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Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy

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Abstract

A growing body of research suggests that traumatic events lead to persisting personality change characterized by increased neuroticism. Relevantly, enduring improvements in Post-Traumatic Stress Disorder (PTSD) symptoms have been found in response to 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. There is evidence that lasting changes in the personality feature of "openness" occur in response to hallucinogens, and that this may potentially act as a therapeutic mechanism of change. The present study investigated whether heightened Openness and decreased Neuroticism served as a mechanism of change within a randomized trial of MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD. The Clinician-Administered PTSD Scale (CAPS) Global Scores and NEO PI-R Personality Inventory (NEO) Openness and Neuroticism Scales served as outcome measures. Results indicated that changes in Openness but not Neuroticism played a moderating role in the relationship between reduced PTSD symptoms and MDMA treatment. Following MDMA-assisted psychotherapy, increased Openness and decreased Neuroticism when comparing baseline personality traits with long-term follow-up traits also were found. These preliminary findings suggest that the effect of MDMA-assisted psychotherapy extends beyond specific PTSD symptomatology and fundamentally alters personality structure, resulting in long-term persisting personality change. Results are discussed in terms of possible mechanisms of psychotherapeutic change.

Keywords

MDMA, posttraumatic stress disorder (PTSD), NEO personality, openness, treatment outcome, psychotherapy, pharmacotherapy

Introduction

The Diagnostic and Statistical Manual of Mental Disorders (DSM-III) formalized the modern conceptualization of posttraumatic stress disorder (PTSD) by providing unifying criteria for symptoms intrinsically linked to a catastrophic event and characterized by persistent re-experiencing, avoidance, and hyperarousal causing psychological distress or impairment in social, occupational, or other important areas of functioning (American Psychiatric Association, 2000). Although there have been minor revisions to these criteria in subsequent DSM versions, this definition has largely been unchallenged despite controversies (Friedman et al., 2011; Spitzer et al., 2007). Many critics have questioned whether the DSM diagnosis of PTSD encompasses the full spectrum of symptoms often associated with PTSD (e.g. psychological fragmentation, loss of a sense of safety, trust, and self-worth, loss of a coherent sense of self) (Herman, 1992). Specifically, the current diagnostic criteria do not capture the profound alterations in personality reported by a subset of individuals exposed to the most severe trauma.

As such, the concept of "complex PTSD" has been introduced to capture pervasive personality change associated with PTSD (Herman, 1992, 1997). While this distinction is not formally recognized within the DSM, the International Statistical Classification of Diseases and Related Health Problems (ICD-10) includes a provisional concept that is in relative accord with this notion, classified as "enduring personality change following a catastrophic experience" (World Health Organization, 1992). Similarly to DSM-III PTSD, this diagnosis requires a precipitating extreme stressor but also notes changes in personality to include pervasive hostility, mistrust, withdrawal, feelings of emptiness, hopelessness, and estrangement. Indeed, impulsivity, negative self-perception, somatization, survivor guilt, hostility, disturbed emotional responses, and low self-esteem have been identified as persisting personality changes that emerge as a result of extreme trauma (Beltran and Silove, 1999). Supportive of these diagnostic criteria, hostile and/or mistrustful attitudes specifically have been identified as

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prominent symptoms following catastrophic experience in a qualitative analysis conducted with 24 trauma clinicians (Beltran et al., 2008). Beltran and colleagues addressed critics' ongoing concerns regarding the reliability, validity, and clinical utility of this diagnostic category, as well as skepticism that personality could be fundamentally altered by events in adulthood (Beltran et al., 2008).

To our knowledge, no study has investigated change in personality associated with PTSD treatment response. While many personality theorists would argue that personality trait is a relatively stable construct throughout much of adulthood and not subject to change, there is evidence that links certain personality features to trauma experience. Specifically, extremely high Neuroticism scores on the NEO Personality Inventory (NEO PI) were found in a sample of Vietnam veterans with combat-related PTSD (Hyer et al., 1994; Talbert et al., 1993). Similarly, higher NEO PI Neuroticism scores were significantly associated with a history of childhood sexual, physical, and emotional abuse in undergraduate college students (Mathews et al., 2008). Finally, a study examining PTSD symptoms in older adults who had suffered myocardial infarction reported a positive correlation between NEO PI (Revised) (NEO PI-R) Neuroticism and re-experiencing, avoidant, and hyperarousal symptoms (Chung et al., 2006). Overall, there is a paucity of studies investigating personality change associated with PTSD. Most studies to date have been descriptive, and it is hard to determine the degree to which change is related to underlying premorbid personality (i.e. vulnerability to PTSD) and whether there are changes that are specific to PTSD.

