given ecstasy's (MDMA) potential serotonergic neurotoxicity, it is plausible that regular ecstasy users would have an elevated prevalence of behavioral executive dysfunction or mood symptoms. However, recent studies have found that the relationship between ecstasy use and psychological symptoms was no longer significant after controlling for marijuana use (e.g., Morgan et al., 2002). The goal of the present study was to examine the relationship between ecstasy exposure and self-reported executive functioning and psychological symptoms after controlling for gender, ethnicity, and other drug use.
Methods: Data were collected from 65 men and women with a wide range of ecstasy use (including 17 marijuana-using controls). Participants were administered the Frontal Systems Behavioral Scale, State-Trait Anxiety Inventory for adults, and the Beck Depression Inventory-2nd edition.
Results: Although 19–63% of the ecstasy users demonstrated clinically elevated psychological symptoms, frequency of ecstasy use did not predict the psychological symptoms. No gender differences or interactions were observed.
Conclusions: These results revealed that, although ecstasy users demonstrate elevated levels of psychological symptoms and executive dysfunction, these symptoms are not statistically associated with their ecstasy consumption. Instead, other drug use (alcohol, marijuana, opioids, and inhalants) significantly predict psychological symptoms in this sample of polydrug users.
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1. Introduction

Ecstasy (which primarily contains 3,4-methylenedioxymethamphetamine, or MDMA) is a popular drug among young adults and adolescents, and the lifetime prevalence rates for use among college students is approximately 10–14% (Boyd et al., 2003; Johnston et al., 2001; Medina et al., 2006). Ecstasy (MDMA) binds to brain serotonin transporters, which prevents serotonin reuptake and increases serotonin receptor activation, although MDMA can also affect dopamine, noradrenaline, acetylcholine and histamine (Parrott, 2001; Reneman et al., 2002a). Numerous animal studies have demonstrated MDMA (ecstasy) induced selective serotonin damage in several species, including rats (O'Shea et al., 1998; Scheffel et al., 1992), squirrel monkeys (Hatzidimitriou et al., 1999), rhesus monkeys (Taffe et al., 2001), and baboons (Scheffel et al., 1998). Further, there is evidence to suggest that ecstasy may be a selective serotonin neurotoxin in humans as well (McCann et al., 1994, 1998, 2005; Reneman et al., 2002b), and females may be at particular risk for ecstasy-induced semi-acute serotonin neurotoxicity (Buchart et al., 2004; Croft et al., 2001a; McCann et al., 1994; Reneman et al., 2001).

Serotonin is involved in the regulation of several behavioral domains, including mood, behavioral control, and vigilance (Brown et al., 1979; Coccaro, 1989; Naughton et al., 2000; Verkes et al., 1998). Given ecstasy's potential neurotoxic effects, one may suspect that regular ecstasy use would be associated with increased mood symptoms such as anxiety and depression and executive dysfunction. Indeed, a growing body of evidence supports the hypothesis that ecstasy users have elevated lev-

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els of both semi-acute (Curran and Travill, 1997; Curran et al., 2004; Verheyden et al., 2002) and chronic psychiatric symptoms, including dysphoria, depression, anxiety, panic attacks, paranoia, obsessionality, hostility, sleep disturbances, impulse control disorders, and eating disorders (e.g., Parrott et al., 2000; Schifano et al., 1998). More specifically, several studies have demonstrated elevated levels of depression (de Win et al., 2004; McCardle et al., 2004; Thomasius et al., 2005) and anxiety (Parrott et al., 2001, 2000; Thomasius et al., 2005) in ecstasy users compared to controls, although not all studies have identified increased depressive symptomotology (Daumann et al., 2001; Parrott et al., 2001, 2000). Studies that examined gender differences have reported that, in general, female ecstasy users report greater acute/sub-acute depressive symptoms compared to male users (Milani et al., 2004; Topp et al., 1999; Verheyden et al., 2002).

Studies examining executive function among ecstasy users have typically used laboratory-based neuropsychological measures, with conflicting results. Some have found working memory, fluency, and abstract reasoning deficits among ecstasy users, especially among male users (Montgomery et al., 2005; Verdejo-García et al., 2005; von Geusau et al., 2004), while others found relatively intact executive functioning among ecstasy users after controlling for other drug use (e.g., Croft et al., 2001b; Fox et al., 2002; Gouzoulis-Mayfrank et al., 2003; Medina et al., 2005). In addition to this inconsistency in the literature about the presence or absence of executive dysfunction in ecstasy users, little attention has been paid to the possible *behavioral* deficits that interfere with everyday function, most commonly caused by prefrontal system damage. These behaviors include impulsivity, disinhibition, apathy, inattentiveness, indecision, emotional lability, and poor mental flexibility (e.g., Malloy and Grace, 2005). Many of these behaviors are difficult to measure during traditional neuropsychological evaluation, as they are more likely to occur within unstructured or ambiguous contexts. Existing research that has examined behavioral symptoms of executive dysfunction in ecstasy users have found, with few exceptions (McCann et al., 1994), elevations in impulsivity or disinhibiton (Gerra et al., 1998; Morgan, 1998; Parrott et al., 2000; Schifano et al., 1998).