Work dating back to the 1960s–1970s investigating mechanisms of personality change suggests that classic psychedelics, when used in a therapeutic context, can cause lasting beneficial change in personality with possible therapeutic implications (Greer and Tolbert, 2007; McGlothlin and Arnold, 1971). In modern research, Griffiths and colleagues studied the effects of oral psilocybin on psilocybin-naive normal volunteers (Griffiths et al., 2006, 2008). In this study, subjects rated the experience positively as causing substantial insight about personal meaning and spiritual growth. Furthermore, sustained positive changes in attitudes and behavior that were reported were validated by similar changes rated by observers familiar with the subjects. Fourteen months later, the same participants rated the psilocybin-occasioned experience as being among the five most personally meaningful and among the five most spiritually significant experiences of their lives, with 64% indicating that the experience increased well-being or life satisfaction. Extending these findings, the effect of psilocybin on changes in the five broad domains of personality using the NEO PI-R found that personality traits of "Openness" increased following a high-dose psilocybin session and were generally sustained in those who had a "mystical" experience during their session more than one year after the session (MacLean et al., 2011). These authors speculated about the potential clinical application and therapeutic benefit of change in the personality variable of Openness as result of pharmacologically induced "mystical" experiences. Consistently with this notion, a correlational link between spirituality and improved functional outcomes in relation to substance use and symptoms of anxiety and depression in cancer patients has been found (Kelly et al., 2011; McCoubrie and Davies, 2006).

Interestingly, ±3, 4- methylenedioxymethamphetamine (MDMA), which shares some properties with psilocybin and other classic psychedelic compounds, has been used in clinical trials as an adjunct, or enhancing agent, for therapeutic change in combination with psychotherapy for PTSD. Initial findings from our group have been promising, showing significant reductions in PTSD symptoms that are on average sustained up to 45.4 ± 17.3 months post treatment after several sessions of MDMA-assisted psychotherapy (Mithoefer et al., 2013; Oehen et al., 2013). While the pharmacological mechanism of action of MDMA as a PTSD treatment is not well understood, MDMA is known to cause serotonin release and release of the neurohormones oxytocin, prolactin, and cortisol (Dumont et al., 2009; Hysek et al., 2012, 2014; van Wel et al., 2012). It is possible that this pharmacology might augment exposure-based therapy by temporarily reducing avoidance, allowing patients to tolerate feelings associated with revisiting the trauma memory and fully engage in the exposure (Mithoefer, 2013). In controlled trials studying MDMA administration in normal volunteers, subjects have reported that the drug produces distinctive subjective pleasurable effects (Cami et al., 2000; Harris et al., 2002; Tancer and Johanson, 2003; Vollenweider et al., 1998), and seems to reduce activity in the left amygdala, a brain area associated with anxiety and stress reactivity (Gamma et al., 2000).

Psychological research suggests that MDMA increases prosocial feelings and behaviors, which, in turn, appears to reduce negative mood when subjects are asked to think of a difficult memory (Bedi et al., 2009, 2010; Carhart-Harris et al., 2014; Frye et al., 2014; Hysek et al., 2012, 2014). Others have proposed inhibition of the fear response to a perceived emotional threat that allows the patient to place the emotional sequelae of past experiences into a realistic perspective in their current emotional lives and relationships as another potential psychological mechanism of change for MDMA (Greer and Tolbert, 2007).To date, no study has investigated the relationship between MDMA and personality changes in subjects with PTSD. While a single catastrophic event can result in PTSD and/or "complex" PTSD with enduring adverse personality changes, it would seem possible that the converse might also be true (i.e. changes in certain personality features could reduce PTSD symptoms). The present study theorized that the profound therapeutic effect of MDMA in PTSD-treatment resistant individuals is influenced by its ability to broaden characteristics of the way an individual feels, thinks, and interacts (as measured by personality changes in Openness). We have previously reported that MDMA treatment is effective at reducing PTSD symptoms. The present study reanalyzed data from Mithoefer et al. (2011, 2013) to investigate whether personality changes were associated with PTSD symptom reduction. Given the strong relationship between PTSD and personality change, it was hypothesized that changes in Openness and Neuroticism would interact with PTSD symptom reduction. Group differences (MDMA-assisted psychotherapy vs. therapy only) in Openness and Neuroticism at baseline and 2-month follow-up also were investigated to test the hypothesis that there would be greater increases in Openness and decreases in Neuroticism in the MDMA treatment group. Lastly, Openness and Neuroticism at baseline and long-term follow-up (LTFU) (following the drug crossover trials) were examined to test the hypothesis that changes in personality following MDMA-assisted psychotherapy would persist.

Methods

The current study is a secondary investigation of purported mechanisms of psychological change associated with our previously reported data of MDMA-assisted psychotherapy (Mithoefer et al., 2011). We analyzed the role of change in Openness and Neuroticism variables from the NEO PI-R to investigate the mechanism of action. Recruitment and study procedures with descriptive details on clinical characteristics have been previously reported (Mithoefer et al., 2011, 2013). Briefly, study entry screening consisted of a Structured Clinical Interview for Axis I Diagnosis (SCID) (First et al., 1997b), the SCID-II module to screen for borderline personality disorder (First et al., 1997a), and Clinician-Administered PTSD Scale (CAPS) with a global severity score of at least 50 (Blake et al., 1990; Hovens et al., 1994; Mueser et al., 2001; Weathers et al., 2001). Subjects were required to meet DSM-IV-R criteria for the diagnosis of crime or war-related chronic PTSD, and to have treatment-resistant symptoms, defined as a CAPS score of $\geqslant 50$ (signifying at least moderate to severe PTSD symptoms) following at least 3 months of prior selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI) treatment in addition to at least 6 months of psychotherapy. Subject exclusion included presence of a major medical conditions, other psychiatric conditions besides PTSD or major depression, or a current substance abuse confirmed by medical examination, ECG, laboratory blood tests, and a urine drug screen. Twenty subjects completed the protocol and the final outcome measures at the 2-month follow-up. The final sample was predominately female (17 females, 3 males) and entirely Caucasian, with a mean age of 40.4 ± 7.2 years.

This study was approved by the Copernicus Group Independent Review Board (IRB), Research Triangle Park, NC, USA. Further details of the methodology and exclusion/inclusion criteria are reported elsewhere (Mithoefer et al., 2011, 2013). This clinical trial was registered on clinicaltrials.gov (NCT00090064).

Measures

Personality measure. The NEO PI-R is a 240-item, well-validated inventory that defines human personality in terms of a five factor model with six facets correlated within each specific trait (Costa and McCrae, 1992). A great deal of research supports the psychometric properties of this personality inventory. The NEO PI-R was created through pooling hundreds of trait measures from self-report questionnaires, peer ratings, and other psychological indices that collectively identified an underlying factor structure of personality traits. Multiple sets of researchers working independently over the last several decades have produced similar factor structure models of personality, which have been highly inter-correlated and factor analytically aligned (Costa and McCrae, 2008; Gignac, 2007).

The present study investigated the factors of Neuroticism and Openness. Neuroticism is captured within the subscales of anxiety, angry hostility, depression, self-consciousness, impulsivity, and vulnerability. Because of the high inter-correlations of these subset indices in factor analytic research models, these traits are described using the global encompassing term of "neuroticism." As such, individuals who score high on the neuroticism facet do not necessarily meet any criteria of diagnosable psychopathology, but rather, are individuals who are more prone to experience anxiety, anger, guilt, envy, or dysphoria when compared with the next person. Such individuals often see the world as threatening and have reduced frustration tolerance to normal everyday stressors.

NEO PI-R Openness is conceptualized by subset scales that measure aspects of fantasy, aesthetics, feelings, actions, ideas, and values. Those who score low on the Openness facet of personality are described as conventional, pragmatic, and traditional in outlook and beliefs. On the other hand, those who score high in Openness tend to be liberal in political beliefs, imaginative, and sensitive to inner feeling and the feelings of others, and generally have a higher need for variety in their lives. Such individuals are apt to seek out new experiences and be more prone to self-examination.

PTSD symptom measure. An independent rater who was not present during psychotherapy (MTW) administered the CAPS, a semi-structured interview that contains a global symptom severity score and a categorical score assessing whether a subject met DSM-IV-R criteria for PTSD diagnosis (Weathers et al., 2001).

Design

As previously reported, all subjects enrolled were randomized to either the placebo or the experimental condition (Mithoefer et al., 2011). Subjects received either two experimental sessions of MDMA-assisted psychotherapy ($N = 12$) or psychotherapy with inactive placebo (lactose) capsule ($N = 8$). Participants, therapists, and the independent rater were blinded to condition assignment. Data analyzed in this study were baseline, 2-month follow-up, and LTFU (mean = 45.4 months, SD = 17.3). The blind was broken after 2-month follow-up, and there was an open-label crossover condition for the placebo therapy group following the same experimental group protocol. In this experimental cohort, all subjects who initially received placebo were offered participation in an open-label crossover arm. Seven of the eight placebo condition subjects elected to participate (the one who did not elect for additional treatment had already experienced sustained benefit from therapy only). Of the original 20 subjects, 16 subjects participated in MDMA-assisted psychotherapy and the LTFU psychological measures. LTFU results and detailed information on participant attrition are presented elsewhere (Mithoefer et al., 2013), but findings showed an enduring and clinically meaningful benefit from MDMA-assisted psychotherapy as measured by the CAPS.

Therapeutic intervention. The therapeutic intervention was performed by a male and female co-therapist team: one a psychiatrist (MM) and the other a psychiatric nurse (AM). Each subject had two introductory sessions, two experimental sessions (with a subset receiving a third session after 2-month follow-up associated with a protocol amendment), and up to four integration sessions after each experimental session. For the experimental sessions, MDMA (125 mg) or placebo, followed in eight cases (four MDMA, four placebo) by an optional supplemental dose (62.5 mg MDMA or inactive placebo), was given. During experimental sessions, subjects were encouraged to focus on periods of introspection interspersed with therapeutic

discussion. Psychotherapy was non-directive and focused on processing trauma-related material as it arose spontaneously. Details of the therapeutic intervention can be found in the Treatment Manual (Mithoefer, 2013).

Analyses

In the present study, all analyses were conducted using IBM SPSS Statistics Version 21.0. Preliminary analyses first examined variable distributions and sample characteristics. Data distributions for continuous variables were visually inspected, and index values for skewness and kurtosis were assessed. One-way analyses of variance (ANOVAs) or when appropriate Chi-Square tests assessed for potential relevant group differences at baseline. Preliminary analysis tested for group differences after initial randomization. There were no significant differences between the control and experimental group for CAPS scores or trauma type at baseline; p-values > .10.