One consistent critique of the current studies is that the observed effects may be due to comorbid polydrug use, which is the norm among ecstasy users (e.g., Parrott, 2001). Indeed, it is difficult to determine whether reported psychological symptoms are due to ecstasy use, or rather to other drugs of abuse such as alcohol, marijuana, and cocaine. In support of the latter hypothesis, recent research has found that the relationship between ecstasy and psychological problems was no longer significant after taking into account other drug use, especially marijuana use (Daumann et al., 2001, 2004; Morgan et al., 2002; Roiser and Sahakian, 2004; Verdejo-García et al., 2005). A related finding is that Lieb et al. (2002) found that ecstasy use is often initiated after the development of an Axis I mood or anxiety disorder. This pattern highlights the need to exclude individuals with independent mood or anxiety disorders that predate their substance use.

Finally, most of the research on the psychological effects of ecstasy abuse is based on comparisons between an ecstasy group, which typically includes individuals with wide variations in usage patterns, and controls. Most studies have not examined exposure effects, although there is preliminary evidence that a positive relationship between *extent* of ecstasy use and increased psychological symptoms exists, in that heavy users demonstrate more impairment compared to light users (Parrott et al., 2000; Roiser and Sahakian, 2004). Therefore, the goal of the present study was to examine the relationship between ecstasy exposure (from none to heavy use) and self-reported executive functioning, anxiety, and depressive symptoms after controlling for frequency of other drug use, gender, and ethnic identification among ecstasy and marijuana users without independent DSM-IV mood or anxiety disorders. It was hypothesized that heavier ecstasy use would be significantly associated with increased levels of psychological symptoms after controlling for other drug use. We also examined gender differences; it was hypothesized that female ecstasy users would demonstrate greater depressive and anxiety symptoms while males would demonstrate increased behavioral symptoms of executive dysfunction.

2. Methods

2.1. Participants

Data were collected in conjunction with a study that focused on the neuropsychological consequences of ecstasy use; see Medina et al. (2005) for more detailed methodology information. Individuals were recruited through advertisements in a free metropolitan newspaper and screened by phone to determine eligibility. Participants were required to be fluent English speakers, 18 years of age or older, and had to fall within one of the predetermined stratified bins of ecstasy exposure (detailed below). Exclusion criteria included mental retardation, major medical or neurologic illnesses including traumatic brain injury, preexisting (independent of substance use) psychiatric conditions, or use of prescribed psychiatric medications.

Axis I psychotic, anxiety, and mood disorders were screened utilizing a modified SCID I/P interview based on DSM-IV-TR criteria (First et al., 2001). Interested participants who had positive responses to the screening questions were discussed in committee; if clear decisions could not be reached then they were re-contacted and administered the appropriate SCID I/P module by a trained interviewer. Individuals who met current diagnostic criteria (*independent* of their substance use) for any psychotic disorder, bipolar disorder, major depressive disorder, or anxiety disorder (generalized anxiety disorder, panic disorder, and post traumatic stress disorder) were excluded from the study.

Once deemed eligible, participants were screened with regard to their lifetime ecstasy use. In order to ensure that there were adequate participants across the expected range of ecstasy use, we utilized a proportional quota sampling technique, stratified by lifetime ecstasy use. The estimated range of ecstasy use was split into four bins prior to data collection in order to collect data from approximately equal numbers of participants across the full range of ecstasy use, balanced for gender. Further, because polydrug use is the norm among ecstasy users and marijuana use is particularly prevalent in this population, marijuana users were recruited to fill the first bin. This resulted in the following distribution: *bin 1* (eight male, nine female marijuana users with *no ecstasy use*); *bin 2* (9 male, 10 female ecstasy users who used 1–60 lifetime tablets); *bin 3* (eight male, six female ecstasy users who used 61–200 tablets); and *bin 4* (nine male, six female ecstasy users who used over 200 tablets). For descriptive purposes, participants in the first bin will be labeled "marijuana-users," and individuals who used ecstasy at least once will be labeled "ecstasy-users" from this point on. It is important to again emphasize that these bins reflect a sampling strategy only and do not represent separate groups in the multiple regression analysis; rather,

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