Within the first set of analyses, mixed-design repeated measure ANOVAs reanalyzed Global CAPS scores (the dependent variable) and between-group differences (MDMA-assisted psychotherapy vs. psychotherapy only) at baseline and 2-month follow-up while adjusting for personality changes. Changes in Openness and Neuroticism (defined as difference score from Visit 1 at baseline to the 2-month follow-up), respectively, served as covariates to investigate the role of personality changes in the relationship between MDMA-assisted psychotherapy and PTSD symptoms. Next, mixed-design repeated measure ANOVAs examined for between-group differences (MDMA-assisted psychotherapy vs. psychotherapy only) in personality change; NEO Openness and Neuroticism scores at baseline and the 2-month follow-up, respectively, served as dependent variables. Following the drug crossover condition, repeated measures of NEO PI-R Openness and Neuroticism at baseline compared with LTFU investigated whether personality changes persisted over time. Correlational analysis examined the relationship between personality change in Openness and Neuroticism. Two-tailed tests were used for all p-values.

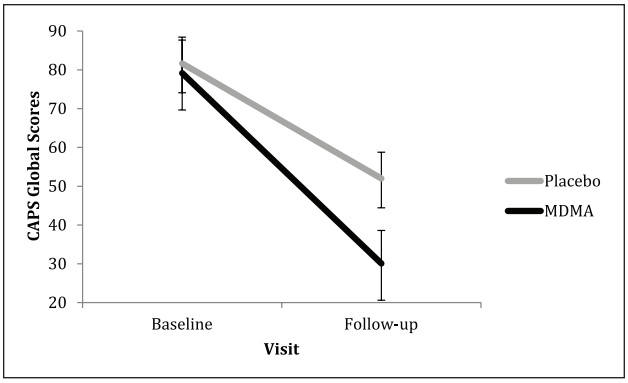

Figure 1. Placebo vs. MDMA-treatment group means and standard errors for Clinician-Administered PTSD Scale (CAPS) Global Scores at baseline and 2 months.
Change in Openness served as a covariate. Results represent the main effect of PTSD symptom reduction and the moderating effect of increased openness on therapy outcomes; all p values < .05.

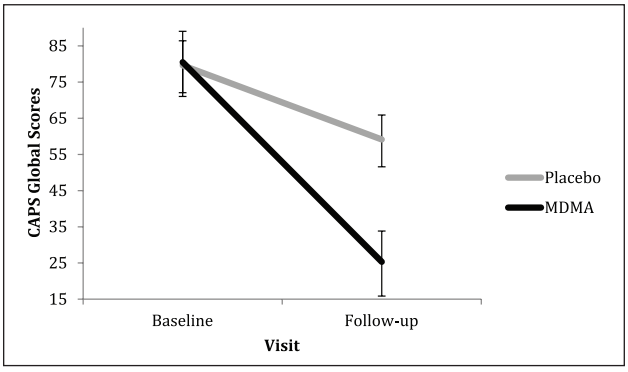

Figure 2. Placebo vs. MDMA-treatment group means and standard errors for Clinician-Administered PTSD Scale (CAPS) Global Scores at baseline and 2 months.
Change in Neuroticism served as a covariate. Results represent the main effect of group and the effect of decreased Neuroticism on therapy outcomes; all p values < .05.

Results

Analyses 1: Group differences at baseline and 2-month follow-up

Descriptive statistics for CAPS Global Scores by treatment group at baseline, 24 months, and LTFU visits have been published elsewhere (Mithoefer et al., 2011, 2013); in brief, groups did not differ at baseline in PTSD symptoms, but subjects showed an enduring and clinically meaningful benefit from MDMA-assisted psychotherapy as measured by their significantly lowered CAPS following drug treatment. In a re-analysis of the CAPS score data (Mithoefer et al., 2011), mixed-design repeated measure tests examined group differences in CAPS Global Scores at baseline and 2-month follow-up with change in personality (Openness and Neuroticism) as covariates.

Figures 1 (Openness) and 2 (Neuroticism) illustrate the mean CAPS scores and standard errors for group differences while adjusting for personality changes. Analysis showed a significant main effect of decreased CAPS scores independent of treatment condition when Openness is included as a covariate: $F(1, 17) = 40.60$, $p < .001$. Importantly, the present analysis also showed a significant interaction between change in Openness and CAPS scores, such that those who had the greatest increase in Openness concomitantly demonstrated greater decreases in PTSD symptoms as measured by the CAPS: $F(1, 17) = 5.68$, $p = .029$. Notably, the previously reported between-group effect of MDMA-assisted psychotherapy improvements in CAPS scores was no longer significant when Openness was adjusted for in the model: $F(1, 17) = 1.44$, $p = .246$. Similarly to Openness, there was a significant main effect of decreased CAPS scores regardless of treatment condition when Neuroticism was used as a covariate in the analyses: $F(1, 17) = 20.48$, $p < .001$. Within this analysis, the group × treatment interaction on the CAPS was significant. Specifically, there was greater improvement in CAPS scores in the MDMA group as compared with the therapy-only group: $F(1, 17) = 6.57$, $p = .02$ when using the covariant Neuroticism. There was also a significant interaction between change in Neuroticism and CAPS scores, such that those who had the greatest decrease

Table 1. NEO scores at baseline and 2-month follow-up by group.

Variable	MDMA (n =12)	Placebo (n = 8)	F =	p =
Neuroticism baseline	67.67 (14.52)	65.88 (11.43)	.086	.773
Neuroticism 2-month	55.833 (15.16)	60.62 (6.65)	.699	.414
Openness baseline	54.58 (15.88)	63.12 (6.66)	2.04	.170
Openness 2-month	57.75 (12.52)	60.00 (8.30)	.198	.662

Table 2. Changes in openness and neuroticism personality traits from baseline to LTFU.

Variable mean (SD)	Baseline	LTFU	$p \leqslant$
Openness	56.40 (15.03)	59.67 (11.91)	.032
Neuroticism	69.00 (13.85)	59.07 (11.76)	.003

in Neuroticism also demonstrated a greater decrease in CAPS score: $F(1, 17) = 18.83$, $p < .001$. Group differences in PTSD symptom reduction were attenuated when Neuroticism was adjusted for in the model: $F(1, 17) = 2.85$, $p = .11$.

Next, mixed-design repeated measure tests respectively examined group differences in Openness and Neuroticism at baseline and 2-month follow-up. No main effect of Openness was found: $F(1, 18) = .001$, $p = .988$. However, there was a significant interaction between Openness and Group: $F(1, 18) = 5.26$, $p = .034$. Visual inspection of average scores indicated that Openness increased within the MDMA group and decreased within the therapy only group from baseline to follow-up. In respect to Neuroticism, results indicated a significant main effect of Neuroticism: $F(1, 18) = 6.94$, $p = .017$; no significant interaction between group and Neuroticism was found: $F(1, 18) = 1.03$, $p = .324$. Table 1 presents descriptive statistics for the NEO scores at baseline and 2-month follow-up by group. Follow-up analyses did not find significant group differences for Openness or Neuroticism at baseline or 2-month follow-up: all p values > .05; notably, our observed power (< .20) was low to detect an effect on the post-hoc analyses. As expected, correlational analysis on changes in personality traits indicated across both groups that as Openness increases, Neuroticism decreases: $r = -.435$, $p = .055$.

Analyses 2: Personality changes following crossover condition across groups at LTFU

To test the hypothesis that MDMA-assisted psychotherapy leads to long-term change in personality, repeated measures examined Openness and Neuroticism at baseline compared with LTFU ratings. Table 2 presents the descriptive statistics for mean differences in Openness and Neuroticism personality traits at baseline as compared with LTFU following MDMA-assisted psychotherapy. Results indicated that there were significant and enduring changes in both Openness and Neuroticism when comparing baseline personality traits with long-term follow-up traits following MDMA-assisted psychotherapy: p values < .05.

Discussion

The present study extends our previous findings on the effect of MDMA-assisted psychotherapy on PTSD symptomatology (Mithoefer et al., 2011, 2013) by providing preliminary evidence that MDMA-assisted psychotherapy influences personality change, which in turn associates with improvement in PTSD symptoms. Our primary finding is that persistent changes in Openness and Neuroticism were found following MDMA treatment. These results provide initial support for the notion that the effect of MDMA-assisted psychotherapy extends beyond specific PTSD symptomatology and fundamentally alters personality structure, resulting in long-term persisting personality change.

The present study indicates that Openness plays an important role in PTSD symptom reduction (as measured by the CAPS), such that those who had the greatest increase in Openness concomitantly demonstrated greater decreases in PTSD symptoms, with this effect being greater in the MDMA-assisted psychotherapy group. These findings are consistent with the notion that increased openness may be a mechanism of therapeutic change. Notably, decreases in Neuroticism also associated with PTSD symptom reduction. It can be argued that the clinical improvement seen on the CAPS and the NEO PI-R may be due to the fact that both instruments are measuring the same clinical phenomenon. While this is possible, there is extensive psychometric data demonstrating the validity and reliability of both the NEO PI-R and CAPS. By definition, personality traits are stable over a lifetime. Our data and others suggest that change in personality plays an influential role in resolution of PTSD as measured by the CAPS. These results provide preliminary support for the specific role of Openness as a psychological mechanism by which MDMA exerts its therapeutic effects.

In the literature, the study of personality change in the laboratory is difficult because it is hard to create a significant life event, and there have been mixed results. Kipper et al. (2009) tested whether the psychopharmacological treatment of panic disorder changed personality patterns. These authors found that even after successful treatment of panic disorder, as measured by a Panic Inventory and Clinical Global Impression, panic disorder patients who were asymptomatic continued to differ from controls in terms of pre/post scores on the Minnesota Multiphasic Personality Inventory showing persisting anxious and neurotic personality characteristics, which they argued were traits of vulnerability. Piedmont (2001), on the other hand, showed personality change on the NEO PI-R in a subset of individuals at 15-month follow-up after successful treatment in a drug rehabilitation program. Costa et al. (2005) also showed personality change as measured by the NEO PI-R after antidepressant treatment for depression,

arguing that personality data were capturing concurrent symptoms and functioning beyond that which would be predicted from severity of depression rating scores. These authors argued that the temporal stability of personality trait is defined biologically and gives rise to characteristic psychological adaptations and maladaptation. Lastly, Tang et al. (2009) argued that high neuroticism is a personality risk factor that reflects genetic vulnerability for depression, and tested whether patients taking an SSRI versus placebo report greater changes in neuroticism. Regression analysis supported the state effect hypothesis that change in personality was more than a mere change of depression-related measurement bias, thereby providing further support for the notion that changes in personality would be expected following successful treatment of PTSD.

Overall, subjects showed a significant reduction in Neuroticism and an increase in Openness personality traits related to MDMA-assisted psychotherapy that was sustained up to 45.4 months post-treatment. Within the field of psychological research, neuroticism has been considered a fundamental personality trait that has long been the focus of much study. Neuroticism has been considered a milder form of psychopathology where there is an enduring pervasive tendency to experience negative emotion sufficient to interfere with effective life adjustment. In this study, there was an overall trend for all subjects to have lower scores on neuroticism post-treatment. Given the relationship between PTSD and heightened negative affect, whether lower scores obtained on the CAPS are a reflection of lower neuroticism, or vice versa, is an open question. More interesting is the effect of change in Openness and the overall trend for all subjects to have higher scores on openness post-treatment. Individuals scoring higher on Openness tend to seek out new experiences and be open to self-examination, factors that can serve to enhance therapeutic change in both behaviors and cognitions. Qualitatively, and consistently with previous work, therapeutic change seemed to be associated with an epiphany-type experience that subjects consistently reported following the MDMA-assisted psychotherapy sessions and reiterated in the long-term follow-up.

To our knowledge, this is the first published report of the therapeutic use of MDMA associating with persisting personality change. There are multiple lines of evidence that suggest personality should be stable throughout life. Behavior genetic research on individual differences of personality, as measured by the NEO in particular, have suggested a strong genetic component that accounts for much common variance in certain personality phenotypes, which argues for relative personality stability throughout life (Bergeman et al., 1993; Riemann et al., 1997). Similarly, research on the genome (de Moor et al., 2012) has found links between NEO personality factors and specific genes, which suggests that personality is stable throughout life. Yet our data, and those of others (MacLean et al., 2011), have shown that personality is susceptible to change. We speculate that there may be epigenetic factors involved in personality change whereby environmental factors such as profound experiences related to trauma or cathartic psychological insight can permanently influence underlying personality traits. Indeed, research indicates that early childhood adversity is associated with DNA methylation at the BDNF promotor region, which is associated with an increased risk of psychopathology (Kundakovic et al., 2015).

There are several limitations of this study. First, although this study was intended to be a double-blind trial, as previously noted, many participants and the therapists were able to correctly guess treatment conditions (Mithoefer et al., 2011), which can influence expectancies about therapy. Possible expectancy effects are particularly interesting in light of the finding that there were initial decreases in Openness but not increases in Neuroticism in the placebo group. Even so, as we previously reported (Mithoefer et al., 2013), the treatment effect was again demonstrated in an open-label crossover study and maintained at the 45.4-month follow-up, and once all participants crossed over to the MDMA condition, there were sustained personality changes. As well, subject ratings were obtained via an independent rater, who was not present during psychotherapy. These facts would be highly inconsistent with a placebo effect; nonetheless, it is possible. Thus, in an ongoing replication trial, we are investigating MDMA as an active placebo in dose response studies to address this question. Second, the main outcome measures of PTSD symptoms and personality traits are based on subjective report. Unfortunately, this limitation is not specific to this study, as clinical diagnosis and assessment of these factors are almost entirely based on subjective report. Lastly, given the investigational nature of the drug, the sample size in the current study was small; nevertheless, despite this limitation, significant group effects were found.

How MDMA-assisted psychotherapy can result in rather abrupt and lasting personality change is a perplexing question. Qualitatively, a consistent subjective theme emerged, with our subjects reporting a profound cathartic experience, often described as going to a "place" (in their mind) where they had never been before. It is interesting to speculate that MDMA acts as a catalyst, increasing openness, and thereby reducing PTSD-related symptoms and associated negative neuroticism. As such, MDMA, and its ability to facilitate personality change, may prove to be a frontline treatment for those with "complex" PTSD. While therapeutic experiences with psychedelic drugs do seem to result in lasting pervasively positive personality change, Pahnke and Richards (1966) had cautioned that the mystical experience is necessary, but not sufficient, for personality change to occur. Likewise, we would argue that the MDMA experience is only therapeutic in the context of psychotherapy. In a non-therapeutic context, it is quite possible that the reverse effect could occur. We speculate that MDMA-assisted psychotherapy facilitates, or "primes," a profound susceptibility for increased openness to experiences, which, in turn, enhances therapy's effectiveness. This notion was supported by our findings that those who had the greatest personality changes following treatment also had significantly greater decreases in PTSD symptoms. Considering that MDMA has been shown to acutely elevate oxytocin levels, it is of interest that personality is affected by pharmacological administration of oxytocin (Cardoso et al., 2012). Future research intends to investigate potential links between reported cathartic experience with MDMA-assisted psychotherapy-linked symptom reduction and personality change.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Mark Wagner received compensation from the sponsor for acting as an independent rater on this study. Rebecca MacAulay has no conflict of interest to declare. Mark Wagner, Michael Mithoefer, and Rebecca MacAulay wrote the manuscript and conducted the analyses for this manuscript. The study sponsor played a role in the study design (the

investigators performed all data collection). Three authors, Berra Yazar-Klosinski, Lisa Jerome, and Rick Doblin, are employed by the sponsor (Doblin, Yazar-Klosinski) or a wholly owned subsidiary of the sponsor (Jerome). Michael Mithoefer is a medical monitor for other studies of MDMA-assisted psychotherapy that are currently being conducted by the sponsor. He and Ann Mithoefer both received payment from the sponsor for conducting this research, while developing a treatment manual, investigator training program, and the design of protocols for additional studies planned by the sponsor.

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References

American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Arlington, VA: American Psychiatric Association.

Bedi G, Hyman D and de Wit H (2010) Is ecstasy an "empathogen"? Effects of +/−3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. *Biological Psychiatry* 68: 1134–1140.

Bedi G, Phan KL, Angstadt M, et al. (2009) Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology (Berl)* 207: 73–83.

Beltran RO and Silove D (1999) Expert opinions about the ICD-10 category of enduring personality change after catastrophic experience. *Comprehensive Psychiatry* 40: 396–403.

Beltran RO, Llewellyn GM and Silove D (2008) Clinicians' understanding of International Statistical Classification of Diseases and Related Health Problems, 10th Revision diagnostic criteria: F62.0 enduring personality change after catastrophic experience. *Comprehensive Psychiatry* 49: 593–602.

Bergeman CS, Chipuer HM, Plomin R, et al. (1993) Genetic and environmental effects on openness to experience, agreeableness, and conscientiousness: An adoption/twin study. *Journal of Personality* 61: 159–179.

Blake DD, Weathers FW, Nagy LM, et al. (1990) A clinician rating scale for assessing current and lifetime PTSD: The CAPS-1. *Behavior Therapy* 13: 187–188.

Cami J, Farre M, Mas M, et al. (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): Psychomotor performance and subjective effects. *Journal of Clinical Psychopharmacology* 20: 455–466.

Cardoso C, Ellenbogen MA and Linnen AM (2012) Acute intranasal oxytocin improves positive self-perceptions of personality. *Psychopharmacology (Berl)* 220: 741–749.

Carhart-Harris RL, Wall MB, Erritzoe D, et al. (2014) The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *International Journal of Neuropsychopharmacology* 17: 527–540.

Chung MC, Berger Z, Jones R, et al. (2006) Posttraumatic stress disorder and general health problems following myocardial infarction (Post-MI PTSD) among older patients: The role of personality. *International Journal of Geriatric Psychiatry* 21: 1163–1174.

Costa PT and McCrae RR (1992) *NEO PI-R Professional Manual*. Odessa, FL: Psychological Assessment Resources.

Costa PT Jr and McCrae RR (2008) The revised NEO personality inventory (NEO-PI-R). In: Boyle GJ, Matthews G and Saklofske DH (eds) *Sage Handbook of Personality Theory and Assessment*. Los Angeles, CA: Sage, pp. 179–198.

Costa PT Jr, Bagby RM, Herbst JH, et al. (2005) Personality self-reports are concurrently reliable and valid during acute depressive episodes. *Journal of Affective Disorders* 89: 45–55.

de Moor MH, Costa PT, Terracciano A, et al. (2012) Meta-analysis of genome-wide association studies for personality. *Molecular Psychiatry* 17: 337–349.

Dumont GJ, Sweep FC, van der Steen R, et al. (2009) Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Social Neuroscience* 4: 359–366.

First M, Gibbon M, Spitzer R, et al. (1997a) *Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II): Interview and Questionnaire*. Washington, DC: American Psychiatric Press.

First MB, Spitzer RL, Gibbon M, et al. (1997b) *Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P, Version 2.0, 4/97 Revision)*. New York: Biometrics Research Department, New York State Psychiatric Institute.

Friedman MJ, Resick PA, Bryant RA, et al. (2011) Considering PTSD for DSM-5. *Depression and Anxiety* 28: 750–769.

Frye CG, Wardle MC, Norman GJ, et al. (2014) MDMA decreases the effects of simulated social rejection. *Pharmacology, Biochemistry, and Behavior* 117: 1–6.

Gamma A, Buck A, Berthold T, et al. (2000) 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans. *Neuropsychopharmacology* 23: 388–395.

Gignac GE (2007) Multi-factor modeling in individual differences research: Some recommendations and suggestions. *Personality and Individual Differences* 42: 37–48.

Greer G and Tolbert R (2007) Therapeutic uses of MDMA. In: Winkelman M and Roberts TB (eds) *Psychedelic Medicine: New Evidence for Hallucinogenic Substances as Treatments*. Westport, CT: Praeger.

Griffiths R, Richards W, Johnson M, et al. (2008) Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology* 22: 621–632.

Griffiths RR, Richards WA, McCann U, et al. (2006) Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl)* 187: 268–283; discussion 284–292.

Harris DS, Baggott M, Mendelson JH, et al. (2002) Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology (Berl)* 162: 396–405.

Herman JL (1992) Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. *J Trauma Stress* 5: 377–391.

Herman JL (1997) *Trauma and Recovery*. New York: Basic Books.

Hovens JE, van der Ploeg HM, Klaarenbeek MT, et al. (1994) The assessment of posttraumatic stress disorder: With the clinician administered PTSD scale: Dutch results. *Journal of Clinical Psychology* 50: 325–340.

Hyer L, Braswell L, Albrecht B, et al. (1994) Relationship of NEO-PI to personality styles and severity of trauma in chronic PTSD victims. *Journal of Clinical Psychology* 50: 699–707.

Hysek CM, Domes G and Liechti ME (2012) MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions. *Psychopharmacology (Berl)* 222: 293–302.

Hysek CM, Schmid Y, Simmler LD, et al. (2014) MDMA enhances emotional empathy and prosocial behavior. *Social Cognitive and Affective Neuroscience* 9: 1645–1652.

Kelly JF, Stout RL and Magill M (2011) Spirituality in recovery: A lagged mediational analysis of Alcoholics Anonymous' principal theoretical mechanism of behavior change. *Alcoholism, Clinical and Experimental Research* 35: 454–463.

Kipper DA, Davelaar PS and Herst S (2009) The relationship between spontaneity and inhibition. *The Arts in Psychotherapy* 36: 329–334.

Kundakovic M, Gudsnuk K, Herbstman JB, et al. (2015) DNA methylation of BDNF as a biomarker of early-life adversity. *Proceedings of*

the National Academy of Sciences of the United States of America 112: 6807–6813.

McCoubrie RC and Davies AN (2006) Is there a correlation between spirituality and anxiety and depression in patients with advanced cancer? *Supportive Care in Cancer* 14: 379–385.

McGlothlin WH and Arnold DO (1971) LSD revisited. A ten-year follow-up of medical LSD use. *Archives of General Psychiatry* 24: 35–49.

MacLean KA, Johnson MW and Griffiths RR (2011) Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *Journal of Psychopharmacology* 25: 1453–1461.

Mathews CA, Kaur N and Stein MB (2008) Childhood trauma and obsessive-compulsive symptoms. *Depression and Anxiety* 25: 742–751.

Mithoefer M (2013) *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder; Version 6*. Available at: http://www.maps.org/research-archive/mdma/MDMA-Assisted-Psychotherapy-Treatment-Manual-Version7-19Aug15-FINAL.pdf (accessed 25 May 2017).

Mithoefer MC, Wagner MT, Mithoefer AT, et al. (2011) The safety and efficacy of {+/−}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: The first randomized controlled pilot study. *Journal of Psychopharmacology* 25: 439–452.

Mithoefer MC, Wagner MT, Mithoefer AT, et al. (2013) Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: A prospective long-term follow-up study. *Journal of Psychopharmacology* 27: 28–39.

Mueser KT, Salyers MP, Rosenberg SD, et al. (2001) Psychometric evaluation of trauma and posttraumatic stress disorder assessments in persons with severe mental illness. *Psychological Assessment* 13: 110–117.

Oehen P, Traber R, Widmer V, et al. (2013) A randomized, controlled pilot study of MDMA (+3, 4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *Journal of Psychopharmacology* 27: 40–52.

Pahnke WN and Richards WA (1966) Implications of LSD and experimental mysticism. *Journal of Religion and Health* 5: 175–208.

Piedmont RL (2001) Cracking the plaster cast: Big five personality change during intensive outpatient counseling. *Journal of Research in Personality* 35: 500–520.

Riemann R, Angleitner A and Strelau J (1997) Genetic and environmental influences on personality: A study of twins reared together using the self-and peer report NEO-FFI scales. *Journal of Personality* 65: 449–475.

Spitzer RL, First MB and Wakefield JC (2007) Saving PTSD from itself in DSM-V. *Journal of Anxiety Disorders* 21: 233–241.

Talbert FS, Braswell LC, Albrecht JW, et al. (1993) NEO-PI profiles in PTSD as a function of trauma level. *Journal of Clinical Psychology* 49: 663–669.

Tancer M and Johanson CE (2003) Reinforcing, subjective, and physiological effects of MDMA in humans: A comparison with d-amphetamine and mCPP. *Drug and Alcohol Dependence* 72: 33–44.

Tang TZ, DeRubeis RJ, Hollon SD, et al. (2009) Personality change during depression treatment. *Archives of General Psychiatry* 66: 1322–1330.

van Wel JH, Kuypers KP, Theunissen EL, et al. (2012) Effects of acute MDMA intoxication on mood and impulsivity: Role of the 5-HT(2) and 5-HT(1) receptors. *PLoS One* 7: e40187.

Vollenweider FX, Gamma A, Liechti M, et al. (1998) Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. *Neuropsychopharmacology* 19: 241–251.

Weathers FW, Keane TM and Davidson JR (2001) Clinician-administered PTSD scale: A review of the first ten years of research. *Depression and Anxiety* 13: 132–156.

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, Switzerland: WHO Press.